NDA 50717

AP Ltr
NA Ltr
Chem
EA + Fonsi
Pharm/Tox
Stat
Clin. micro

Clin. Pharm
+ Bio
Bio
FDA Corres

AP Ltr

NA Ltr

NDA 50-717

DEC 19 1996

Zambon Corporation
Attention: Dr. Foma Rashkovsky
Acting Director of Regulatory Affairs
Forest Laboratories, Inc.
One Meadowlands Plaza
East Rutherford, NJ 07073

Dear Dr. Rashkovsky:

Please refer to your September 29, 1994 new drug application (and your resubmission dated June 28, 1996) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Monurol™ (fosfomycin tromethamine) 3 gram sachet.

We acknowledge receipt of your amendments dated June 28, October 23, and October 31, 1996.

This new drug application provides for single-dose therapy in the treatment of uncomplicated urinary tract infection.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling dated December 19, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-717. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anti-Infective Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Beth Duvall-Miller
Consumer Safety Officer
(301) 827-2125

Sincerely yours,

David Feigal, Jr., M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE

cc:
Original NDA 50-717
HFD-520/Div. Files
HFC-130 (include labeling)
HFD-92 (include labeling)
HFD-473 (include labeling)
HFD-500 (include labeling)
HFD-638 (include labeling)
HFD-735 (include labeling)
HFD-2/M. Lumpkin
HFD-520/Label File/B. Duvall-Miller
HFD-520/ActDivDir/D. Feigal
HFD-520/DepDir/L. Gavrilovich
HFD-520/CSO/B. Duvall-Miller
HFD-520/SMO/J. Soreth 12/19/96
HFD-520/Pharm/S. Joshi
HFD-520/Micro/P. Dionne
HFD-520/BioPharm/F. Pelsor 12/19/96
HFD-520/Chem/J. Timper
HFD-520/BioStat/S. Bell
HFD-104/D. Feigal
HFD-101/L. Carter (with labeling)
HFD-830/E.Sheinin
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-021/J.Treacy (with labeling)

Concurrence Only:
HFD-520/SCSO/J. Bona For CMO 12/19/96
HFD-520/SMO/J. Soreth 12/19/96
HFD-520/SPharm/R. Osterberg 12/19/96
HFD-520/ActSChem/D. Katague DK 12/19/96
HFD-520/SMicro/A. Sheldon HNS for ATS
HFD-520/BioStat/D. Lin 12/19/96
HFD-520/ActDivDir/D. Feigal

drafted: bdm/December 19, 1996/M:\NDAAPP\N50717AP.WPD
r/d Initials:
final: BDM 12/19/96

APPROVAL

SEP 20 1995

NDA 50-717

Forest Laboratories, Inc.
Attention: Michael M. Rosen, Ph.D.
Director of Regulatory Affairs
909 Third Avenue
New York, N.Y. 10022-4731

Dear Dr. Rosen:

Reference is made to your new drug application (NDA) dated September 29, 1994, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for MONUROL® (fosfomycin tromethamine) sachet.

We also acknowledge receipt of your additional communications dated October 14, 18 and 24, and December 15, 1994; and January 1 and 27, February 3 and 16, March 22, April 28, May 15, June 13, 14, 20, 21 (two submissions) and 30, and July 7, 1995.

We have completed our review of this application, and it is not approvable at this time.

Under section 507 of the Act and 21 CFR 314.125(b)(5) of the implementing regulations, these applications have failed to provide substantial evidence consisting of adequate and well-controlled studies, as defined in 21 CFR 314.126, that fosfomycin tromethamine will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labelings. Specifically, the two pivotal studies conducted in the U.S. show an unacceptable eradication rate for cystitis. Moreover, the safety profile of fosfomycin given as a 3 gram single dose offered no advantages over standard treatment regimens. If you contemplate further studies with fosfomycin, you might consider an alternative dosing regimen (e.g., 2 grams daily for three days) and potentially increase the drug's efficacy and improve its safety profile.

It is not always clear from case record data how patients who failed fosfomycin therapy were further managed. In addition, the evaluation of patients who developed diarrhea after fosfomycin ingestion is often not recorded. The inclusion of such data in any future trial with fosfomycin would be very important in assessing the overall risk/benefit of the drug.

Further, as part of our commitment to provide you with a complete assessment of your NDA, the deficiencies noted in each section of your NDA are detailed as follows:

I. COMMENTS REGARDING THE CLINICAL AND STATISTICAL SECTIONS OF THIS NDA:

Clinical/Statistical:

Based on our review of the clinical studies and the recommendation of the July 20, 1995, Advisory Committee, we have concluded that the product does not offer a risk/benefit profile which would justify the approval of this application at this time. Specifically,

1. The two studies submitted to support this indication show this product to be both clinically and statistically inferior to drug products already approved for this indication.

2. The two studies demonstrated that this single-dose product provided no safety advantage over the multiple-day drug regimens currently approved.

In addition, we would like to let you know that the clinical site inspections are still ongoing.

CANDA/HARDCOPY DEFICIENCIES:

Please note that the following items are listed to provide feedback to you on the adequacy of the CANDA/hardcopy submitted for the review of this application. The following suggestions would improve the quality of the submission, both electronic and hardcopy and expedite the review:

1. Provide a listing of patients where the clinical or microbiological outcome documented by the investigator is different from the outcome as recorded by the company medical monitor.

2. Flag patients who received concomitant antimicrobials, and QC the case record forms to verify that other antimicrobial use is not documented.

3. Patients who received other antimicrobials for UTI signs or symptoms or for a positive urine culture post-therapy, should be assessed as FAILURES.

4. All failures must be carried forward in the analysis.

5. Assess treatment failures as failures, even if their follow-up falls outside of pre-defined time windows.

6. Place all investigators' comments, regardless of their place in the CRF, in one electronic file.

7. Record, in a numeric field, the number of days post-therapy that each follow-up visit occurred, including unscheduled visits.

II. COMMENTS REGARDING THE CHEMISTRY, MANUFACTURING, AND CONTROLS SECTION OF THIS NDA:

1. Please provide accelerated as well as real time data to substantiate your requested expiry period of two years.

2. Determine the water vapor permeability of the sachet pouch container closure system for the drug product.

3. Use the uninverted chemical nomenclature sanctioned and employed by the International Union of Pure and Applied Chemistry (IUPAC) and the World Health Organization (WHO) in the description section of the label.

4. Please see the attachment for our comments regarding your environmental assessment.

III. COMMENTS REGARDING THE MICROBIOLOGY SECTION OF THIS NDA:

1. Based on our review of the microbiology data submitted, we have determined that the following organisms are resistant to fosfomycin--they have MIC_{90} values which exceed the susceptibility breakpoint.

   Staphylococcus saprophyticus--MIC_{90} values were > 64 µg/mL.

   Enterobacter species--we now normally require each species to be studied and listed in the labeling. The MIC_{90} values for species other than *Enterobacter aerogenes* were > 64 µg/mL.

   Providencia rettgeri--MIC_{90} values were > 64 µg/mL.

   Providencia stuartii--MIC_{90} values were > 64 µg/mL.

   Pseudomonas aeruginosa--Not usually an urinary tract pathogen. MIC_{90} values were > 64 µg/mL.

   Xanthomonas maltophilia--Not usually an urinary tract pathogen. MIC_{90} values > 64 µg/mL.

2. Based on our analyses of the study submitted, the QC limits for *Escherichia coli* ATCC 29922 should be mm

instead of mm. It appears that an error was made when the data from Barry's study were interpreted. Gavan statistics indicated limits of mm, but this included only 94.2% of the data. It was suggested that the range be extended mm on each end, but since no zones of mm were found in the collaborative study, a range of mm is indicated.

FDA knows that there is some controversy regarding QC ranges for this drug, especially for MIC QC limits. Although only one collaborative study was submitted to the NDA (performed in 1991), two other MIC studies were submitted to the scientific community (performed in 1994 and 1995). The 1994 study did not confirm the results of the 1991 study so a new 1995 study was performed. Only the 1991 study for zone diameters has been submitted. Another 1994 study was performed. FDA must have all data to determine QC ranges.

3. The statement

should be deleted. The same statement is made later but in a more appropriate manner;

4. The statement

should be deleted since the evidence for this is presented in only one brief study and this does not seem to be the primary mode of action of this drug.

IV. COMMENTS REGARDING THE BIOPHARMACEUTICS SECTION OF THIS NDA:

In any resubmission of this application, please provide the following information:

1. The total recovery from urine and feces after a single 3 g dose was % following intravenous administration and % following oral administration. Please provide information accounting for the remaining % of the drug. This information can be obtained by conducting an *in vivo* mass balance study.

You may also consider performing the following *in vitro* experiments to characterize the profile of fosfomycin in gastrointestinal *milieu*.

gastrointestinal milieu.

a. Provide a pH stability profile with kinetic rate constants for degradation of fosfomycin dissolved at 37°C in buffer solutions pH 1.2, 4.5, 6.5, 7.5. Also, for these solutions provide the rate constants and assay values for the 4 degradation products: glycolic derivative; 1-hydroxy-2-trometamoyloxy-n-propyl fosfonic acid; tromethamine fosfate ester; and trometamoyloxy fosfomycin dimer. Perform the study in each buffer solution up to 12 hours.

b. Simulate gastric passage by adjustment of a solution of the drug substance to be pH 1.2 for 2 hours, then subsequently at pH 4.5 for 2 hours, pH 6.5 for 2 hours, and pH 7.5 for 2 hours. Assay and evaluate, as above, the degradation of the drug substance at each test station in the experiment.

2. Some PK parameters obtained from non-compartmental analysis in study report #1 did not match those obtained from compartmental analysis. Please explain the difference.

3. Mean total recovery (A_{∞}) result of fosfomycin in urine (0-infinity) summarized in Table A6-8 (study report #1) for treatment A (1433 mg) is different from that listed in Table 19 (1128). The result of 1433 will give a urine recovery of 48% rather than 38% which is the reported recovery value for the study. The mean A_{∞} for treatment B is 1082 mg in both tables mentioned above. However, if averaging the individual recovery in Table A6-8, the A_{∞} value should be 1580 mg (53%). Among the individual results in Table A6-8, subject 8 has a A_{∞}value of 6210.9 mg which is more than doubled amount of drug given (3000 mg). If subject 8 is considered an outlier, the mean A_{∞} of fosfomycin is 1360 mg. Please explain these calculations.

4. Please define the value of λ_z used to calculate A_{∞}. The value obtained from the non-compartmental analysis is different from the one obtained from compartmental analysis, and the use of the wrong λ_z will produce a wrong A_{∞}. Therefore, it may be more proper to use urine recovery from 0-84 hours rather than A_{∞}. Eighty four hours cover more than 14 half-lives. The urine recovery values from 0-84 hours are 37.6 for fast condition and 36.1 for fed condition.

5. Your submission of December 15, 1994, stated that the evidence of lack of metabolites "an examination of the chromatograms generated from the urine and fecal samples after oral and I.V. administration of fosfomycin from study R/3700/0002 (Study Report #1) revealed no peaks other than fosfomycin indicating that fosfomycin is probably not metabolized". This observation can only support that fosfomycin has absorption under this condition, but cannot rule out the existence of other metabolites.

6. Please provide experimental data showing that the ionized state of fosfomycin is likely to be reactive leading to its degradation.

7. Please provide data to determine if dosage adjustment is necessary in patients with renal impairment, including the safety data and urinary concentration data for a 3 g dose to uremic patients.

8. The amount of sucrose is fairly large in the dosage form. There might be a correlation between the amount of sucrose used and one of the adverse reactions, diarrhea.

9. The model used in Study Report #2 for oral data fitting is one compartmental model with first order absorption. The fitting is poor. According to study #1 and I.V. data in this study, the disposition of fosfomycin is described by a two compartmental model. Therefore, the one compartmental model used in this study is not proper. The λ_z value obtained from the one compartmental fitting may not reflect the terminal elimination rate. Thus, the absolute bioavailability values calculated based on λ_z values might not be accurate. Urine recovery data may be a better measurement of the bioavailability than the AUC values calculated from wrong λ_z values. Please note the misuse of this PK model.

10. Some of the assay validation data and assay results for study #2 were documented under study #3. Please correct this error.

PHASE 4 COMMITMENT

V. COMMENTS REGARDING THE PHARMACOLOGY/TOXICOLOGY SECTION OF THIS NDA:

Based on our review, we believe that fosfomycin should be designated Pregnancy Category C instead of Pregnancy Category B. The teratogenic effects noted were: wavy ribs and delayed/retarded ossification of bones in the rat; increased abortions, fetal resorptions and reduced fetal body weights in the rabbit.

VI. COMMENTS REGARDING INSPECTIONS OF THE SITES INVOLVED IN THE MANUFACTURE OF THIS PRODUCT:

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with current good manufacturing practices (CGMP) is required before this application may be approved.

Within 10 days after the date of this letter, you are required to amend this application, or notify us of an intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.120. In the absence of such action on your part, the FDA may proceed to withdraw this application. Any amendment ("resubmission" for user fee purposes) should respond to **all deficiencies** listed. A partial response will not be processed as a resubmission and, therefore, the resubmission user fee review clock will not be re-activated until complete responses to all deficiencies have been received.

Should you have any questions concerning this application, please contact Ms. Maureen P. Dillon-Parker, Project Manager, at 301-443-0257.

Sincerely yours,

David W Feigal 9-19-95

David Feigal, M.D.
Acting Deputy Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
NDA 50-717
NY-DO
HFD-520
HFC-130
HFD-82
HFD-500
HFD-638
HFD-735
HFD-2/Lumpkin
HFD-520/DepDir/Gavrilovich
HFD-520/SMO/Albrecht/init 8/10/95 9/18/95
HFD-520/MO/Soreth/init
HFD-520/SPharm/Osterberg/init 9/19/95
HFD-520/Pharm/Joshi/init 9/13/95
HFD-520/SMicro/Sheldon/init 9/14/95
HFD-520/Micro/Dionne/init 9/18/95
HFD-520/SChem/Roy/init 9/18/95
HFD-520/Chem/Timper/init 8/10/95 9/19/95
HFD-713/SStat/Harkins/init A&N 9/19/95
HFD-713/Stat/Turney/init AT/AdH 9/19/95
HFD-426/SBiopharm/Pelsor/init 8/10/95 9/19/95
HFD-426/Biopharm/Wang/init 8/10/95 9/19/95
HFD-521/SPMS/Bona/init
HFD-521/PMS/Dillonparker

Concurrence:

HFD-520/DepDir/Gavrilovich 9/19/95
HFD-520/SupMO/Albrecht
HFD-521/SPMS/Bona 9/18/95

NDAFILE\N50717.FNL rd/8/8/95 rd 8/17/95, 9/15/95

NOT APPROVABLE

Chem

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 50-717

CHEM.REVIEW #: 1 **REVIEW DATE:** 12/27/94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
Original	9/28/94	9/29/94	12/28/94
Amendment	12/15/94	12/16/94	12/28/94

NAME & ADDRESS OF APPLICANT:

Zambon Group S.p.A.
Fine Chemicals Division
Via Dovaro 36045 Almisano di Lonigo (Vicenza) Italy

AGENT:
The authorized agent in the United States is

Zambon Corporation
One Meadowlands Plaza
East Rutherford, NJ 07073, USA

DRUG SUBSTANCE NAME

Established: Fosfomycin trometamol
USAN: Fosfomycin tromethamine
Code #: Z1282

PHARMACOLOGICAL CATEGORY/INDICATION:
Antibacterial, urinary tract

ROUTE OF ADMINISTRATION:
Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

$C_3H_7O_4P \cdot C_4H_{11}NO_3$ 259.20

(1) Phosphonic acid, (3-methyloxiranyl)-, (2R-cis)-, compd, with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1); (2) (1R,2S)-(1,2-Epoxypropyl)phosphonic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).

CAS-78964-85-9.

Related documents:

DMF

DMF

DMF

DMF

DMF

DMF

CONSULTS:

A consult has been submitted on 12/27/94 to Dr. P. Vincent, CDER environmental reviewer. Method validation packages have been sent to the FDA New York FDA laboratory and the FDA Antibiotic Drug Branch laboratory for evaluation. A consult was sent to the Labeling and Nomenclature Committee to evaluate the tradename, Monurol.

REMARKS/COMMENTS:

The drug substance review has been accomplished in DMF , for fosfomycin tromethamine. The DMF holder is Zambon Group S.p.A., Vicenza, Italy. Synthesis and controls for the drug substances should be referenced to that document. There is one item outstanding pertaining to an alternate source of primary material in the synthesis of the drug substance. Stability data for the drug product currently has data to 18 months.

CONCLUSIONS & RECOMMENDATIONS:

Request that a nonapproval letter issue at this time. The deficiencies noted pertaining to chemistry, manufacturing, and controls are addressed to the firm with regard to labeling, the container closure, and stability. Consults for the methods validation and environmental assessment are outstanding at the time of this review. The establishment inspections have been requested. The methods validation have been sent to 2 FDA laboratories for evaluation.

JTim 12/29/94

J. Timper

cc: Org. NDA 50-717
HFD-520/Division File
HFD-520/SBRoy/Acting SUPVCHEM 2/10/95
HFD-520/Timper/CHEM 12/28/94
HFD-520/Soreth/MO
HFD-520/Joshi/Pharm
HFD-520/Soprey/Micro 2/16/95
HFD-520/Dillon-Parker/CSO
HFC-130/JAllen

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 50-717

CHEM.REVIEW #: 2 REVIEW DATE: 8/2/95

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
Original	9/28/94	9/29/94	12/28/94
Amendment	12/15/94	12/16/94	12/28/94

Current summary of completed sections: 8/2/95

NAME & ADDRESS OF APPLICANT:

Zambon Group S.p.A.
Fine Chemicals Division
Via Dovaro 36045 Almisano di Lonigo (Vicenza) Italy

AGENT:
The authorized agent in the United States is

Zambon Corporation
One Meadowlands Plaza
East Rutherford, NJ 07073, USA

DRUG SUBSTANCE NAME

Established: Fosfomycin trometamol
USAN: Fosfomycin tromethamine
Code #: Z1282

PHARMACOLOGICAL CATEGORY/INDICATION:
Antibacterial, urinary tract

ROUTE OF ADMINISTRATION:
Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

$C_3H_7O_4P \cdot C_4H_{11}NO_3$ 259.20

(1) Phosphonic acid, (3-methyloxiranyl)-,(2R-cis)-, compd, with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1); (2) (1R,2S)-(1,2-Epoxypropyl)phosphonic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).

CAS-78964-85-9.

Related documents: See review #1.

CONSULTS:

Environmental assessment: A consult was sent on 12/27/94 to Dr. P. Vincent, CDER environmental reviewer. The review was completed on 3/3/95 and deficiencies were cited.

Method validation packages have been sent to the FDA New York FDA laboratory and the FDA Antibiotic Drug Branch laboratory for evaluation. This evaluation is not yet accomplished.
A consult was sent to the Labeling and Nomenclature Committee to evaluate the tradename, Monurol. The name was found acceptable on 3/15/95.

REMARKS/COMMENTS:

The drug substance review has been accomplished in DMF , for fosfomycin tromethamine. The DMF holder is Zambon Group S.p.A., Vicenza, Italy. Synthesis and controls for the drug substances should be referenced to that document. There are no unresolved deficiencies in the DMF. Stability data for the drug product submitted with the NDA was for 6 months. The Establishment Evaluation Request has not been completed by FDA inspectors at the time of this review. Review #1 completed on 12/28/95.

CONCLUSIONS & RECOMMENDATIONS:

Recommend that a not approvable letter be issued. The deficiencies noted in review #1 are attached. Deficiencies pertaining to the environmental assessment are attached.

JT 8-2-95

J. Timper

cc: Org. NDA 50-717
HFD-520/Division File; HFD-520/SBRoy/~~Acting~~ SUPVCHEM 8/9/95
HFD-520/Timper/CHEM 8/2/95; HFD-520/Soreth/MO
HFD-520/Joshi/Pharm; HFD-520/Soprey/Micro
HFD-520/Dillon-Parker/CSO; HFC-130/JAllen

8/14/95

#414

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mille, Chair, (HFD-600) MPN II

FROM: Division of ANTI-Infectives HFD- 520
Attention: JIM TIMPER Phone 443-6714

DATE: 1-24-95

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Monurol NDA/ANDA# 50-717

Company Name: Zambon Corporation

Established name, including dosage form: Fosfomycin Trometh... Oral powder 2 grams (to be used immediately after dilution in 3 to 4 ounces of tap water)

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy): Antibacterial, urinary tract

Initial comments from the submitter: (concerns, observations, etc.)
It is stated several ways.
Monurol (Fosfomycin Trometh...)
Monurol (Fosfomycin Trometh...), Sachets
Monurol (fosfomycin trometh...) 3gm sachets

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 93

Consult #414 (HFD-520)

MONUROL

Fosfomycin Tromethamine
Oral Powder 3 grams

A review revealed several names which sound or look like the proposed name: Monosyl, Monopril, Norel Plus Capsules. Due to differences in product strength and in dosage form, the Committee does not believe there is a significant potential for confusion involving any of these names with the proposed name.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Joan Keith Mille, Chair 3/15/95

NOTE: The Committee notes that Martindale's and the USP Dictionary of USAN and International Drug Names list the proprietary name for this product as MONURIL [note spelling]. The Committee's decision as stated above would also apply to this variation of the proposed tradename.

COMPLETED

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 50-717

CHEM REVIEW #: 3 **REVIEW DATE:** 7/19/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
Original	9/28/94	9/29/94	12/28/94, Review #1
Amendment	12/15/94	12/16/94	12/28/94, Review #1 8/2/95, Review #2
Amendment	6/28/96	6/28/96	7/19/96, Review #3

Review #2 notes completion of the consult for trade name evaluation and completion of the DMF review for drug substance (Adequate). No corresponding documents to the NDA file for review.

NAME & ADDRESS OF APPLICANT:

Zambon Group S.p.A.
Fine Chemicals Division
Via Dovaro 36045 Almisano di Lonigo (Vicenza) Italy

AGENT:

The authorized agent in the United States:
Zambon Corporation
One Meadowlands Plaza
East Rutherford, NJ 07073, USA

DRUG SUBSTANCE NAME

Established: Fosfomycin trometamol
USAN: Fosfomycin tromethamine
Code #: Z1282

PHARMACOLOGICAL CATEGORY/INDICATION:

Antibacterial, urinary tract

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

$C_3H_7O_4P \cdot C_4H_{11}NO_3$ 259.20

(1R,2S)-(1,2-Epoxypropyl)phosphonic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).

CAS-78964-85-9.

Related documents:

DMF

DMF

DMF

DMF

DMF

DMF

CONSULTS:

- The firm's response to the environmental assessment review performed by Dr. P. Vincent, CDER environmental reviewer was sent for review to Nancy Sager, Environmental Review Officer, on 7/17/96.
- Method validation packages have been sent to the FDA New York FDA laboratory and the FDA Antibiotic Drug Branch laboratory for evaluation. The result of that evaluation has not been provided at this time.
- A consult was sent to the Labeling and Nomenclature Committee to evaluate the tradename, Monurol. The name was found acceptable on 3/15/95.
- An EER update was made on 7/17/96: #10532.

REMARKS/COMMENTS:

- The drug substance review has been accomplished in DMF , for fosfomycin tromethamine. The DMF holder is Zambon Group S.p.A., Vicenza, Italy. Synthesis and controls for the drug substances should be referenced to that document. There are no issues that still require resolution; the DMF is satisfactory.
- Updated stability data provided in the current submission supports the 2 years expiration dating requested by the firm.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable regarding chemistry, manufacturing, and controls. The application is approvable since the EER (inspection request) and the resubmission of the Environmental Assessment consult are not completed at this time; see consults above. The methods validation have been sent to 2 FDA laboratories for evaluation and that has not been completed and provided to the division at this time.

JTh 7/19/96

J. Timper

cc: Org. NDA 50-717
HFD-520/Division File
HFD-520/SBRoy/Team Leader Chemistry JT 7/22/96
HFD-520/Timper/CHEM 7/19/96
HFD-520/Soreth/MO
HFD-520/Joshi/Pharm
HFD-520/Dionne/Micro
HFD-520/Dillon-Parker/CSO

NOV 4 1996

DF

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 50-717 **Chem. Review:** 4 **Review Date:** 11/1/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment (BZ)	6/28/96	6/28/96	7/3/96

NAME & ADDRESS OF APPLICANT: Zambon Group S.p.A.
Fine Chemicals Division
Via Dovaro 36045 Almisano di
(Vicenza) Italy

AGENT: Zambon Corporation
One Meadowslands Plaza
East Rutherford, NJ 07073

DRUG PRODUCT NAME:
Proprietary: Monurol
Nonproprietary/USAN: Fosfomycin Tromethamine
Code Name#: Z1282
Chem. Type/Ther. Class: 1S

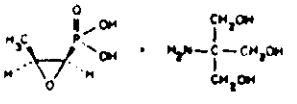
ANDA Suitablility Petition/DESI/Patent Status: n/a
PHARMACOLOGICAL CATEGORY/INDICATION: Antibacterial, urinary tract
DOSAGE FORM: Sachets, powder filled
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

$C_3H_7O_4P \cdot C_4H_{11}NO_3$ 259.20

(1) Phosphonic acid, (3-methyloxiranyl)-,(2R-cis)-, compd, with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1); (2) (1R,2S)-(1,2-Epoxypropyl)phosphonic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).

CAS-78964-85-9.



REMARKS/COMMENTS:

- The environmental assessment is acceptable and a FONSI is attached to this review.
- Method validation is not completed at the time of this review.
- Stability data support 24 months expiration dating.

CONCLUSIONS & RECOMMENDATIONS:

Recommend approval regarding chemistry, manufacturing, and controls when an acceptable EER is issued.

11/1/96
J. Timper

cc: Org. NDA 50-717
HFD-520/Division File
HFD-520/Dunn/HFD-830 11/4/96
HFD-520/Timper/Chem 11/1/96
HFD-520/Soreth/MO
HFD-520/Joshi/Pharm
HFD-520/Sheldon/Micro
HFD-520/Dillon-Parker/CSO
HFC-130/J Allen

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

NDA#: 50-717 REVIEW DATE: 3/4/97 MAR - 4 1997

REVIEWER: J. Timper

DOCUMENT DATE	CDER DATE	ASSIGNED DATE
2/19/97	2/20/97	2/26/97

NAME & ADDRESS OF SPONSOR:
Zambon Corporation
One Meadowlands Plaza
East Rutherford, New Jersey 07073

U.S. AGENT:
n/a

PHARMACOLOGICAL CATEGORY/INDICATION:
Single dose urinary tract infection.

ROUTE OF ADMINISTRATION:
Oral

DRUG PRODUCT NAME:

Proprietary: Monurol

Nonproprietary/USAN: Fosfomycin Tromethamine

Remarks:

Package printing

The instructions printed on the package holding the sachet should correspond to the "Preparation" section of the package insert labeling. The statement for dosing instructions should be:

J. Timper JTh 3/4/97
Chemist, HFD-520

EA + Fonsi

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 50-717

MONUROL™

(fosfomycin tromethamine)

Oral Powder 3 grams

Division of Anti-Infective Drug Products

(HFD-520)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

MONUROL™

(fosfomycin tromethamine)

Oral Powder 3 grams

NDA 50-717

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for MONUROL®, Zambon Corporation has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) in the Tier 0 format which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Fosfomycin tromethamine a chemically synthesized drug which is administered as an oral powder (3 grams) in the single dose treatment of uncomplicated urinary tract infections (acute cystitis). The drug substance is manufactured by the Zambon Group, S.p.A., Vicenza, Italy. The finished drug product is manufactured by INPHARZAM SA, Switzerland. The finished drug product will be used throughout the United States by patients.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at the distribution site, in accordance with the solid waste regulation requirements. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

9/16/96
DATE

Prepared by,
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

9/17/96
DATE

Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

DF
NDA 50717

HFD-520/C. Debellas copy to NDA/original
HFD-357/FONSI File 50717
HFD-357/Docket File
HFD-205/FOI COPY

FOREST LABORATORIES, INC.

ABBREVIATED ENVIRONMENTAL ASSESSMENT

for

Zambon Corporation

East Rutherford, New Jersey

March 1996

Prepared By

ESPL ENVIRONMENTAL CONSULTANTS CORP.

110 GREENWICH STREET
NEW YORK, NY 10006
(212) 587-1287

ABBREVIATED ENVIRONMENTAL ASSESSMENT STATEMENT FOR NEW DRUG APPLICATION MONUROL ™ (FOSFOMYCIN TROMETHAMINE) SACHET

This report has been prepared in accordance with the 21 CFR Chapter 1, April 1, 1994 Edition Part 25.31a(a) Format 1; and revised in accordance with the Federal Register, Vol. 61, No.8, January 11, 1996.
Abbreviated Environmental Assessment for Proposed Approvals of FDA-Regulated Products

Prepared

For: **Forest Laboratories, Inc.**
909 Third Ave.
24th Floor
New York NY 10022

For: **Zambon Corporation**
One Meadowland Plaza
East Rutherford NJ 07073

By: **ESPL Environmental Consultants Corporation**
110 Greenwich Street
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Contact

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Michael M. Rosen Ph.D.
Director, Regulatory Affairs
Tel: (212) 421-7850
Fax: (212) 750-9152

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Appendix A:	Confidential Information
Appendix B:	Material Safety Data Sheet
Appendix C:	Citation and Statement of Compliance with Environmental Regulations

1.0 DATE

Original Submission:	September 1994
Amendment Submission:	March 1996

2.0 NAME OF APPLICANT/PETITIONER

Zambon Corporation

3.0 ADDRESS

One Meadowlands Plaza
East Rutherford, NJ 07073

Town:	East Rutherford
State:	New Jersey
Contact Company:	Forest Laboratories, Inc. 909 Third Ave. 24th Floor New York NY 10022
Contact Person:	Michael M. Rosen Ph.D. Director, Regulatory Affairs (212) 421-7850

4.0 DESCRIPTION OF PROPOSED ACTION

The intent of this report is to provide sufficient information as specified in the Codes of Federal Regulations, Food and Drugs, 21 CFR Part 25.31a, and consistent with 40 CFR Part 1500.4(J) and 1502.21.

a. REQUESTED APPROVAL

MONUROL™ [fosfomycin tromethamine, USAN], a human drug product, is a new phosphonic acid derivative with antibacterial activity. It is active at a low concentration against the most common gram-positive and gram-negative bacteria involved in urinary infections. The effectiveness and safety of MONUROL™ has been demonstrated in two adequate and well controlled clinical trials conducted in the United States. The approval being sought for MONUROL™ is for the single dose, (3 gm fosfomycin as the free base) oral treatment of uncomplicated urinary tract infection (UTI) in adults and children over 12 years of age. Zambon Corporation is requesting the approval to produce MONUROL™ in sachet in Cadempino, Switzerland, and to ship the packaged product to the United States. Forest Pharmaceuticals, Inc. (FPI), subsidiary of Forest Laboratories, Inc. will be receiving the MONUROL™ sachets and will distribute them from their St. Louis, Missouri facility for use. ~~Since the drug substance, drug product and packaging occurs in foreign country facilities, an Abbreviated Environmental Assessment (AEA) is provided.~~ See page 2-039

b. NEED FOR THE ACTION

UTI is one of the most common infections diagnosed in the clinic or hospital setting. UTIs are second only to respiratory tract infections as problems encountered by practicing physicians. Most UTI's respond well to oral antibiotic therapies when those antibiotics are taken as directed. The benefit of MONUROL™ for the treatment of uncomplicated UTI lies in the drug's ability to produce excellent bacteriological and clinical results after only a single dose in the majority of women treated. The benefit of MONUROL™ is a single-dose agent for the treatment of uncomplicated UTI, its effectiveness, ease of use and improved compliance out weighs the low risk associated with the use of the drug.

Zambon Group, S.p.A., the parent company of Zambon Corporation is the developer of MONUROL™, who will manufacture the product at the Cadempino, Switzerland facility of their INPHARZAM SA, subsidiary. It is requested that approval be given, by the FDA, for the use of this drug in an environmentally sound, economically reasonable, and socially acceptable manner.

c. LOCATION WHERE THE PRODUCTS WILL BE PRODUCED

The drug substance [fosfomycin tromethamine, USAN], is manufactured at Zambon Group, S.p.A., Fine Chemicals Division, located at Via Dovaro - 36045 Almisano Di Lonigo Vicenza, Italy. The facility is located in a flat industrial estate with the surrounding area being relatively hilly. The surrounding area is rural and the climate temperate.

As stated in the Drug Master File page 82, no intermediates have been identified, different from the active substance fosfomycin tromethamine.

The manufacturing facility of INPHARZAM SA, for MONUROL™ is located at Via Industrial, 6814 Cadempino, Switzerland. This facility is located in an industrial estate with the surrounding area being relatively flat. This estate includes various light industrial oriented services. The climate of Cadempino, Switzerland is cold in the winter and mild in the summer. Winter precipitation and frequent snows, result in a good accumulation of soil moisture by spring and minimize drought during summer on most soils.

The packaged product will be shipped to the United States. FPI facility located at 13622 Lakefront Drive, Earth City, Missouri, will receive the packaged drug products for warehousing and distribution out of their facility throughout the United States. The consistent pattern of climate in St. Louis is cold winters and long, hot summers. The environment at and adjacent to the location from where MONUROL™ will be distributed is a light industrial park, bordered by industrial, institutional area.

d. LOCATION WHERE THE PRODUCTS WILL BE USED

The finished product will be used throughout the United States by patients and is not limited to a certain geographical region of

the country. MONUROL™ will be used at hospitals, clinics, physician's offices and/or patients' homes (prescribed to the patient for use) by the patient. The ultimate use of the product will be treatment of uncomplicated UTI. The user's environment for MONUROL™ will be in and adjacent to hospitals clinics, and patient's residence, and generally will be in commercial, institutional, and residential environments.

e. LOCATION WHERE THE PRODUCTS WILL BE DISPOSED OF

Disposal of the product may be needed due to manufacturing activities in the form of discarded out of specification lots, from the discarding of returned and rejected goods or from end users. The rejected products will be disposed of at the distribution site, in accordance with the solid waste regulation requirements.

Since the product will be used throughout the United States by patients, the disposal methods by the end user will vary. At U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures and/or that in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

The physical and chemical characteristics of MONUROL™ does not require a controlled method of disposal of the waste generated. MONUROL™ is a white granular powder with a characteristic odor of Mandarin and is very soluble in water with a pH 4-5. Under normal conditions, MONUROL™ will not remain in the environment for any significant period because of the high ratio of dilution and the susceptibility to biodegradation. Therefore, upon the need for disposal or termination of the drug, or individual empty or partially empty units of finished product, granular powder residue, will eventually end-up in a municipality site, and treated as regular solid waste. Disposal of unused product and used empty containers should be in approved waste disposal sites and specific for each medical facility. Incineration may be used as an optional method of disposal, if preferred by the solid waste management facility, but it is not the required method. Although, the waste

generated is non-regulated, care shall be taken to assure proper disposal.

APPEARS THIS WAY
ON ORIGINAL

5.0 IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION

MONUROL™ [fosfomycin tromethamine, USAN], is a phosphonic acid derivative and is the mono-acid salt of fosfomycin with trometamol. Its antibacterial activity in the body is due to fosfomycin which inhibits bacterial cell wall synthesis.

The following section provides a description of the materials used in the formulation of the drug product. Information related to impurities and degradates are reported in ZPD/94/31. "Identification and Characterization of Fosfomycin Trometamol Degradation Products Z1282DA, Z1282DB and Z1282DC", prepared by the Research and Development Department of the Pharmaceutical Division, Enclosure N° 26 to the DMF Analytical Test Specifications and Methods are reported in DMF Section F, page 117 to 127,1.

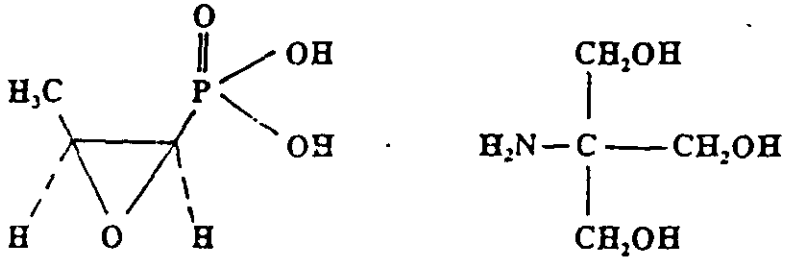
a DRUG-SUBSTANCE

NOMENCLATURE:

Chemical Name:	**fosfomycin tromethamine, USAN**
CAS Reg. #:	78964-85-9
Molecular Weight:	259.2
Molecular Formula:	$C_7H_{18}NO_7P$
Physical Phase:	Solid
Additives:	None

DEGRADATION PRODUCTS:

Glycol derivative: NMT 0.5%
Z1282 DA: NMT 0.5%
Z1282 DB: NMT 0.2%
Z1282 DC: NMT 0.2%



b. EXCIPIENTS

Chemical Name:	**Mandarin Flavor**
Physical Phase:	Solid
Additives:	Sucrose, Gum Arabic, Butylhydroxyanisol
Chemical Name:	**Orange Flavor**
Physical Phase:	Solid
Additives:	Dextrines, Gum Arabic
Chemical Name:	**Saccharin, BP-USP**
CAS Reg. #:	81-07-2
Molecular Weight:	183.18
Structural Formula:	$C_7H_5NO_3S$
Physical Phase:	Solid
Additives:	None
Chemical Name:	**Sucrose, Food grade**
CAS Reg. #:	57-50-1
Molecular Weight:	342.3
Structural Formula:	$C_{12}H_{22}O_{11}$
Physical Phase:	Solid
Additives:	None
Chemical Name:	**Purified Water Eur. Ph***
CAS Reg. #:	7732-18-5
Molecular Weight:	18.02
Structural Formula:	H_2O
Physical Phase:	Liquid
Additives:	None

* Water is removed during process

Notes: **Appendix A contains confidential information concerning the composition of each MONUROL™ sachet.**

Appendix B contains Material Safety Data Sheets (MSDS).

6.0 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The central question in an assessment of environmental impact is: What effects will the proposed action have on the environment of the area affected by the action? More important, are any of these predicted effects adverse, or could they be cause for concern? (Usually, the term environmental impact is reserved for those effects considered significant, especially when they are undesirable or potentially adverse, or those that call for a mitigation or intervention of some kind).

This section addresses the questions and concerns raised by the introduction of substance into the environment. Its scope is the result of several influences: United States Environmental Protection Agency (USEPA), Missouri Department of Natural Resources. Division of Environmental Quality regulations and recommendations, local agencies, research findings, and the experience of consultants, with similar projects.

The basis for organizing the study and for presenting the results is a list of environmental issues or "parameters" judged relevant to the current project.
The drug substance fosfomycin tromethamine (USAN), is manufactured by Zambon Group S.p.A., Fine Chemicals Division, located at Via Dovaro- 36045 Almisano Di Lonigo, Vicenza Italy. The drug product is manufactured by INPHARZAM SA, Division of Zambon Group, S.p.A., located at Via Industrial 6814 Cadempino, Switzerland. Since the production of the drug substance and drug product occurs at a foreign country facility, appropriate certification concerning environmental compliance has been compiled in Appendix C. The following contains a description of the substances expected to be emitted and the controls exercised:

a. & b. LIST OF SUBSTANCES EXPECTED TO BE EMITTED AND CONTROL EQUIPMENT EXERCISED

The drug substance fosfomycin tromethamine (USAN), is manufactured in Lonigo, Italy. Substances that are emitted are at low levels and are not likely to have a significant environmental impact. This facility maintains an on-site waste disposal system, which is authorized by the local authorities to treat solid waste, process waste waters and air emissions, by

the use of scrubbers and activated sludge. Controls are already designed into the production system in order to response to all appropriate environmental national and local law.

The production of the drug will take place in Switzerland. The INPHARZAM SA facility is constructed and designed to operate in full compliance with current standards and FDA's good laboratory and manufacturing practices. Although no controls are required, this facility maintains HEPA filters with an efficiency rating of 99.997% and a neutralization process (See Appendix C for compliance citation by Switzerland authorities). The facility has all required permits by both federal and cantonal Swiss environmental protection laws and regulations to operate plants for the production of pharmaceutical substances. The federal and cantonal Swiss Department of Environmental Protection has confirmed that substances released to the environment as a result of the production of MONUROL™ at INPHARZAM SA, does not constitute a threat to the environment.

FPI is in compliance with all emission requirements set forth by federal, state and local statutes and regulations applicable to the distribution and warehousing of MONUROL™, in its facility at 13622 Lakefront Drive, Earth City, Missouri. Since, there are no emissions associated with the warehousing and distribution of MONUROL™, control equipment would not be required. In addition said facility meets all applicable Federal Occupation, Safety and Health Administration (OSHA) requirements.

c. CITATION OF AND STATEMENT OF COMPLIANCE WITH APPLICABLE EMISSIONS LEVEL

PRODUCTION SITE

The drug substance is manufactured in Lonigo, Italy. The plant is authorized to produce active substances for pharmaceuticals by the Ministry of Health (DM n° 343 of 01/10/1991) and specific authorization has been granted for fosfomycin tromethamine (Min 800.8/91.22/2364). This facility maintains an on-site scrubber towers and activated sludge. The plant is authorized by local authorities to treat solid waste, chemical waste waters and fumes emitted from production. A statement of compliance with all Applicable Federal, State and local emission requirement has been provided in Appendix C.

The production of the drug will take place in Switzerland. The INPHARZAM SA, facility is constructed and designed to operate in full compliance with current standards and FDA's good laboratory and manufacturing practices.

The federal and cantonal Swiss Department of Environmental Protection has confirmed that the substances released to the environment as a result of the production of MONUROL™ at INPHARZAM SA, do not constitute a threat to the environment.

Additionally, the facility has all the permits required by both federal and cantonal Swiss environmental protection laws and regulations to operate plants for the production of pharmaceutical substances. A statement of compliance with all Applicable Federal, State and local emission requirement has been provided in Appendix C.

DISTRIBUTION & WAREHOUSING

The distribution and warehousing of the drug product will be from FPI facility located at 13622 Lakefront Drive, Earth City, Missouri.

AIR EMISSIONS

Under section 114 of the Act (42 U.S.C.7414), U.S. Environmental Protection Agency has been given the broad authority to evaluate the compliance status of emissions released by any source of pollutant. The Act imposes restriction on air emissions and on emissions of hazardous or toxic air pollutants. Air emissions are regulated through issuance of permit by the state and through emission limits adapted by the state in accordance with Missouri State Implementation Plans (SIPs). Subsequent to this Act, the distribution site is exempt from all air emission requirements promulgated by USEPA., Missouri state and local agencies.

LIQUID WASTE

The discharge of waste water from a source of discharge is regulated under Federal Water Pollution Control Act (33 U.S.C.1251), and referred to as the National Pollution

Discharge Elimination System (NPDES) permit. The waste water effluent to the sanitary sewer from the subject facility is far below effluent limitation and standards for any significant industrial user (SIU) contributing to the public work treatment plant. The proposed action does not release any substance other than the sanitary waste and therefore does not require a discharge permit.

SOLID WASTE

Solid waste generated will be discarded by a private handler, Environmental Waste Management, for landfill. The solid disposal methods are conducted in accordance with the solid waste disposal regulations of the State of Missouri and county of St. Louis imposed on the facility.

d. THE EFFECT OF THE APPROVAL OF THE PROPOSED ACTION WILL HAVE UPON COMPLIANCE WITH CURRENT EMISSIONS REQUIREMENTS AT THE PRODUCTION SITE

PRODUCTION SITE

The drug substance fosfomycin tromethamine (USAN) is produced in Lonigo, Italy. This production will not have an effect with the current emission requirements set forth by the Regional Authority (See Appendix C).

The drug product is manufactured in Cadempino Switzerland. Appendix C contains a statement released by the federal and cantonal Switzerland environmental protection authority revealed that the production site has all the permits required by both federal and cantonal Swiss environmental protection laws and regulations to operate plants for the production of pharmaceutical substances and is in compliance with current emission requirements.

DISTRIBUTION SITE

FPI facility is designed for the distribution and warehousing of pharmaceutical products and meets all applicable requirements. It is anticipated that the proposed action does not have an effect on compliance with current emission requirements

because the emission requirement does not apply to the facility due to the nature of the operation.

AIR EMISSIONS

There is no air emission source at the subject site (FPI facility) due to the nature of the operation, i.e. only distribution of the drug products. The approval of the proposed action will not change the current emission requirements at the distribution site.

LIQUID WASTE

Liquid waste generated as a result of distribution and warehousing operation is minimal. The approval of the proposed action will not change the current emission requirements at the distribution site (FPI facility).

SOLID WASTE

The FPI facility records indicated that combined waste generated at the facility is 40 yd^3/week. It is estimated that the solid waste generated as a result of distribution and warehousing operation is minimal and has no significant environmental effect.

e. QUANTITIES AND CONCENTRATIONS OF SUBSTANCES EXPECTED TO ENTER THE ENVIRONMENT

The drug substance entering the environment as a result of use and disposal, has been estimated based on total fifth year production estimates. If the following Expected Introduction Concentration (EIC) calculation is less than 1 ppb, it is unlikely to have a significant effect on the environment. Since the EIC was calculated to be 0.12 ppb it is unlikely to have a significant effect on the environment. Therefore, Tier 0 has been met. Appendix A contains confidential information concerning the production estimates of MONUROL™ sachet and calculation of the EIC.

12.0 LIST OF PREPARERS

Forest Laboratories, Inc.
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Professional Experience:	22 Years, Academic Research, and Pharmaceutical Industry

Zambon Corporation
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East Rutherford NJ 07073

M. Caimi, Ph.D.	Corporate Quality Assurance Manager
Professional Experience:	20 Years, Pharmaceutical Industry
Fabio Dotto, Ph.D.	Production Director
Professional Experience:	20 Years, Pharmaceutical Industry
Patricia Thomas	VP, Regulatory Affairs
Professional Experience:	20 Years Pharmaceutical Industry

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Professional Experience:	12 Years, Engineering, Environmental Science and Pollution Control

Sidney Rosen, P.E.
Professional Experience:

Project Manager
42 Years, Engineering
Environmental Science and
Pollution Control

13.0 CERTIFICATION

"The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment".

M. Caimi	Corporate QA Director
Print Name	Title
M Caimi	02.29.96
Signature	Date
Fabio Dotto	Production Director
Print Name	Title
Signature	29/02/96
	Date
Patricia Thomas	VP, Regulatory Affairs
Print Name	Title
Patricia Thomas	March 4, 1996
Signature	Date

14.0 REFERENCES

American Chemical Society, Washington D.C., 1990

American Conference of Governmental Industrial Hygienists (ACGIH) Inc.

American Society for Testing and Materials (ASTM)

Codes of Federal Rules and Regulations
- 21 CFR Part 25.31(a)
- 40 CFR Part 1550.4(J) and 1502.21

Food & Drugs Administration
- Center for Drugs Evaluation & Research, Ms. Nancy Sager, Acting Supervisor, Environmental Assessment Team and Ms. Christina Good
- Center for Drugs Evaluation & Research Division of Communications Management, HFD-210, Guidance For Industry, For The Submission of an Environmental Assessment in Human Drug Applications and Supplements

Handbook of Chemical Property Estimation Methods, W.J. Lyman, W.F. Reehl, and D. H. Rosenblatt

Handbook of Environmental Data on Organic Chemicals, Verschureren, Lasala, A.M., Jr., W.E. Harding, and R.J. Archer, 1964

St. Louis County Department of Health

St. Louis Regional Department of Natural Resources
- Division of Environmental Quality Waste and Water Group

"Technical Assistant Document (TAD) 2.00" FDA Environmental Assessment Technical Assistance Handbook, NTS PB 87-175354

United States Department of Agriculture, Soil Survey of St. Louis County & St. Louis, Missouri

United State Department of Commerce, 1974, Census of Agriculture, Bureau of the Census, State and County Data, Vol. 1, pt. 32, sec. IV, 85-90 pp.

U.S. Geological Survey Water Resources Investigation
Report 84-4334 / Report 86-4317 / Report 88-4076

United States Environmental Protection Agency,

- Office of Air Quality Planning and Standards
- Air & Waste Management Division, Hazardous & Solid Waste Program Branch
- Division of Hazardous Waste Management

Zambon Corporation,

- DMF

ACRONYMS

ASTM:	American Society for Testing and Materials
CAS:	Chemical Abstract Service
CFR:	Codes of Federal Rules and Regulations
EA:	Environmental Assessment
FDA:	Food and Drug administration
FONSI:	Finding of no Significant Impact
FPI:	Forest Pharmaceuticals, Inc.
ft^3:	Cubic Feet
GLP:	Good Laboratory Practice
gpd:	Gallon per Day
GRAS:	Generally Recognized as Safe
HHS:	Department of Health and Human Services
IND:	Investigational New Drug Application
m^3:	Cubic Meter
NDA:	New Drug Application
NEPA:	National Environmental Policy Act of 1969
NMT:	Not More than
OSHA:	Occupational Safety and Health Administration
OTC:	Over the Counter
PDP:	Product Development Protocol
PMA:	Premarket Approval Application
SIPs:	State Implementation Plan
TSCA:	Toxic Substance Control Act
U.S.C.:	United States Code
yd^3:	Cubic Yard
Yr:	Year
ug:	Microgram

APPENDIX B:

Material Safety Data Sheet

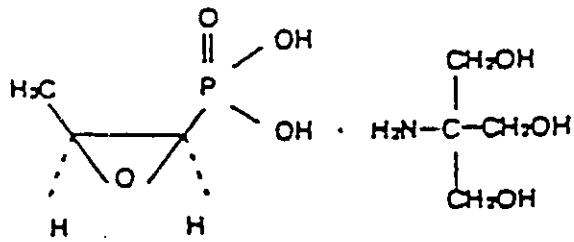
MONURIL
(Fosfomycin Trometamol)

1. DESCRIPTION

A. NAMES

Generic Name:	Fosfomycin Trometamol
Laboratory Code:	Z 1282
Chemical Name:	Mono (2-ammonium - 2 - hydroxy - methyl-1, 3 propandiol) (2R-cis)-(3-methyloxiranyl) phosphonate
Proprietary Name:	Monurik®
Pharmacological Class:	Antibacterial, urinary tract

B. STRUCTURAL FORMULA



=

Molecular Formula:	$C_7H_{18}NO_7P$
Molecular Weight:	259.2

C. PHYSICAL AND CHEMICAL PROPERTIES

Appearance/General Characteristics:

White or near white crystalline powder, characteristic citrus fruit flavor

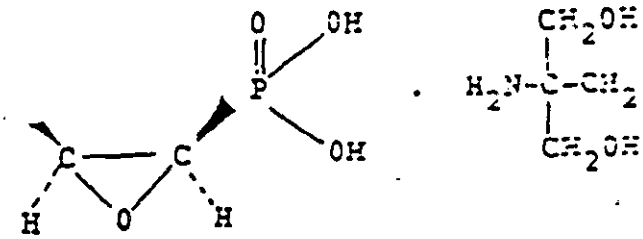
Solubility:

Fosfomycin trometamol is:

- Very soluble in water
- Slightly soluble in 95% Methanol
- Slightly soluble in Ethanol
- Insoluble in Acetone
- Insoluble in Ether
- Insoluble in Chlorinated Solvents

Melting Point:	between 116°C and 122°C
Specific Rotation:	between -12.5 and -13.5 (50 mg/ml aqueous solution)
pH:	between 4.0 and 5.0 (5% w/v aqueous solution)

Product	: Fosfomycin trometamol
Empirical Formula	: $C_7H_{18}NO_7P$
Structural Formula	:



Molecular Weight	: 259.2
CAS No.	: 78964-85-9
Chemical name	: Mono(2-ammonium-2-hydroxymethyl-1,3-propandiol) (2R-cis)-(3-methyloxyranyl)phosphonate
Physical form	: Hygroscopic, white crystalline powd
Solubility	: very soluble in water, slightly soluble in 95% ethanol and methanol, insoluble in acetone, ether and chlorinated solvents.
Melting point	: 116° to 122°C
Lower flammable limit	: 160 mg/ml in air.
Autoignition temperature	: 130°C

The data contained herein are based on biographical sources currently available to us; therefore these data are not to be taken as a warranty or representation for which Zambon Group S.p.A. assumes legal responsibility.

Disaster hazards	: The product is assumed to be combustible and can ignite spontaneously; so an accurate control of temperature is required during manufacturing operations. When heated to decomposition it emits toxic fumes of carbon oxides and nitrogen oxides and phosphorous oxides. As the oxyranic ring is present explosive proprieties of the substance cannot be excluded but confirmation of this cannot be found in literature.

Toxicity : No toxicological data is currently available in literature.
On the basis of toxicological data of Fosfomycin and Trometamol a slight toxicity of Fosfomycin trometamol can be hypothized. Epoxides are usually highly reactive and instable compounds and can then interfere with structures and physiological processes with consequent harmful effects on health. Principal toxic manifestations are eyes and lungs irritation and dhermatitis.

Health hazard	: It can be irritant to skin and eyes and have a sensibilizating action
Storage Precautions	: The product is hygroscopic, preserve in tight closed and resistent containers with a desiccant inside, away from easily flammable substances and from heat sources, in a cool and dry place.
Handling precautions	: Avoid prolonged or repeated exposures, contact and inhalation. The wearing of gloves, goggles and dust-mask is recommended. Dust suction equipment and eye-washing fountains should be arranged.
Special Fire Fighting	: Wear gas mask; nebulized water, carbon dioxide, chemical powder and foam should be employed as extinguishing media.

The data contained herein are based on biographical sources currently available to us; therefore these data are not to be taken as a warranty or representation for which Zambon Group S.p.A. assumes legal responsibility.

Spillages : Collect with tools which do not cause any sparks, wash the floor and contaminated objects with soap and water and treat the residuals and the washings as toxic and noxious refusals.
Place spillage in appropriate container for waste disposal (incinerator); previously verify explosive proprieties of the substance.

EMERGENCY TREATMENT RECOMMENDED

eyes : irrigate thoroughly with running water for at least 15 minutes. If irritation and burning persist consult a specialized doctor.
skin : remove contaminated clothing, wash the skin with plenty of soap and water.
ingestion: if irritation effects are present do not provoke vomit, allow the patient to drink much water or milk. Administer active charcoal.
inhalation: remove the unfortunate from exposure place.

The data contained herein are based on biographical sources currently available to us; therefore these data are not to be taken as a warranty or representation for which Zambon Group S.p.A. assumes legal responsibility.

MANDARIN FLAVOR
(TANGERINE 15228-71)

Is Manufactured by:

Givaudan S.p.A.
Via G. Di Vittorio
20090 Segrate, Milan (Italy)
(See informative notes of the manufacturer - Encl. 13)

2- 058

PRODUCT	MANDARIN FLAVOUR AG 15228			COMPILER 09/5/94
CODE	9901869	SAMPLE QUANTITY	200 g	
REFERENCE				D. C. Q. 10.5.94
RE-ANALYSIS	1 year	Page	1/5	

COMPOSITION : **natural flavouring substances atomized with arabic gum and mixed with sucrose.**

SPECIFICATIONS

1) DESCRIPTION	(R)	:	light yellow powder with a characteristic mandarin odour
2) IDENTIFICATION OF SUCROSE		:	corresponds
3) IDENTIFICATION OF ARABIC GUM		:	corresponds
4) IDENTIFICATION OF THE AROMATIC FRACTION	(R)	:	corresponds
5) WATER (K.F.)	(R)	:	≤ 7.0%
6) ESSENTIAL OIL CONTENT	(R)	:	6.0 - 8.0% (v/w)
7) BULK DENSITY	(R)	:	0.4 - 0.6 g/ml
8) MICROSCOPIC EXAMINATION		:	complies

NOTES

- (R) : indicate routine tests
- SUPPLIER : Givaudan
- PACKAGING AND STORAGE : preserve in well-closed containers protected from humidity

ORANGE FLAVOR
(ORANGE 74016-71)

is manufactured by:

Givaudan S.p.A.
Via G. Di Vittorio
20090 Segrate, Milan (Italy)
(See informative notes of the manufacturer - Encl. 13)

INPHARZAM S.A.	SPECIFICATIONS AND METHOD OF ANALYSIS	METHOD n° A/74 Date 04/94

PRODUCT	ORANGE FLAVOUR 74016-71			COMPILER
CODE	9901070	SAMPLE QUANTITY	200 g	
REFERENCE				D. C. Q.
RE-ANALYSIS	1 year	Page	1/5	

COMPOSITION : **natural and nature identical flavouring substances combined with maltodextrin.**

SPECIFICATIONS

1) DESCRIPTION	(R)	:	yellow powder with a characteristic orange odour
2) IDENTIFICATION OF MALTODEXTRIN		:	corresponds
3) IDENTIFICATION OF THE AROMATIC FRACTION	(R)	:	corresponds
4) WATER (K.F.)	(R)	:	≤ 7.0%
5) ESSENTIAL OIL CONTENT	(R)	:	12 - 16 % (v/w)
6) BULK DENSITY	(R)	:	0.4 - 0.6 g/ml
7) MICROSCOPIC EXAMINATION		:	complies

NOTES

- (R) : indicate routine tests
- SUPPLIER : Givaudan
- PACKAGING AND STORAGE : preserve in well-closed containers protected from humidity

APPENDIX C:

Citation and Statement of Compliance with Environmental Regulations

Zambon Group

FINE CHEMICALS DIVISION
CHEMICAL PLANT
ZAMBON GROUP S.P.A.
36040 ... VICENZA - ITALY
VIA DOLARO
PHONE (0444) 720555
TELEX 480411 ZAMBON
TELEFAX (0444) 831782

Lonigo, February 7th, 1996

CERTIFICATE OF COMPLIANCE

ZAMBON GROUP S.p.A. certifies that its manufacturing facility of Lonigo is:

1. in compliance with all local and national environmental laws;
2. in compliance with all emission requirements set forth in all permits;

   and:
3. that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

ZAMBON GROUP S.p.A.

Inpharzam s.a.
CH-6814 Cadempino
Casella postale 200
Tel. 091 58 41 11
Tel. 091 58 19 91
Telex 844 521 iph ch
Telefax 091 56 43 51

Vs. rif. Ns. rif. Cadempino, 01-February-1996

CERTIFICATE OF COMPLIANCE

INPHARZAM SA certifies that its manufacturing facility of Cadempino is:

1. in compliance with all local and national environmental laws;

2. in compliance with all emission requirements set forth in all permits; and:

3. that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

INPHARZAM S.A.

General Manager
Dr. Paolo Fioravanti

Production Manager
Dr. Fabio Dotto

Bellinzona 10 gennaio 1994

Repubblica e Cantone
del Ticino

Il Dipartimento del territorio

CERTIFICATO DI PROTEZIONE AMBIENTALE

ENVIRONMENTAL PROTECTION CERTIFICATION

La Divisione dell'ambiente del Dipartimento del territorio certifica che l'attività produttiva della ditt

INPHARZAM SA
ZONA INDUSTRIALE
6814 CADEMPINO

viene svolta nel pieno rispetto della normativa vigente in materia di protezione ambientale.

I controlli periodici, eseguiti dalle istanze cantonali competenti, non hanno evidenziato situazioni non conformi alla citata legislazione.

The Department for environmental protection ("Dipartimento del territorio") confirms that the company

INPHARZAM SA
ZONA INDUSTRIALE
6814 CADEMPINO

has all the permits required by both federal and cantonal Swiss environmental protection laws and regulations to operate plants for the production of pharmaceutical substances.

During our regular inspections of the plants it has always be ascertained a completely satisfactor environmental situation.
We assess too, that the equipment and process for the production of Monuril, a granulate of Fosfomycin Trometamol, are kept under control and are in compliance with all cantonal and federal Swiss environmental laws.

./.

2 - 065

Locarno

La Divisione dell'ambiente del Dipartimento del territorio è in particolare responsabile per l'applicazione delle seguenti leggi.

The Department for environmental protection is the authority, that is competent on the territory of the canton Ticino to enforce particularly the following federal and cantonal laws and regulations

- Legge federale sulla protezione dell'ambiente del 07.10.1983
  Federal Law on the protection of the environment
- Ordinanza contro l'inquinamento atmosferico del 16.12.1985
  Air pollution control regulation
- Ordinanza sulle sostanze pericolose per l'ambiente del 09.06.1986
  Regulation on the containment of environmentally hazardous substances
- Ordinanza sul traffico dei rifiuti speciali del 12.11.1986
  Regulation on the handling of hazardous waste
- Ordinanza tecnica sui rifiuti del 10.12.1990
  Technical waste-matter regulation
- Ordinanza contro l'inquinamento fonico del 15.12.1986
  Noise protection regulation
- Ordinanza sull'esame di impatto ambientale del 19.10.1988
  Regulation on environmental compatibility audits
- Legge federale contro l'inquinamento delle acque del 24.01.1991
  Federal law on water protection
- Ordinanza sulle immissioni delle acque di rifiuto del 08.12.1975
  Regulation on the introduction of waste-water into the public sewage system
- Ordinanza generale sulla protezione delle acque del 19.06.1972
  General regulation on water protection
- Ordinanza sulla classificazione dei liquidi nocivi alle acque del 28.09.1981
  Regulation on the protection of water against water endangering substances
- Prescrizioni tecniche sui depositi liquidi del 21.06.1990
  Regulation on equipment for the storage and reloading of water endangering substances

DIPARTIMENTO DEL TERRITORIO

Il Direttore della Divisione dell'ambiente:
arch. Marcello Bernardi

Il Capo Sezione protezione aria e acqua:
dott. Mario Camani

Ufficio delle canalizzazioni
Ufficio degli impianti di depurazione e
Ufficio delle industrie e degli idrocarburi
Laboratorio
Via Carlo Salvioni 2a
telefono 092 24 37 51
092 24 38 12
fax 092 24 44 33

Repubblica e Cantone
del Ticino
Dipartimento del territorio
Divisione dell'ambiente

Funzionario incaricato

telefono

Sezione della protezione dell'aria e dell'acqua
6501 Bellinzona

Spettabile
INPHARZAM S.A.

6814 Lamone – Cadempino

Bellinzona
12 settembre 1994

Ns. riferimento Vs. riferimento

CERTIFICATE

As a controlling authority we confirm that the effluent of the wastewater pretreatment plant of Inpharzam S.A., in Cadempino are regularily monitored.
All the analyses performed during 1994 have been found to be conform with the requirements of the Federal Swiss Law concerning Water Protection and of the Ordinance for Wastewater Discharge.

Sezione protezione aria e acqua
Il Capo Sezione: Ufficio industrie e idrocarburi:

p.o. Dott. M. Camani Dott. E. Crivelli

EMISSION PERMIT TABLE

Permits for Lonigo, Italy Facility		
Emission	Authorizing Agency	Permit #
Air	Regional Authority	DGR 3319
Waste Water	Regional Authority	DGR 3318
Solid Waste	Regional Authority	DGR 3319

EMISSION PERMIT TABLE

Permits for Cadempino, Switzerland Facility		
Emission	Authorizing Agency	Permit #
Air	Department of Environmental Protection	See NDA, Section 3 00798-799
Waste Water	Department of Environmental Protection	See NDA, Section 3 00801 Appendix F
Solid Waste	Department of Environmental Protection	----------

Pharm/Tox

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

Date CDER Received: 01/30/95
Date Assigned: 02/01/95
Date Review Started: 02/02/95
Date 1st. Draft Completed: 02/02/95
Date Review Accepted by Supervisor: 02/03/95

NDA # 50-717 (Safety Update dated 1/27/95)

Number of Volumes: One

Drug: **MONUROL™ (Fosfomycin Tromethamine)**

Sponsor: Forest Laboratories Inc. as AGENT for Zambon Corp., East Rutherford, NJ
Contact Person: Michael M. Rosen 212/421-7850

Category: Antibiotic

Review Objectives: To incorporate an ADME study in the NDA.

Index of Studies: One study (see below)

Effect of Probenecid on the Serum Levels and Urinary Excretion of Fosfomycin Tromethamine.

Zambon Group (R&D), Report No. DBI 13/92 SM, 1-7 dated 6/30/92. This study does not have GLP statement.

Study Objective: Probenecid (PB) inhibits the renal tubular secretion of some antimicrobial agents. The aim of the present study was to estimate the effect of PB on the serum levels and urinary excretion of fosfomycin tromethamine (FT). Amoxicillin (AMX) was used as positive control.

Methodology:

Animals: Female Swiss CD-1 mice weighing approximately 23-25 g and 5 to 6 weeks of age.

Serum Levels: Two experiments were conducted at two different times on a total of 280 mice. In each experiment four groups of 35 mice each were treated orally (gavage) as follows:

1. FT 50 mg/kg (as fosfomycin).
2. FT 50 mg/kg (as fosfomycin) **and** PB 17 mg/kg.
3. AMX trihydrate 50 mg/kg (as amoxicillin).
4. AMX trihydrate 50 mg/kg (as amoxicillin) **and** PB 17 mg/kg.

At 5, 10, 30, 60, 120, 240, and 360 minutes following oral treatment 5 mice of each group were sacrificed and blood samples taken.

Urinary Levels: Four experiments were conducted at four different periods on a total of 160 mice. In each experiment

four groups of 10 mice were treated orally (gavage) to the four groups listed above for serum levels.

The pooled urine was collected, in metabolic cage for each group at the following intervals (h) following oral treatment: 0-2, 2-4, 4-6, 6-24 and 24-48 hours.

Results:

Serum Levels: There was no apparent difference in the fosfomycin concentration within both regimens. The concentrations were not statistically different at each time interval.

Urinary Levels: For fosfomycin, alone or with PB, the concentration for each period within corresponding regimens did not appear to differ statistically.

Different results were observed when AMX was co-administered with PB. Higher and statistically different serum levels of AMX were found between 30 and 120 minutes after administration of both drugs. The higher levels of AMX was ascribed to the delay in antibiotic excretion due to the effect of PB on the kidney tubules. In fact, lower amounts of AMX appeared in the urine at the first collection period (0-2 h) in the group treated with AMX and PB.

The results showed that FT, differently from AMX, was not eliminated by kidney via tubular secretion therefore, PB did not influence its pharmacokinetic benavior.

In other words, the results showed that PB did not alter the serum or urine concentrations of fosfomycin confirming that its renal elimination occurred via glomerular filtration. On the contrary, serum and urinary levels of AMX, used as control drug and known to be eliminated via tubular secretion, were strongly influenced by simultaneous administration of PB.

Comments & Recommendation: None.

2/3/95

S.R. Joshi, D.V.M., Ph.D.

cc:
Orig.NDA
HFD-340
HFD-520
HFD-520/Pharm/Joshi
HFD-520/MO/Soreth
HFD-520/Chem/Timper
HFD-520/Micro/Soprey
HFD-520/CSO/Dillon-Parker
HFD-520 /rd init. by REOsterberg
R/D/2/2//FT/2/3/95 /SRJ
N-50-717.SU

Concurrence Only
HFD-520/Dep.Dir/L.Gavrilovich
HFD-520/SPharm/REOsterberg

REO 2/6/95

2/10/95

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

Date CDER Received: 09/30/94
Date Assigned: 10/05/94
Date Review Started: 10/06/94
Date 1st. Draft Completed: 11/14/94
Date Review Accepted by Supervisor: 12/30/94

NDA # 50-717 **[Previous NDA # 20-477]**
(Original Submission dated 9/29/94 and Amendments dated 10/18/94 and 10/24/94)

Number of Volumes: 24 (original) + 2 (amendment)

Drug: **MONUROL™ (Fosfomycin tromethamine; USAN), Sachets**
Drug Code: **Z-1282**

Sponsor: **Zambon Corporation, East Rutherford, NJ**

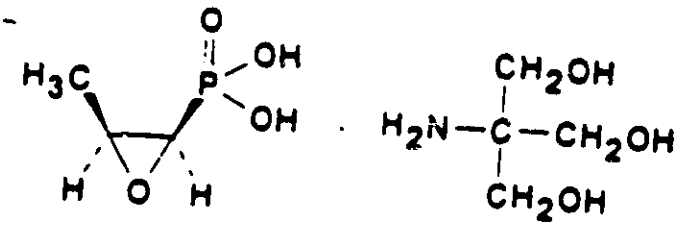
U.S. Agent: **Forest Laboratories of New York, New York**
Contact Person: **Michael M. Rosen, Ph.D. 212/421-7850**

Category: Antibiotic

Human Dosage: (proposed) A single dose of 3 grams powder dissolved in 4 oz. of tap water.

Indication: Urinary tract infection (uncomplicated)

Chemistry: Fosfomycin tromethamine and Fosfomycin trometamol, being one and the same have identical structural formula:



Formulation:

Ingredient	mg/sachet
Fosfomycin tromethamine (equivalent to fosfomycin base 3,000 mg) Z-1282	5,631.0
Mandarin Flavor	
Orange Flavor	
Saccharin	
Sucrose	

TOTAL WEIGHT	

removed during processing

Related Submissions: IND

Review Objectives: Review preclinical data with regard to safety for the proposed marketing of the drug product.

Index of Studies: Please see next page.

INDEX OF STUDIES: *Fosfomycin Tromethamine*

Item #	Study	Study#	Ref #	NDA Vol	NDA Page
5.4	**ACUTE TOXICITY STUDIES**				
5.4.1.1	MOUSE: Oral	217	4*	14	667
5.4.1.2	MOUSE: Oral	4	5	14	704
5.4.1.3	MOUSE: Intravenous	4	6	14	741
5.4.1.4	MOUSE: Intraperitoneal	1216	7	14	778
5.4.1.5	MOUSE: Intraperitoneal	4	8*	14	809
5.4.2.1	RAT: Oral	1215	9*	14	856
5.4.2.2	RAT: Oral	4	10	14	894
5.4.2.3	RAT: Intravenous	4	11	14	931
5.4.2.4	RAT: Intraperitoneal	1213	12*	14	968
.2.5	RAT: Intraperitoneal	4	13	15	1011
5.4.3.1	RABBIT: Oral	1214	14*	15	1048
5.4.3.2	RABBIT: Intravenous	5	15	15	1085
5.4.4.1	DOG: Oral	1218	16*	15	1090
5.4.4.2	DOG: Intravenous	6	17	15	1128
	SUBCHRONIC TOXICITY STUDIES				
5.5.1.1	RAT: 4-Week Oral	88-3324	18*	15	1143
5.5.1.2	RAT: 12-Week Oral	16T19A	19	16	1545
5.5.1.3	RAT: 13-Week Oral	HW16277-124	20*	17	1910
5.5.2.1	DOG: 4-Week Oral	88-3325	21*	18	2416
5.5.2.2	DOG: 4-Week Oral	93-3181	22*	19	2716
5.6.1	**CHRONIC:** DOG: 26-Week		23	19	3021
5.7	**CARCINOGENICITY STUDIES - NONE**				
5.8	**SPECIAL TOXICITY:** RAT: 2-Week Oral	6277-123	24*	20	3143
	REPRODUCTION STUDIES				
5.9.1.1.1	**SEGMENT I - RAT**	9/TR-36	25	20	3260
5.9.1.1.2	**SEGMENT I - RAT**	406-002	26*	20	3410

5.9.2.1.1	**SEGMENT II - RAT: Oral**	10/TR-28	27	**21**	3677
5.9.2.1.2	**SEGMENT II - RAT: Oral**	406-003	28*	**21**	3817
5.9.2.2.1	**SEGMENT II - RABBIT**	11/TR-37	29	**21**	4001
5.9.2.2.2	**SEGMENT II - RABBIT**	406-004	30*	**22**	4112
5.9.3.1.1	**SEGMENT III - RAT**	12/TR-32	31	**22**	4306
5.9.3.1.2	**SEGMENT III - RAT**	406-005	32*	**23**	4493
	MUTAGENICITY STUDIES:				
5.10.1	**IN VITRO NON-MAMMALIAN CELL SYSTEM**				
5.10.1.1	Reverse Mutation- S.typhimurium	1212	33*	**23**	4820
5.10.1.2	Genetic Conversion - Sacch.cerevisie	1212	34	**23**	4884
5.10.1.3	Forward Mutation - S.pombe	1212	35	**23**	4896
5.10.2	**IN VITRO MAMMALIAN CELL SYSTEM**				
5.10.2.1	Gene Mutation in Chinese Hamster Cell	116022	36*	**23**	4909
5.10.2.2	Chromosome Aberration - Human Lymphocytes	116022	37*	**24**	4970
5.10.2.3.1	**IN VIVO** - Mouse Micronucleus Test	1159	38*	**24**	5020
5.11	**Absorption, Distribution, Metabolism & Excretion (ADME)**		39,40,41	**24**	5050
5.12.1	Tissue Distribution & Mass Balance		43	**24**	5486
5.12.2	Placental Transfer		44	**24**	5546
5.13	Toxicology of Degradation Products		45	**24**	5583

* **Studies marked with asterisk were conducted in compliance with the U.S. FDA GLP requirements.**

Unless specified otherwise, all studies were conducted in the applicant's laboratories, viz. Zambon Research Group, S.p.A., Rome/Milan, ITALY

TOXICOLOGY

ACUTE TOXICITY STUDIES: See next page

ACUTE TOXICITY STUDIES: Studies 1 thru 14 (Ref.# 4 to 17)

Species/Strain	Route of Administration	No./Sex	Dose (mg/kg) [not adjusted for Fosfomycin base)	Mortality	LD_{50} (mg/kg)	Ref. No.
MOUSE:						
-CD-1(ICR)	Oral(Gavage)	10/sex	5000	No Mortality		4
tbred CD-1	Oral(Gavage)	10/sex	10,000	No Mortality		5
tbred CD-1	I.V.	10 males	1300 to 4200	72/150	1,652	6
-CD-1(ICR)	I.P.	10/sex	4000, 5000	45/90	4,441 - ♂♂ 4,344 - ♀♀	7
tbred CD-1	I.P.	10/sex	4750-6000-♂♂ 4000-7000-♀♀	64/130 - 1 hr postdosing	5553 - ♂♂ 5149 - ♀♀	8
RAT:						
:CD(SD)BR	Oral(Gavage)	10/sex	5000	No mortality		9
rague-Dawley	Oral(Gavage)	10 males	13000 to 16000-♂♂	24/40	14553 -♂♂	10
rague-Dawley	I.V.	10 males	1100 to 1700-♂♂	38/70	1364 - ♂♂	11
rague-Dawley	I.P.	10/sex	3400 to 5000-♂♂ 3400 to 5000-♀♀	36/90	4539 -♂♂ 4342 -♀♀	12
rague-Dawley	I.P.	10/sex	4000 to 8500	74/170	6389 -♂♂ 6016 -♀♀	13
RABBIT:						
w Zealand ite	Oral(Gavage)	3/sex	2000	No mortality		14
w Zealand ite	I.V.	Males	2/1200,3/1600,1/2000	4/6 (1/2000, 3/1600)	1360 - ♂♂	15
DCG:						
agle	Oral(Gavage)	2/sex	2/2000, 2/2000	No mortality		16
agle	I.V.	2/sex	2/130, 2/260	No mortality		17

SUBCHRONIC TOXICITY:

15. Four-Week Oral Toxicity Study in Rats via Gastric Intubation With Z-1282 (Fosfomycin Tromethamine). (Ref # 18)
Project No. 88-3324

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated Aug. 3, 1989.

Dates of Treatment: 11/4-6/88 to 12/6/88.

Material Tested: Z-1282; Lot No. 00000/89314

Animals: CD (SD) rats, 28-day old and weighing 176-221 g males and 147-173 g females at initiation.

Dose Selection: determined by sponsor (Zambon).

Experimental Groups:

Group	Test Material	Dose Level* (mg/kg/day)	Dose Volume (ml/kg/day)	No.of Rats	
				♂♂	♀♀
I.	Controls**	0	10	15	15
II.	Z-1282(Low)	200(106.5)	10	15	15
III.	Z-1282(Mid)	800(426.1)	10	15	15
IV.	Z-1282(High)	3200(1704.3)	10	15	15

* Equivalent fosfomycin content in parenthesis.
** Distilled water (the vehicle)

Thee rats were administered the dose orally, by intubation, daily (7 days/week) for 31-33 days consecutively.

Results:

General: One high dose male died on day 1; cause of death - dosing error; rat replaced by One mid-dose female died accidently on day 29.

There were no treatment-related clinical signs.

Ophthalmoscopy: Conducted at pretest and at termination, there was no indication of dose or compound-related ocular effects.

Body Weight & Food Consumption: These parameters in the drug treated animals were comparable (or greater) to those in the controls.

Clinical Pathology: A dose-related increase in cholesterol occurred in treated rats at termination. Differences from control values were most significant in the high-dose males and females. Statistically significant increases in SGPT and slight increases in SGOT as compared to control values were also observed in high-dose males and females. These may be suggestive of an effect on liver function. [Histologically: no major liver lesions]

Organ Weights: Absolute and relative liver weights of the high-dose males and females were statistically significantly greater than those in the controls. The absolute weight of the kidneys was also slightly increased in the high-dose males.

Pathology: [control and high dose groups.]. One gross morphologic finding that appeared of greater incidence was distended uterus in 3/15 high-dose females. Severity of this abnormality was similar in high-dose and control females.

Conclusion: Based on the increase in cholesterol in the mid- and high dose animals and the increase in liver weights in the high-dose animals, the no effect level (NOEL) was 200 mg/kg/day of Z-1282 administered orally in rats for a period of 4 weeks.

16. Z-1282 - Twelve Week Oral Toxicity Study in the Rat.
Ref# 19

On NDA pp. 5-01546 and -47, Dr. L. Fonanomi, M.D., Head Toxicological Dept of Zambon states, "This study was conducted by Zambon Laboratories, Italy (March-June 1980). At that time the GLP regulations were not operative in Italy. [GLP regulations became effective in Italy on June 26, 1986].

"In retrospective audit report submitted to FDA on Nov. 19, 1991, two main observations had been pointed out:

1. Histological slides were not prepared for animals of groups A-D and E and that continued in the study for 16 weeks.

2. Records of dosage preparations were maintained inconsistently."

Animals: Sprague-Dawley CR/CD rats; 18/sex/group.

Groups: Controls and Z-1282 @ 250, 1000, or 4000 mg/kg b.w. [Equivalent fosfomycin content: 133.15, 532.60, 2130.4, respectively]

Route of Administration: Oral (by gavage), once daily.

Duration of Study: 12 weeks of treatment followed by a 4-week recovery (no treatment) period.

Results:

- There was no drug-related mortality.

- SGOT and SGPT levels were elevated at the high dose [both SGOT and SGPT levels returned to normal after 4-week recovery period].

- Liver weight increases and kidney weight increases were evident in high dose males and in high dose females.

- In females kidney weight increases were noted also at 250 and 1,000 mg/kg, respectively.

- Ceca were enlarged (distended) in males and females at 4,000 mg/kg. Areas of mucosal inflammation were observed in the terminal ileum and colon.

- Histopathologic examination of kidneys from control, and from high dose rats, showed changes characteristic of spontaneous nephropathy.

- Treatment effects did not persist during recovery.

- No histopathologic changes were observed in tissues from rats at the end of treatment, and in tissues from rats at the end of recovery period.

Conclusions: No effect level (NOEL) of 1000 mg/kg of Z-1282.

17. 13-Week Oral Gavage Toxicity Study with Fosfomycin Tromethamine in Rats. Ref # 20

This study was conducted by
Project No. HWI-6277-124 in compliance with the FDA GLP requirements. The final report was dated June 10, 1994.

Study Dates: (in life) 8/31/93 to 12/30/93

Material Tested: Fosfomycin tromethamine, batch No. 06700/30888; white powder, 100% pure.

Animals: : CD BR VAF/Plus rats 5 weeks old and weighing 183.9 to 264.5 g (♂♂) and 124.5 to 164.9 g (♀♀)

Study Design:

Group	Test Material	Dose Level* (mg/kg/day)	Dose Volume (ml/kg/day)	No.of Rats	
				♂♂	♀♀
1.	Controls**	0	20	16***	16
2.	Z-1282(Low)	250(133.1)	20	16	16
3.	Z-1282(Mid)	1,000(532.6)	20	16	16
4.	Z-1282(High)	4,000(2130.4)	20	16	16

* Equivalent fosfomycin content in parenthesis.
** reverse osmosis (RO) water
*** Up to 6 animals/sex/group were selected at random and designated as recovery animals. The recovery animals were dosed for at least 13 weeks, then allowed 4-week post-treatment of reversibility period.

Treatment: [redacted] were dosed orally (gavage) once daily for 13 weeks.

Results:

General: One high dose (4,000 mg/kg) female [redacted] died during week 2; necropsy indicated gavage error.

Clinical Observations: Rats given 4,000 mg/kg showed swollen abdomen, malformed feces, and brown perianal hair-coat. This finding was consistent with the enlarged (higher) cecum weights. One mid-dose female also had swollen abdomen. Histologically no changes in the G.I. tract of treated animals.

Body Weights: Mean body weights and body weight gains for female rats at the 1,000- and 4,000 mg/kg were **generally higher** than those of the controls. This was due to increased cecum weights. Mean food consumption was generally higher for both male and female rats of the 1,000- and 4,000 mg/kg groups.

Clinical Pathology: [hematology, blood chemistry, and urinalysis]

- Test article-related changes were only seen in animals treated with 1,000- and 4,000 mg/kg and with few exceptions were reversed during recovery. The changes included:

- **lower** RBC count, hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and platelet count at the 4,000 mg/kg level;

- Lower urine pH in males given 1,000 or 4,000 mg/kg and in females given 4,000 mg/kg;

- lower total protein at the 4,000 mg/kg level;

- lower globulin in males given 4,000 mg/kg and in females given 1,000- or 4,000 mg/kg;

- lower creatinine in females given 4,000 mg/kg;

- higher alanine aminotransferase in males given 4,000 mg/kg;

- higher calcium in males given 4,000 mg/kg;

- higher inorganic phosphorus in males and females given 4,000 mg/kg;

- lower chloride in males given 4,000 mg/kg.

All these findings were **reversed** by week 18, except lower globulin in males and females given 4,000 mg/kg and higher inorganic phosphorus in males given 4,000 mg/kg.
[Also see histopathology report]

Organ Weights: Test article-related changes in organ weights in both sexes at the **terminal** sacrifice included increased cecal and liver weights, and decreased pituitary weights in **all** treated groups, and increased kidney weights in the high (4,000 mg/kg) dose group.

At the **recovery** sacrifice, only significantly increased weights persisted and only for males.

Gross Pathology: Test article-related changes macroscopic changes included enlarged ceca in most treated groups and reddening or mottling of mesenteric lymph nodes in the high-dose males.

Histopathology: Conducted by
see report dated April 19, 1994 [NDA vol. 17, pp 5-02406].

Histopathology report was not submitted in its entirety in the original submission of the NDA.

In response to my request, the applicant submitted the two volumes [volume 1, pp 1-420; volume 2, pp 1-272] of the histopathology report. (NDA Amendment dated 10/18/94)

Histopathology Report

- Although certain clinical pathologic variables appeared lower (of statistical significant) at 1000- and 4000 mg/kg (namely: red cell count, hemoglobin, hematocrit, and platelet count), there was reportedly no histopathologic evidence to support the statistical inferences of significance. Bone marrow cellularity and hemopoiesis were unremarkable. There was no evidence of neutropenia (w.b.c. and differentials were within normal limits). There was no evidence of tissue hemosiderosis to suggest red cell breakdown (hemolysis). There was no macroscopic hint at necropsy of any clotting deficiency (bleeding) that could be linked with (significant) platelet depletion. None of the findings were indicative of overt organ or tissue toxicity. There was no drug-related mortality. All deviations were not of record following a 4-week period of recovery. Except for persistence of kidney weight increase, no latent untoward reaction was observed.

- Apparent values for total protein and globulin in males at the 4000 mg/kg level, and lowered globulin in females given 1000 and 4000 mg/kg, respectively, were without biologic significance since mean body weights for females at the 1000 and 4000 mg/kg levels were generally higher than those of the control group, suggesting that male and female rats were not nutritionally deprived, and suggesting therefore that liver function was adequate for protein synthesis. Moreover, glucose and BUN values of all test groups were within limit of control values.

- **Ceca** were enlarged in all test groups after 13 weeks of treatment; a 4-week recovery period reduced the incidence of cecal enlargement. This was attributed to the antibiotic as test material.

- In the **liver**, there was no evidence of drug-induced enzyme induction, intrahepatic cholestasis, degenerative or proliferative change and drug allergy (eosinophilic or granulomatous inflammation.

- In the **kidney**, there was no evidence of: i) renal impairment (proximal tubular degeneration); ii) interstitial nephritis (immunologic mechanism); iii) nephrocalcinosis; and iv) renal papillary necrosis.

Conclusions: A no-observable-effect-level (NOEL) could not be established for this study because enlarged cecum and increased cecal weights were observed in all treated groups. Animals treated with 4,000 mg/kg also had evidence of perianal staining and malformed feces suggesting a more pronounced effect on the gastrointestinal tract at this dose than at the lower dosages.

These effects on the gastrointestinal tract may be due to a pharmacologic effect of the test article's antibiotic action. After taking into consideration the gastrointestinal related effects and increased organ weights, in which there were neither histologic char s nor suggestion of overt toxicity, a no-adverse-effect level (NOAEL) of 1,000 mg/kg was determined based upon possible test-article related effects on body weights in males at 4,000 mg/kg.

18. Four-Week Oral Toxicity Study in the Dog via Capsule Administration with Z-1282. (Ref. # 21)

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated August 16, 1989.

Dates of Treatment: 10/20/88 to 11/16-21/88

Material Tested: Z-1282; Lot No. 00000/89314 in gelatin capsules.

Animals: Beagle dogs. At the initiation of treatment 6-month old and mean weight were 7.4 (6.8-8.5) kg in males and 6.7 (5.2-7.4) kg in females. 4/sex/group.

Dose Selection: determined by sponsor (Zambon).

Experimental Groups:

Group	Test Material	Dose Level* (mg/kg/day)	No.of Dogs	
			♂♂	♀♀
I.	Controls**	0	4	4
II.	Z-1282(Low)	100(53.3)	4	4
III.	Z-1282(Mid)	300(159.8)	4	4
IV.	Z-1282(High)	1,000(532.6)	4	4

* Equivalent fosfomycin content in parenthesis.
** gelatin capsules.

Procedure: The dogs were administered the dose orally, in gelatin capsules, daily (7 days/week) for 28-33 days consecutively.

Results:

General: There was no mortality and physical observations showed no adverse, treatment-related effects.

Body Weight: The most significant effect in body weights occurred in the high dose males, whose weights were approximately 10% lower than weights of control males during the first 3 weeks of the study and 8% lower at termination. Body weight effects were considered to be slight to moderate in the mid dose females (8 to 10%) and moderate to severe in the high dose females (11 to 14%). These body weight effects in the high dose males and the mid-and high dose females were generally more pronounced during the early part of the study and appeared to become less marked over time.

Food Consumption: Food consumption of the mid- and high dose males and females was slightly lower or statistically significantly lower than the control values during week 1 of the study but generally comparable to control values for the remainder of the study.

Ophthalmoscopic Examination: No treatment-related effects.

Clinical Chemistry: A statistically significant increase in aspartate aminotransferase as compared to the control values was observed in high dose males at termination of the study.

Hematology, Urinalysis: No treatment-related effects.

Organ Weights: Absolute and relative **testes** weights of the high dose males were slightly but statistically significantly lower than controls. [Histologically no lesions in the testes reported; 1 high dose male had atrophy of the prostate].

Absolute and relative **liver** weights of the low-, mid- and high dose males and females were slightly but statistically significantly greater than those of the control dogs. [Histologically no liver abnormality reported]

Pathology: No treatment-related lesions were reported at necropsy or on histopathology.

Conclusions: Based on the body weight effects seen in females receiving 300 mg/kg/day, the no adverse effect level (NOAEL) was determined to be **100 mg/kg/day** of Z-1282 in this study.

19. A Four-Week Toxicity Study of Fosfomycin Trometamol (MONUROL) In the Dog via Capsule Administration. (Ref # 22)

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated April 28, 1994.

Reviewer's Note: This 4-week oral dog study is a repeat of a similar study (# 18 reviewed above) conducted previously by

Treatment Dates: 1/13/94 to 2/14/94.

Material Tested: Fosfomycin Trometamol; Lot No. 06700-30888; 100% active ingredient.

Animals: Beagle dogs. At the initiation of treatment dogs were 6-month old and mean weights were 10.3 (9.6-11.5) kg in males and 8.7 (7.5-10.1) kg in females. 4/sex/group.

Dose Selection: determined by sponsor (Forest Laboratories).

Experimental Groups:

Group	Test Material	Dose Level* (mg/kg/day)	No.of Dogs	
			♂♂	♀♀
I.	Controls**	0	4	4
II.	Fosfomycin Trometamol(Low)	100(53.3)	4	4
III.	Fosfomycin Trometamol(Mid)	300(159.8)	4	4
IV.	Fosfomycin Trometamol(High)	1,000(532.6)	4	4

* Equivalent fosfomycin content in parenthesis.
** gelatin capsules.

Procedure: The dogs were administered the dose orally, in gelatin capsules, daily (7 days/week) for 28-33 days consecutively.

Results:

General: All dogs survived. Clinical signs associated with drug treatment consisted of emesis and unformed/watery stools which were seen primarily in males and females treated with 1,000 mg/kg/day (high dose group) and decreased over time.

Body Weight & Food Consumption: Clear effects on these parameters were evident only in high dose males and females. High dose males and females exhibited mean body weight losses during the first one or two weeks of treatment and gained weight during the remaining weeks. However, because of the initial body weight losses, the body weights of these animals never caught up with the body weights of the control dogs.

Mean food consumption values for the high dose males and females were statistically significantly lower than concurrent control values. No toxicologically significant changes in body weight or food consumption were seen in both sexes of the mid- or the lower dose.

Ophthalmoscopic Examination: It was performed at termination and revealed no effect of drug administration.

Clinical Pathology: There were no effects on hematology or clinical chemistry parameters. Urinalysis performed at termination showed a trend towards decreased pH values in high dose dogs. According to the investigators, this decease was not an unexpected result with highly acidic (pH 4.4) Fosfomycin Trometamol and was not considered toxicologically significant.

Organ Weights: No drug effects were noted.

Pathology: Both gross and microscopic examination revealed no findings which were considered to represent systemic toxic effects of the drug. Microscopic changes in the gall bladder were attributed to changes in the functional activity were seen in dogs from all treated groups.

Conclusions: Based on clinical signs (emesis, watery stools) and body weight losses seen in the high dose group, the no observed adverse effect level of the drug was **300 mg/kg/day.**

Toxicokinetics: Mean serum Fosfomycin Trometamol concentrations increased linearly with dose for both sexes of dogs. No differences in the mean serum Fosfomycin Trometamol concentrations were observed between day 1 and day 28, indicating constant exposure of the drug during the study period.

20. **Pharmaco-toxicological Report on Z-1282. Twenty-six weeks toxicity in the dog. (Ref. # 23)**

This study does not contain a GLP statement. The final report was dated April 1982. The study (Study 8) was conducted by Zambon Pharmaceutici S.p.A. Research Laboratories, Bresso (Milano), ITALY, between April and November 1981.

Materials Tested: Z-1282 (Fosfomycin contents = 53 26%) and Calcium Fosfomycin (Fosfomycin contents = 71.13%). Z-1282 was administered in the form of extemporaneously prepared aqueous solutions diluted with fresh whole milk.

Animals: Beagle dogs ranging in age from 9 to 13 months, and weighing 8.4 to 14.5 kg (♂♂) and 6.5 to 12.4 kg (♀♀).

Dose Selection: Dose levels were selected by Zambon's investigators, and were based on the results of two previous studies, one in dog (1) and one in man (2) listed on p. 23 of the report. Quoted verbatim from the report:

"Results of the study in the dog showed that:

- Oral Z-1282 (at) 100 mg/kg produced peak plasma fosfomycin levels of about 40 mcg/ml at hour 2 after dosing. Levels fell to 0 mcg/ml at hour 6. At hour 24, 51% of the dose was excreted in the urine.

- Oral calcium fosfomycin (at) 200 mg/kg produced peak plasma fosfomycin levels of about 35 mcg/ml at hours 3-4 after dosing. At hour 24, 27% of the dose was excreted in the urine.

"Results of the study in man showed that:

- A single oral dose of fosfomycin (at) 2 g (corresponding to Z-1282 50 mg/kg) produced a peak plasma fosfomycin level of about 20 mcg/ml at hour 2 after dosing. Computerized simulation of repeated oral of fosfomycin 2 g at 6 hour intervals showed attainment of a steady state after 4-5 doses which produced peak plasma fosfomycin levels of about 35 mcg/ml.

"On the basis of these results the following dose levels were selected for the present study.

- Lowest Z-1282 oral dose: 100 mg/kg/day
This dose is capable of producing peak plasma fosfomycin levels comparable to those attainable in man after oral Z-1282 at 50 mg/kg t.i.d.

- Highest Z-1282 oral dose: 1000 mg/kg/day.
This dose is capable of producing peak plasma fosfomycin levels in the dog about 3 times higher than those attainable after 100 mg/kg/day. A higher dose level was not selected because preliminary tests showed that chronic administration of Z-1282 at doses over 1000 mg/kg/day produced severe toxic effects after a few days (vomiting and diarrhea with mucoid and blood-streaked feces.

- Calcium fosfomycin oral dose: 200 mg/kg/day
This dose is capable of producing plasma fosfomycin levels approximating those attainable by Z-1282 at 1000 mg/kg/day."

Treatment Groups:

Group	Drug	Dose * (mg/kg/day)	No. of Dogs	
			Males	Females
A	Placebo**	---	4	4
B	Z-1282	100 (53.3)	3	3
C	Z-1282	300 (159.8)	3	3
D	Z-1282	1,000 (532.6)	4	4
E	Calcium fosfomycin	200	4	4

* Equivalent fosfomycin content in parenthesis.
** milk

The drugs were administered orally once daily, 7 days/week for 26 weeks.

At the end of treatment, all dogs/sex/group were sacrificed except 2 dogs/sex of groups A, D and E which were kept under observation for 6 weeks after the end of treatment, and then sacrificed.

Results:

General: There was no mortality. Diarrheal episodes were observed in all high-dose dogs and to a lesser extent in mid-dose dogs. In the low-dose and calcium fosfomycin group these episodes only slightly exceeded those of controls. These episodes began on day 3 of dosing in females and after 1 week in males. These episodes "produced no signs of distress and did not affect normal food consumption."

Body Weight: No marked changes in body weight were observed except for a marked decrease in 1 female dog of group D and 1 male and 1 female of group E.

Ophthalmoscopic and EKG Examination: There were no drug-related effects.

Hematology Blood Chemistry and Urinalysis: There were no drug-related effects on these parameters.

Pathology: Macro- and microscopic examination did not reveal differences from control and treated groups.

Conclusion: "Oral administration of Z-1282 at doses up to 1000 mg/kg/day for 26 weeks was well tolerated in the dog. The diarrheal episodes prevailed at doses far higher than those

administered to man and were dose-dependent, common to Z-1282 and calcium fosfomycin, and (were) reversible."

Bioavailability of Test Drugs:

Z-1282:
Plasma fosfomycin levels in 6 dogs given Z-1282 at 100 mg/kg (i.e. 53 mg/kg of fosfomycin) were determined on days 0, 84, and 168 of treatment in blood samples collected 2, 4, and 24 hours after dosing.

Mean plasma fosfomycin levels were 28.8 mcg/ml at hour 2 and 17.2 mcg/ml at hour 4.

Calcium fosfomycin:
Plasma fosfomycin levels in 8 dogs given oral calcium fosfomycin at 200 mg/kg (i.e. 142 mg/kg of fosfomycin) were determined on days 0, 84, and 168 of treatment in blood samples collected at 4, 6, and 24 hours after dosing.

Mean plasma fosfomycin levels were 17-18 mcg/ml at hour 4 and 28-30 mcg/ml at hour 6.

Comparative Bioavailability:
Fosfomycin was absorbed more readily and in amounts 2-3 times greater after Z-1282 than after calcium fosfomycin.

There were no marked differences in absorption data between days 84 and 168.

SPECIAL TOXICOKINETIC STUDY

21. 2-Week Oral Gavage Toxicokinetic Study with Fosfomycin Tromethamine in Rats. (Ref.# 24)

Lab. Project ID:

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated May 15, 1994.

Study Dates: August 25, 1993 to September 8, 1993.

Study Objective: To assess the toxicokinetics of Fosfomycin Tromethamine, when administered daily by oral gavage to rats for at least 2 weeks.

Methodology: There were 198 male and 198 female :CD BR VAF/Plus rats assigned to 5 groups

Group	Dose Level* (mg/kg)	Dose concentration (mg/ml)	No. of Animals	
			Male	Female
1. Control	0	0	6	6
2. Low	250(133.2)	25	48	48
3. Mid-Low	500(266.3)	50	48	48
4. Mid-High	1,000(532.6)	100	48	48
5. High	2,000(1065.2)	200	48	48

Dose Volume = 10 ml/kg

Blood samples were collected (cardiac puncture) immediately postdose and approximately 0.5, 0.75, 1.5, 3, 6, 8, and 12 hours postdose on days 1 and 15 from 3 rats/sex/group/interval in groups 2 thru 5 and immediately postdose only from animals in group 1.

Serum samples were harvested and shipped overnight to Sponsor (Forest Lab.) for analysis of Fosfomycin Tromethamine. Animals were sacrificed and discarded **without necropsy** after blood collection. Fosfomycin serum concentrations were determined by a validated gas chromatography method using nitrogen-phosphorus detection (NPD). Sensitivity of the analytical method was **less than 1 µg/ml**.

Mean drug serum concentrations versus time curves were constructed for each dose and sex to obtain the following toxicokinetic parameters: time for maximum drug concentrations, T_{max}, maximum drug concentration, C_{max}, area under the curve, **AUC** and elimination half-life, $t_{1/2}$.

Results:

General: All animals survived. There were no clear differences in body weight, food consumption or clinical signs in drug-treated animals compared with the controls.

Toxicokinetics: **Report TK/3700/0001** dated April 18, 1994 submitted by Forest Laboratories, Inc. [NDA volume 20, pp 5-03229 to 03259]

- No differences were observed for T_{max}, C_{max} and AUC between male and female rats.

- C_{max} values in male and female rats increased linearly with increasing doses, from 250 to 2000 mg/kg/day. No apparent differences were observed for the fosfomycin serum

concentrations. Day 15 C_{max} values were higher than Day 1 C_{max} values at 500, 1000 and 2000 mg/kg/day dose levels.

- The overall mean ± SD values for T_{max} for male and female rats were 1.3 ± 0.60 hours.

- AUC_{0-12} values increased linearly with dose after single dose (day 1) and at steady-state (day 15).

- The $t_{1/2}$ for fosfomycin in male rats were generally shorter compared to female rats at 250 and 500 mg/kg/day doses; whereas, at the 1000 mg/kg/day dose, the $t_{1/2}$ values were similar, approximately 2.5 hours. The $t_{1/2}$ values showed non-linear elimination at the highest dose level, with $t_{1/2}$ values for female rats ranging from hr and for male rats ranging from hour.

REPRODUCTION STUDIES:

22. Fertility Study of Oral Z-1282 in the Rat: Ref. # 25

This study does not contain a GLP statement. The final report was dated 1982. The study (Expt. No. TR 36) was conducted by Zambon Pharmaceutici S.p.A. Research Laboratories, Bresso (Milano), ITALY, between March -June 1981.

Material Tested: Z-1282, batch No.8

Animals: CD (SD) BR rats

No. of Animals: 96 Females (24 per dosage group)
96 Males (24 per dosage group)

Method, Frequency and Duration of Treatment: Oral (by intubation) once daily.

Males (F0 generation) daily for at least 63 before mating, during the mating period and then until necropsy.

Females (F0 generation) daily for at least 14 days before mating, during the mating period and then during gestation period until 7th day post-coitus.

Mating Period: maximum of 14 days.

Groups:

Group	Z-1282* (mg/kg/day)	Volume (ml/kg/day)	Concentration of Z-1282 (mg/ml)
A. Control	0	10	0
B Low-dose	250(133.2)	10	25
C. Mid-dose	500(266.3)	10	50
D. High-dose	1000(532.3)	10	100

* Equivalent fosfomycin content in parenthesis.

Necropsy: On the 21st day of gestation, the females were killed and maternal organs checked, the uteri were removed and findings were recorded as listed below:

- number of implantation sites (Salewski's method)
- number of dead fetuses;
- number of early resorptions;
- number of late resorptions;
- number of viable fetuses;
- individual fetal weight;

and various indices obtained from the above numbers.

Results:

F-0 Generation:

There was no mortality

- soft feces and dilated stomachs were observed in all treated group males.

- Body weight was unaffected by treatment.

- slight reduction of food intake in the males of the treated groups.

- No alterations were observed during necropsies at term.

Reproductive Performance: The fertility, the mating and the gestation indices of F0 were all in the normality range.

Observations on "litter of F1 Generation:

Implantation Sites: These were similar in control and treated groups.

Viable Fetuses: Litter size of all groups were within the normal limits.

Dead Fetuses: One dead fetus was found in the high-dose (1000 mg/kg/day) group.

Resorptions: The individual and mean group values were within the normal range.

Post-implantation losses: The individual values of these losses were very low, only one low-dose female and one mid-dose female had values higher than 20%

Body Weights of Viable Fetuses: The individual and mean group values were within range in all groups.

External Examination: One fetus belonging to a low-dose litter (B7/3) had a major malformation (ANURIA). According to the investigators, "this phenomenon cannot be related to the administration of the drug, because it was found only in one fetus.

Visceral Examination: [Wilson technic performed only on control and high-dose groups] "No fetus with appreciable alterations was observed."

Skeletal Examination: The fetus with ANURIA was observed for skeletal examination.

One skeleton of the litter B4/1 showed wavy ribs (minor anomaly).

Some "Variations" either in treated or control groups were sporadically observed. "These **differences in the pattern of ossification,** likely, represent no more than transient retardation of the osteogenesis and are common findings in the skeletal examination of rats."

23. Fertility and General Reproduction Study of Fosfomycin Tromethamine administered Orally via Gavage to :CD BR VAF Plus Rats (Segment I Evaluation). Ref. # 26

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated April 6, 1994.

Material Tested: Fosfomycin Trometamol; Lot # 06700/30888.

Test Article Preparation: Solutions of Fosfomycin Trometamol were prepared daily at concentrations of **0, 25, 50 and 100 mg/ml,** such that dosages of **0(vehicle), 250, 500 and 1000 mg/kg/day,** respectively were administered at a volume of **10 ml/kg.**

Animals: :CD BR VAF/Plus, 6 weeks old males, and 9 weeks old females. **30 rats per dose group.**

Dose Selection: By the Sponsor.

Dose Groups:

Group	Dose* (mg/kg/day)	No. of Rats per sex	Rat Numbers Males	Female
I	(vehicle)	30	9501-9530	9621-9650
II	250 (133.2)	30	9531-9560	9651-9680
III	500 (266.3)	30	9561-9590	9681-9710
IV	1,000 (532.6)	30	9591-9620	9711-9740

* Equivalent fosfomycin content in parenthesis.

Treatment: Rats were dosed orally (via gavage) once daily according to the following schedule:

F0 Males: 70 days prior to mating, throughout the 21-day mating period and up to the day before their scheduled sacrifice.

F0 Females: 15 days prior to mating, throughout 21-day mating period and dosing continued until the day before scheduled sacrifice on:

(1) - Day 20 of presumed gestation (rats assigned to **Caesarian section**)- 35 to 48 daily dosages;

(2) - Day 25 of presumed gestation (rats assigned to **natural delivery that did not deliver** a litter) - 40 to 61 daily dosages;

(3) - **Day 21 of lactation (rats that delivered litters)** - 56 to 72 daily dosages.

F1 generation: Although the F1 generation pups were possibly exposed to the test article in utero during gestation or via maternal milk during the postpartum period, the offspring were not directly administered the test article.

Gross Necropsy:

F0 males were sacrificed after the completion of mating period (21 days)

F0 Females (Caesarian sectioning): These were sacrificed on day 20 of presumed gestation; they were evaluated for corpora lutea, the no. and distribution of implantation sites, and early or late resorption.

Each fetus was removed from the uterus; one-half of the fetuses in each litter were fixed in Bouin's solution and one-half in alcohol for future evaluation. [malformations]

F0 Females (natural delivery)

Those which did not deliver litters: were killed on day 25 of presumed gestation.

Those which delivered: On day 7 postpartum - all litters with 9 or more pups were culled to 8 pups/litter- **4 pups/sex/litter**- these constituted **F-1 generation pups**.

Results:

F0 Generation Male Rats: All males rats survived. Soft and liquid feces occurred in 3, 3 and 2 rats in the 250, 500 and 1000 mg/kg/day dosage groups. On necropsy one low-dose group rat had a spermatocele; this was not considered treatment-related. [Testes were not examined microscopically.]

The mating and fertility parameters (days in cohabitation, fertility index) were unaffected by the test article.

F0 Generation Female Rats:

A. **Mortality and Clinical Observation:** No female rats died before scheduled sacrifice and no gross necropsy lesions occurred. Soft and liquid feces occurred in statistically significant ($P \leq 0.01$) number of rats given 500 and 1000 mg/kg/day dosages.

B. **Body Weights: Premating:** At premating, body weight gains were statistically significant ($P \leq 0.05$ to $P \leq 0.01$) in all groups administered the test article for days 1 to 8 of the dosage period and in the 1000 mg/kg/day dosage for days 1 to 15. All groups administered the test article had increased weights compared to the controls.

Gestation: Average body weight gains and body weights did not differ significantly among the groups for the entire gestation-period (days 0 to day 20 of gestation). The average weight of the rats in the groups administered the test article continued to be higher than the control group averages.

Lactation: During lactation, average body weight gains were significantly increased ($P \leq 0.05$ to $P \leq 0.01$) on days 7 to 14 of lactation for all groups administered the test article. Average body weights were statistically significantly changed ($P \leq 0.01$) in all dosage groups on day 14 of lactation and in the 1000 mg/kg/day dosage group on days 1 and 21 of lactation. These increases were probably more related to the normal variation during lactation and not related to test article.

C. **Food Consumption:** **Premating:** Absolute (g/day) feed consumption values premating were statistically significantly ($P \leq 0.05$) reduced in the 250 and 500 mg/kg/day dose groups for days 8 to 15 of dosage. Relative (g/kg/day) feed consumption values were statistically significantly reduced ($P \leq 0.05$) in the 250 and 1000 mg/kg/day groups for days 1 to 8 of the dosage period.

Gestation: During gestation, absolute and relative feed consumption values were generally increased for all intervals compared to the controls. Significant increases ($P \leq 0.05$ to $P \leq 0.01$) in absolute feed consumption occurred in all dosage groups on days 7 to 14 and 0 to 20 of gestation, in the 500 and 1000 mg/kg/day groups on days 14 to 20, and the 500 mg/kg/day group on days 0 to 7 of the gestation. Relative feed consumption values were statistically significantly increased ($P \leq 0.01$) for the 250 and 1000 mg/kg/day dosage groups on days 7 to 14 of gestation. These increases were related to the increased body weights in these groups.

Lactation: During lactation, absolute and relative feed consumption values were comparable among the dosage groups for all intervals evaluated.

D. **Estrous Cycling, Mating and Fertility:** [see Table C-15 of the Report]

Dosages of test article as high as 1000 mg/kg/day did not affect estrous cycling or any mating and fertility parameters.

E. **Caesarean-Sectioning, Litter Observations and Fetal Gross External Alteration:** [see Tables C-16 and C-17 of the Report]

Each dosage group had 12 to 15 litters available for evaluation.

Administration of dosages as high as 1000 mg/kg/day did not affect any parameter evaluated at Caesarean-sectioning. The litter averages for corpora lutea, implantation, litter sizes, live fetuses, early and late resorptions, percent live male fetuses, live fetal body weights, number of dams with any resorptions and percent resorbed conceptuses per litter were comparable among the four dosage groups and did not significantly differ.

No gross external fetal alterations occurred. All fetuses appeared normal.

F. Natural Delivery and Litter Observations: [Tables C-18 to C-21].

Pregnancy occurred in 12 to 15 of the rats in each dosage group assigned to natural delivery. All pregnant rats delivered a litter.

Evaluation of natural delivery and litter data did not reveal any adverse effects of dosages of the test article as high as 1000 mg/kg/day. There were no biologically important differences among the dosage groups in the durations of gestation, numbers of dams with stillborn pups, the number of dams with live-born pups per number of pregnant rats, number of live-born pups, stillborn pups, pup body weights, percent male pups, viability and lactation indices or the numbers of litters with pup deaths.

The incidence of clinical and necropsy observations in the pups was comparable among the groups.

Conclusions: Fosfomycin Trometamol at doses as high as 1000 mg/kg/day did not affect any reproductive parameters in the male or female rats of this study.

24. Teratogenesis Study in the Rat with Z-1282 Administered by Oral Route. Ref. # 27 Expt. No. TR 28

This study does not contain a GLP statement. The final report was dated May 1982. The study (Expt. No. TR 28) was conducted by Zambon Pharmaceutici S.p.A. Research Laboratories, Bresso (Milano), ITALY, between March -June 1980.

Study Dates: Start of mating: March 18, 1980
Start of treatment: March 24, 1980
Start of F0 delivery: May 8, 1980

Material Tested: Z-1282, batch No.6 was dissolved in distilled water to provide concentrations of 25-, 50- and 100 mg/ml for the dosages of 250, 500 and 1000 mg/kg/day in a volume of 10 ml/kg/day which was constant for all dose groups.

Animals: CD (SD) BR rats; 25 females/dosage group

Groups: Group 1: vehicle
Group 2: 250 (133.2) mg/kg/day of Z-1282
Group 3: 500 (266.3) mg/kg/day of Z-1282
Group 4: 1000 (532.6) mg/kg/day of Z-1282

[Equivalent fosfomycin content in parenthesis.]

Method, Frequency and Duration of Treatment: Oral (by intubation) once daily from 6th to 15th day of gestation.(mating/sperm positive day = day 0)

Experimental: At the end of gestation period 15 pregnant females were sacrificed and their fetuses were examined. The remaining females were allowed to deliver and the F1 generation was checked until weaning.

Necropsy: On the morning of day 21 of gestation, 15 females/group were sacrificed and their fetuses were evaluated for teratogenesis.

Observations on the Fetuses:

External Examination: All fetuses were examined for deviation of their external appearance.

Visceral Examination: One-third of the viable fetuses were fixed in Bouin's solution for subsequent sectioning by Wilson's technic.

Skeletal Examination: The remaining fetuses were fixed in 96% ethanol and then stained by Alizarine Red S.

Observations on Litters After Spontaneous Delivery:

The remaining females, which were not sacrificed on gestation day 21 were allowed to deliver. The pups were observed up from birth to day 21 (weaned). After weaning the pups were sacrificed.

Results:

Maternal: There was no mortality. The mean body weight gain in drug-treated females was similar to that in the controls. There were no differences in food consumption between the drug-treated groups in the first and third week of gestation. During the second week (organogenesis phase) there was a moderate and dose-related reduction in food intake. This reduction was statistically significant.

Group mean values for implantation sites (ranged from were similar for all experimental groups and were in the range of normal variability.

Observations on Fetuses:

- The mean number of viable fetuses were within the normal range, no dead fetuses were observed at the Caesarian section.

- A low incidence of resorptions was observed in all groups, the number of resorptions per litter was always in the normal range (less than 1.0).

- The mean group values of the viable fetuses body weight were similar in all experimental groups.

A slight reduction in mean fetal body weights in the low-dose group was due to the presence of a litter B-6 that presented a considerably lower body weight.

External Examination: No fetus with major malformation was observed at the examination, four fetuses belonging to the litter B-6 exhibited poor viability. [these pups had lower body weights also; see above]

Visceral Examination: No major malformation was observed during visceral examination.

Some minimal modifications, likely happened by chance, were observed in the fetuses of low-dose group.

Skeletal Examination: The major part of the "modifications (classified as **Variations)**" observed during the examination of skeletal structures was **delay in the ossification of the skeletal districts (sic).** According to the investigators, "this phenomenon was present either in treated or control groups with various incidence. These differences in the pattern of ossification, likely, represent a transient delay of osteogenesis and are common findings in the skeleton of rat fetuses."

Wavy ribs, observed in 4 fetuses of the low dose group, were the only modifications classified as anomalies.

No malformation was found during the check of skeletons. The incidence of skeletons unaffected by abnormalities was similar in all groups and ranged within 81.2% and 89.3%.

Observations on F1 Generation: No substantial differences between the treated and control groups was observed in data obtained from F1 generation.

25. Developmental Toxicity (Embryo-fetal toxicity and teratogenic potential) Study of Fosfomycin Trometamol Administered Orally via Gavage to Crl:CD BR VAF/plus Presumed Pregnant Rats. Ref. # 28

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated January 17, 1994.

Study Dates: Day 0 of Presumed Gestation 8/18-23/93
Dosage Period (day 6 thru 15) 8/24-9/7/93
Caesarian Section (day 20) 9/7-12/93

Material Tested: Fosfomycin Trometamol; Lot 06700/30888

Test Article Preparation: Solutions of Fosfomycin Trometamol were prepared daily at concentrations of 0, 25, 50 and 100 mg/ml, such that dosages of 0(vehicle), 250, 500 and 1000 mg/kg/day, respectively were administered at a volume of 10 ml/kg.

Animals: :CD BR VAF/Plus; rats were mated in 25 presumed pregnant/dose group.

Dose Selection: By the Sponsor.

Dose Groups:

Group	Dose* (mg/kg/day)	No. of Rats Female Rats	Rat Numbers Pregnant Females
I	(vehicle)	25	
II	250 (133.2)	25	
III	500 (266.3)	25	
IV	1,000 (532.6)	25	

* Equivalent fosfomycin content in parenthesis.

Treatment: Rats were dosed orally (via gavage) once daily from day 6 thru day 15 of pregnancy.

Gross Necropsy: All rats were sacrificed on day 20. The number of corpora lutea in each ovary were recorded. The uterus of each rat was examined for pregnancy, number of implantations, live and dead fetuses and early and late resorptions were recorded.

Examination of Fetuses for Terata: Approximately one-half of the fetuses in each litter were examined for soft tissue alterations by Wilson's sectioning technique. The remaining fetuses in each litter were eviscerated, cleared, stained with alizarin red and examined for skeletal alterations.

Results:

A. Mortality, Clinical and Necropsy Observations: All rats survived until scheduled sacrifice. One high dose group rat was apparently injured on or after day 15 of gestation; the litter in this rat was essentially normal, with the exception that fetal body weights were slightly reduced.

B. Maternal Body Weights and Body Weight Changes: Transient, statistically significant ($P \leq 0.01$) increases in maternal body weight gains occurred in all drug-treated groups on days 6 to 9 of gestation. Average body weight changes were in drug-treated groups were comparable to those in the control group. Average body weights on day 16 of gestation (1 day post-treatment) in drug-treated groups were within 2.2% of the control group values.

During the post-dosage period (days 16 to 20 of gestation), body weight gains were reduced ($P > 0.05$) in all drug-treated groups and significantly reduced ($P \leq 0.05$) in the high-dose (1000 mg/kg/day) group to 94.3%, 91.6% and 76.4% of the control group value. The high dose group value was considered biologically important, because the difference from the control group value was more than 10%.

This decrease in high dose group was due to one high-dose dam having a litter of only one early resorption and one high-dose dam being injured. When the values for these dams were excluded from the analyses of body weight data, the significant increases ($P \leq 0.05$ to $P \leq 0.01$) in body weight gains remained present in the groups given the test article; and the reduction in body weight gain in the 1000 mg/kg/day dose group during the post-dosage period was less severe (85.9% of the control group value), but remained biologically important. Average body weights in the three groups given the test article were within 1% of the control group value on day 20 of gestation.

C. Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values: These generally followed the trend in body weight and body weight gains.

D. Caesarean-Sectioning and Litter Observations: There were 21(84.0%), 23(92.0%), 18(72.0%) and 22(88.0%) pregnant rats Caesarian sectioned on day 20 of gestation in the 0(Vehicle), 250, 500 and 1000 mg/kg/day dosage groups, respectively.

No Caesarean-sectioning or litter parameters were affected by administration of the test article to the dams at dosages as high as 1000 mg/kg/day. The litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, fetal body weights, and the percentage of male fetuses (sex ratio) were comparable among the four(all) dosage groups and did not differ significantly.

E. Fetal Alterations: [Table 9 to 13 of the Report]

Fetal alterations were defined by the investigators as:

1) **malformations** (irreversible changes that occur at low incidence in this species and strain);

2) **variations** (common findings in this species and strain and reversible delays of accelerations in development).

	Vehicle	Test Article (mg/kg/day)		
No. Examined	0	250	500	1000
No. of litters	21	23	18	21
No. of Live Fetuses	294	339	263	304
No. Examined for:				
Soft tissue alterations	144	163	128	147
Skeletal alterations	150	176	135	157

The 1000 mg/kg/day dose group had significant increases ($P \leq 0.05$ to $P \leq 0.01$) in the number of litters, the number of fetuses and the percent fetuses per litter with an alteration. These observations reflected increases in the incidences of skeletal variations (reversible delays in development) in this dosage group [significantly increased ($P \leq 0.05$ to $P \leq 0.01$) numbers of litters had delayed ossification of the sternum and pelvis and reduced average numbers of ossified metatarsals].

Exclusion of the values for the litter of high dose dam , which was injured and had persistent weight loss and severely reduced food consumption after day 15 of gestation, identified that the statistical significance of these parameters principally reflect the values for this litter.

After exclusion of the values for this litter, the percent of fetuses with any alteration per litter, the litter and fetal incidences for incompletely and not ossified sternebrae, the fetal incidences for incompletely and not ossified pubes and ischia and not ossified pubes and for incompletely ossified ischia alone as well as for ossified numbers of metatarsals were no longer significant ($P > 0.05$), and these values were within the ranges observed historically at the Test Facility

All other fetal gross external or skeletal alterations in the 1000 mg/kg/day dose group and all fetal gross external or skeletal malformations and variations in the 250 and 500 mg/kg/day dose groups were also considered by the investigators unrelated to the test article because the values were neither statistically significant nor dose-dependent.

All alterations in the fetuses in this study are described below:

E.1. Fetal Gross External Alterations (Summary Table 10)

One 250 mg/kg/day dose group fetus (10426-2) had a hemorrhagic area on the back.

E.2. Fetal Soft Tissue Alterations (Summary Table 11)

No soft tissue alterations occurred in any fetus.

E.3. Fetal Skeletal Tissue Alterations (Summary Table 12 & 13)

Malformations: The 1st and 4th of the seven lumbar vertebrae were left and right hemivertebra, respectively, in 250 mg/kg/day (low-dose) group fetus ; this fetus also had absent, unilateral, bifid or asymmetric ossification of the centrum of the 2nd, 5th, 13th or 14th thoracic vertebra and 5th lumbar vertebra, as well as a variation in sternal ossification (incomplete ossification of the 1st sternal center).

Variations: All skeletal variations were reversible delays in fetal ossification. The fetal and litter incidences of delayed ossification in the sternebrae and pelvis were significantly increased ($P \leq 0.01$), and the litter average for ossified metatarsal bones were significantly reduced ($P \leq 0.05$) in the 1000 mg/kg/day dose group, as compared to the control group values.

Conclusions (Investigators'): The developmental no-observable-adverse-effect level for the test article is 1000 mg/kg/day.

26. Teratogenesis Study in Rabbit with the Test Article Z-1282 Administered by Oral Route: Ref. # 29

This study does not contain a GLP statement. The final report was dated May 1982. The study (Expt. No. TR 37) was conducted by Zambon Pharmaceutici S.p.A. Research Laboratories, Bresso (Milano), ITALY, between April -June 1981.

Study Dates:
Start of mating: April 16, 1981
Start of treatment: April 22, 1981
End of Killing: June 18, 1981

Material Tested: Z-1282, batch No.8 was dissolved in distilled water to provide concentrations of 100-, 200- and 400 mg/ml for the dosages of 100, 200, and 400 mg/kg/day in a volume of 1 ml/kg/day which was constant for all dose groups.

Animals: New Zealand White rabbits; 10 presumed pregnant rabbits/group. The females were mated in the investigator's lab. (Sperm positive day = day 0)

Dose Selection: Preliminary teratogenic studies with Z-1282 at oral doses of 188, 375, 938, 1875 mg/kg/day in the rabbit showed that signs of maternal toxicity began to show at 375 mg/kg/day dose level. Therefore, 400- was chosen as the maximum dose and 100 mg/kg/day (2x higher than the daily clinical dose in humans).

Dose Levels:
Group A: Vehicle (distilled water)
Group B: 100 (53.3) mg/kg/day of Z-1282
Group C: 200 (106.3) mg/kg/day of Z-1282
Group D: 400 (213.0) mg/kg/day of Z-1282
[Equivalent fosfomycin content in parenthesis.]

Treatment: All rabbits were dosed orally by gavage, once daily from day 6th to day 18th of gestation.

Necropsy: On day 28 of gestation, the does were killed by dislocation of cervical vertebrae. All fetuses were killed by injection.

Results:

OBSERVATION ON DAMS:

Mortality:

Six females died during the study, but death not related to treatment.

Group	Dose Level (mg/kg/day)	Animal No	Day of death (gestation day)
A	0		4th (prior to treatment)
B	100		16th (misintubation) 5th (prior to treatment)
D	400		8th (misintubation) 22nd necropsy-Negative 12th " - "

Clinical Signs: Soft feces were observed sporadically in all drug treated and control males.

Body Weight: A moderate reduction in body weight occurred in all treated animals during the first period of treatment (day 6 to 9 of gestation).

Necropsies of Dams at Term: There were no changes which could be clearly related to treatment. Purulent pneumonia was likely due to misintubation in a mid-dose dam This animal was excluded from the computing data.

Fertility: The fertility indices for all experimental groups (71%-80%) were in the normal range.

Resorptions, Post-Implantation Losses: The administration of Z-1282 gave rise to an increase in the mean number of resorptions per litter; this phenomenon was more marked only in the mid-dose group[. The post-implantation loss d.d not show any significant difference between the drug-treated and control groups even if mean percent values of treated groups was slightly out of the normal range observed in the rabbit.

Implantation Sites: Group mean values of implantation sites were in the normal range.

Abortions: One low-dose female aborted during the study.

OBSERVATIONS ON FETUSES:

Viable Fetuses: The mean number of viable fetuses was slightly higher in mid-dose group (200 mg/kg/day) and in high-dose group (400 mg/kg/day). This phenomenon was related to the higher number of implantation sites in these groups.

Dead Fetuses: Seven dead fetuses were distributed in all experimental groups with low incidence.

Body Weight of Viable Fetuses: The mean body weight showed a reduction (between 5 and 8%) in all treated groups. However, the decrease was very low, not dose-related, not significant and was not considered to be of biological importance.

External Examination: At the necropsy 2 fetuses (both belonging to a litter of low-dose group) with external **minor** anomalies (abnormal flexure of forelimbs). This was considered to be spontaneous change because of its low incidence.

Visceral Examination: No fetus with visceral anomalies.

Skeletal Examination: One fetus with "malformation" was found: the fetus, belonging to the litter of mid-dose showed irregular ossification of one thoracic vertebra.

Either in treated or control group groups and with a similar incidence were also observed some skeletal "modifications classified as minor anomalies and variations"; these differences in the pattern of ossification, likely, represent no more than transient retardation of osteogenesis and according to the

investigators were common findings in the skeletal examination of rabbit fetuses.

27. **Developmental Toxicity (Embryo-fetal toxicity and teratogenic potential) Study of Fosfomycin Trometamol Administered Orally via stomach tube to New Zealand Rabbits.**
Ref. # 30

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated January 17, 1994.

Study Dates: Arrival Date of Rabbits: 8/13/93
Dosage Period (day 6 thru 18) 8/15-30/93
Caesarian Section (day 29) 9/7-10/93

Material Tested: Fosfomycin Trometamol; Lot 06700/30888

Test Article Preparation: Solutions of Fosfomycin Trometamol were prepared daily at concentrations of **0, 25, 50 and 100 mg/ml,** such that dosages of **0(vehicle), 250, 500 and 1000 mg/kg/day,** respectively were administered at a volume of **10 ml/kg.**

Animals: New Zealand White rabbits; 20 pregnant/group

Dose Selection: By the Sponsor.

Dose Groups:

Group	Dose* (mg/kg/day)	No. of Female Rabbits	Rabbit Numbers Pregnant Females
I	(vehicle)	20	
II	250 (133.2)	20	
III	500 (266.3)	20	
IV	1,000 (532.6)	20	

* Equivalent fosfomycin content in parenthesis.

Treatment: Rabbits were dosed orally (via stomach tube) once daily from day 6 thru day 18 of pregnancy.

Gross Necropsy:

All surviving rabbits were sacrificed on day 29 of presumed gestation and necropsied. The number of corpora lutea in each ovary was recorded. The uterus was excised and examined for pregnancy, number and distribution of implantations, early and late resorptions and live and dead fetuses. Each fetus was

weighed, sexed and examined for gross external, soft tissue and skeletal alterations.

Results:

A. Mortality, Clinical and necropsy observations:

Mortality: Two mid-dose (500 mg/kg/day) group females were found dead on day 26 of gestation. These deaths were drug-related because these females had reduced body weight and reduced food consumption.

Doe : The litter consisted of 8 fetuses and 2 late resorptions; the fetuses appeared normal for their developmental age.

Doe : The litter consisted of 2 fetuses that appeared normal for their developmental age.

Abortions: Abortions occurred in 0, 4(20%), 7(36.8%) and 9(47.4%) pregnant does in the vehicle, 250, 500 and 1000 mg/kg/day dose groups. One control group doe and one high dose group doe delivered on day 29 of gestation.

The deaths, abortions and premature delivery were considered as secondary effects of the test article's antibiotic action on the gastro-intestinal system.

Clinical & Necropsy Observations: Clinical observations attributable to the antibiotic activity included absent/no feces, dried feces, soft or liquid feces in drug-treated groups.

B&C. Maternal Body Weights and Feed Consumption: Persistent, significant reductions ($P \leq 0.05$ to $P \leq 0.01$) in maternal body weights occurred in all drug-treated groups beginning on days 14-15 of gestation. These reductions were preceded by reduced food consumption.

D. Caesarean-Sectioning and Litter Observations:

Caesarian-section observation were based on 19, 16, 10 and 9 pregnant does on day 29 of gestation in the four groups, respectively.

Groups given 250 mg/kg/day and higher doses of Fosfomycin Trometamol had significant increases ($P \leq 0.05$ to $P \leq 0.01$) in the litter averages for early resorptions and in the numbers of does with any resorption; these dosage groups also had significantly reduced ($P \leq 0.01$) fetal body weights. The 500 and 1000 mg/kg/day dose groups had increased litter averages for the total number of resorptions ($P \leq 0.05$ to $P \leq 0.01$) and

the percentage of resorbed conceptuses (P≤0.01). These effects of the test article did not significantly affect live litter sizes, although the average number of live fetuses tended to be reduced in the high dose group.

All other Caesarean-sectioning parameters were unaffected by the test article. The significant increase (P≤0.05) in the average number of implantations in the mid-dose group was considered unrelated to the test article because the value was not dose-dependent.

E. Fetal Alterations:

Significant increases (P≤0.05 to P≤0.01) in the number of fetuses with any alteration observed and the percentage of fetuses with any alteration per litter occurred only in the high-dose 1000 mg/kg/day group. These observations were based on the reduced number of fetuses available for examination in the 1000 mg/kg/day dose group (51 fetuses), compared with the control group number (142 fetuses).

High dose group fetal incidences (P≤0.05 to P≤0.01) included short snout, micrognathia, an internasal ossification site, short nasal-frontal suture, large parietal suture, short mandibles, large posterior fontanelle, and angulated hyoid-alae.

The investigator states, "These observations were considered unrelated to the test article because litter incidences were not significant, observations generally occurred in fetuses from only one high dose litter and the value for increased skeletal variation, such as internasal ossification site, fell within the ranges observed historically at the Test Facility."

Conclusions:

The maternal no-observable-adverse-effect-level (NOAEL) for Fosfomycin Trometamol is less than 250 mg/kg/day. The 250, 500 and 1000 mg/kg/day dosages caused abortions, reduced body weight and food consumption; the 500 mg/kg/day dosage also caused 2 deaths, and the 1000 mg/kg/day also caused one premature delivery.

Reviewer's Note: The fetal NOAEL for Fosfomycin Trometamol could not be determined from this study.

28. Perinatal and Postnatal Toxicity Study in Rats with Test Article Z-1282: Ref. # 31 Expt. No. TR 32

This study does not contain a GLP statement. The final report was dated May 1982. The study (Expt. No. TR 32) was conducted by

Zambon Pharmaceutici S.p.A. Research Laboratories, Bresso (Milano), ITALY, between September 1980 to March 1981

Study Dates:

Start of mating [F0]: September 3, 1980
Start of treatment [F0]: September 19, 1980
Start of mating [F1]: January 18, 1981
End of necropsies [F2]: March 23, 1981

Material Tested: Z-1282, batch No.7 was dissolved in distilled water to provide concentrations of 25-, 50- and 100 mg/ml for the dosages of 250, 500 and 1000 mg/kg/day in a volume of 10 ml/kg/day which was constant for all dose groups.

Animals: CD (SD) BR rats; F0 generation: 20 females/dosage group

Groups: Group A: vehicle
Group B: 250 (133.2) mg/kg/day of Z-1282
Group C: 500 (266.3) mg/kg/day of Z-1282
Group D: 1000 (532.6) mg/kg/day of Z-1282
[Equivalent fosfomycin content in parenthesis.]

Method, Frequency and Duration of Treatment: Oral (by intubation) once daily from 15th postcoitum day to 21st day postpartum. F0 generation only.

Experimental Design/Methodology: F0 generation females were allowed to deliver pups [F1].

F1 generation rats were checked for morphological, behavioral and reproductive development; F1 were mated; F2 generation rats were observed for morphological development until weaning.

F1 Generation: During their first 30 days of life all F1 generation pups were subjected to morphological and behavioral tests.
On day 30th post-partum 440 F1 generation pups (55 males and 55 females per experimental group) were allocated to the following subgroups:

SUBGROUP 1: 15 males per experimental group;
SUBGROUP 2: 25 males and 25 females per experimental group;
SUBGROUP 3: 15 males and 30 females per experimental group.

The remaining 138 pups were sacrificed on day 30 post-partum and were necropsied.

Observations on F1 Generation:

All F1 pups they were observed for:

1. **Litter size and viability:**
2. **Culling:** on postpartum day 1, litters were reduced (maximum of 10 (5/sex) pups);
3. **Body weight:** Postpartum days 1, 4, 21, and 30.

4. **Pinnae detachment:** by postpartum day 4.
5. **Eye opening:** by postpartum day 14.
6. **Righting on surface:** postpartum day 2.
7. **Auditory startle reflex:** postpartum day 15.
8. **Postural adjustment:** postpartum day 18.

Subgroup 1: (15 young male rats) These were subjected to:

1. **Rota-rod test:** postpartum day 32 ± 1
2. **Thermoregulation test:** postpartum day 50 ± 3
3. **Necropsy:** After completion of all tests.

Subgroup 2 (25 males + 25 females) These were subjected to:

1. **Water maze test:** postpartum day 43 ± 3.
2. **Percent regular estrous cycles:** postpartum day 60
3. **Testes examination:** postpartum day 60 ± 1 & necropsy
4. **Necropsy of females of SUBGROUP 2:** after estrous cycle check.

Subgroup 3: (15 males + 30 females)

PREMATING:
1. **Clinical signs:** postpartum days 45, 60, 75, 90, 105.
2. **Body weights:** postpartum days 45, 60, 75, 90, 105.

Mating of rats of Subgroup 3: On postpartum day 110 ± 10, house 1 ♂ and 2 ♀♀ for 14 days. (avoid mating siblings)

Females presumed to be pregnant were allowed to litter.

Males: necropsy after the mating period.

POSTMATING:
1. **Clinical signs:**
2. **Body weights:**
3. **Partum:** Duration of gestation, problems at labor.
4. **Necropsy:**

Females that delivered after weaning(postpartum day 21)
Females that did not deliver: kill on postcoitum day 25.

Observations on F2 Generation:

1. **Litter size and viability**

2. **Body weights:** on postpartum days 1, 4 and 21.
3. **Mortality:** on postpartum days 1, 4 and 21.
4. **Necropsy:** all F2 pups on postpartum day 21.

RESULTS:

I. **OBSERVATIONS ON F0 GENERATION:**

1. **Mortality:** None; one female (A15) died during lactation period, death caused by cage overflowing of water,

2. **Fertility:** It was in the normal range.

3. **Maternal Body Weights during Gestation & Lactation:** Similar to control values. A treatment related increase in body weight gain was observed between gestation day 7 and 14 and between lactation day 1 and 21.

4. **Clinical Signs:** No relevant signs.

5. **Necropsy of F0:** No adverse findings; exception that 5 females each of groups B, C, and D were not pregnant.

6. **Post-implantation Loss:** These ranges between 5.9 (250 mg/kg) and 10.9 (500 mg/kg), these values were in the normal range.

II. **OBSERVATIONS ON F1 GENERATION:**

II A. **All F1 Generation Pups:**

1. **Partum, litter size and viability:** Spontaneous deliveries occurred in normal period. The survival index was normal in all groups.

2. **Body Weights:** These were normal.

3. **Morphological Development:** Eye opening and pinna detachment were normal.

4. **Behavioral Development:** Postural adjustment, righting reflex, and auditory reflexes were normal.

II B. **F1 Generation SUBGROUP 1:**

1. **Rota-rod Test:** In all groups improvements in performances were observed; the best results were observed in the control and high-dose groups.

2. **Thermoregulation Test:** At 50th day were normal.

II C. F1 Generation SUBGROUP 2:

1. **Water maze Test:** Mean times of escape were similar for all experimental groups,

2. **Estrous Cycle:** The percentage of regular estrous cycle verified at the second month of life was in normal range.

3. **Testes Examination:** At gross necropsy, one rat was found to have hypotrophic testes that weighed 0.8 g. Absolute and relative testes weights did not show any significant difference.

II D. F1 Generation SUBGROUP 3:

1. **Pre-mating period- body weights:** The body weight trend from weaning to mating was regular for both sexes in all experimental groups.

2. **Mating:** The fertility rate of F1 generation was satisfactory in all groups.

3. **Body Weight:** The mean body weight of pregnant females showed significantly lower values in low- and high-dose groups at post-partum day 21.

4. **Partum:** Mean gestation lengths were similar in all groups.

III. NECROPSIES OF F1 GENERATION: No gross changes were observed.

1. **Post-implantation loss:** These ranges between 1.8% (high-dose) and 9.3% in controls.

IV. OBSERVATIONS ON F2 GENERATION:

1. **Litter size & Viability:** The survival index normally ranged from 95.9% in mid-dose to 98.6% in controls. The mean number of viable fetuses at birth and at weaning were similar in all groups.

2. **Body Weight:** The mean body weight values presented statistical significance at different scheduled times and for different groups. However, these reductions were not dose related and were without toxicological meaning since they were within 10% in comparison with control group.

Mean body weights of F2 generation were lower than those of F1 generation; this difference was possibly

due to larger litter size of F2 generation not subjected to culling at birth.

3. **Necropsy:** No gross changes were observed in all F2 generation animals.

Conclusions:

- The administration of Z-1282 did not affect any parameters in F0 generation not even at high dosage.

- The parameters measured in F1 generation (body weight, morphological development, behavior tests) were in all instances in the range of normality.

- The reproductive performance of F1 generation was unaffected by drug treatment.

- The observation in F2 generation during lactation period (body weight and viability) did not show any differences among the groups.

29. Perinatal and Postnatal Reproduction Study of Fosfomycin Trometamol administered Orally via Gavage to Female Rats(Segment III Evaluation. Ref. # 32. Protocol 406-005

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated January 17, 1994.

Study Dates:

Arrival Date of Rats:	7/27/93
Mating Period:	8/8/93 - 8/13/93
Dosage Period (gestation day 15 thru postpartum day 25)	8/24/93 - 9/25/93

Material Tested: Fosfomycin Trometamol; Lot 06700/30888

Test Article Preparation: Solutions of Fosfomycin Trometamol were prepared daily at concentrations of **0, 25, 50 and 100 mg/ml,** such that dosages of **0(vehicle), 250, 500 and 1000 mg/kg/day,** respectively were administered at a volume of **10 ml/kg.**

Animals: :CD BR VAF/Plus [Sprague-Dawley] rats; 25 pregnant rats/group.

Dose Selection: By the Sponsor.

Dose Groups:

Group	Dose* (mg/kg/day)	No. of Rats Female Rats	Rat Numbers Pregnant Females
I	(vehicle)	25	
II	250 (133.2)	25	
III	500 (266.3)	25	
IV	1,000 (532.6)	25	

* Equivalent fosfomycin content in parenthesis.

Treatment: Rats were dosed orally (via gavage) once daily from day 15 of presumed gestation through day 25 of lactation.

Results:

- No deaths occurred before schedule sacrifice and all pregnant dams delivered litters.

- Soft or liquid feces occurred in one mid-dose group rat and in 18 ($P \leq 0.01$) high-dose rats during the lactation period. All other clinical and necropsy observations were unrelated to the test article.

- Body weight gains and body weights were slightly increased (day 15 to 20 of gestation) in low-dose and higher doses of Fosfomycin Trometamol. On day 20 of gestation all average body weights were within 4% of the control value. Body weight gains for days 15 to 20 of gestation were 9.7%, 5.2% and 14.1% above the control group value for the low-, mid- and high dose groups, respectively. These increases in body weight gains were statistically significant ($P \leq 0.01$) in the mid- and high dose groups on days 4 to 7 of lactation and for the entire lactation period. Reflecting the increased body weight gains in the three drug-treated groups, body weights were significantly increased ($P \leq 0.05$ to $P \leq 0.01$) in the mid- and high dose groups on days 7 thru day 21 of lactation.

- Absolute (g/day) and relative (g/kg/day) feed consumption values were significantly reduced ($P \leq 0.05$ to $P \leq 0.01$) on days 15 to 20 of gestation in all drug-treated groups; relative feed consumption values on days 0 to 21 of gestation were significantly reduced ($P \leq 0.01$) in the low- and high dose groups.

During lactation, absolute feed consumption values were significantly increased ($P \leq 0.05$ to $P \leq 0.01$) in the three drug-treated groups; relative feed consumption values were comparable and did not significantly differ during lactation.

- Administration of Fosfomycin Trometamol at doses as high as 1000 mg/kg/day did not affect any parameter evaluated at natural delivery or during the 21-day lactation period (durations of gestation and parturition, averages for implantations and live litter sizes, number of indices, sex ratios, body weights and clinical and necropsy observations).

- Pup viability and growth were enhanced in the drug-treated groups; these groups had significantly fewer ($P \leq 0.05$ to $P \leq 0.01$) pups cannibalized or found dead on days 2 to 4 postpartum. The viability indices were significantly increased ($P \leq 0.01$) in the mid- and high dose groups. Pup body weights were significantly increased ($P \leq 0.05$ to $P \leq 0.01$) in the drug-treated groups on day 21 of lactation.

Reviewer's Comment:

Please note that all F^1 generations pups were sacrificed on 21 days postpartum [of F0 generation dams].

F1 generation pups were neither tested for behavioral nor reproductive performance [as was done in the Segment III study conducted by Zambon Laboratories].

MUTAGENICITY STUDIES:

A- In Vitro Non-Mammalian Cell System: Ref. # 33, 34, 35

Parameter	Salmonella typhimurium	Saccharomyces cervisiae	Schizosaccharomycees pombe
Study Ref. No	33	34	35
Laboratory	Zambon Research		
GLP Study-Year	Yes (1989)	No (1983)	No (1983)
Strain	TA-98,TA-100, TA-1535,TA-1537 TA-1538	Not applicable	Not applicable
Fosfomycin Tromethamine Concentration	10, 30, 100, 300,1000 mcg per plate	250, 500, 1000 ppm/plate*	250, 500, 1000 ppm/plate*
Result	No increase in the reversions in S. strains with or without metabolic activation	No significant increase in the frequency of genetic conversion with or without metabolic activation	No significant increase in the frequency of genetic conversion with or without metabolic activation

* Study with fosfomycin, not with fosfomycin tromethamine.

B- In Vitro Mammalian Cell System: Ref. # 36, 37

Parameter	Chinese Hamster Cells	Lymphocytes
Study Ref.#	36	37
GLP (Year)	Yes (1989)	Yes (1989)
Strain	V-79	Human
Fosfomycin Tromethamine	625 to 10,000 mcg/ml	46.4 to 10,000 mcg/ml
Results	in concentrations up to 36.8 mM did not increase the frequency of mutations.	in concentrations up to 10,000 mcg/ml did not increase the frequency of mutations.

Both studies were conducted by

C. **Mutagenicity Evaluation of Z-1282 in the In Vivo Mouse Micronucleus Test:** Ref. # 38.

This study was conducted by Zambon Farmaceutici S.p.A. Laboratories, Study No. 1159 in compliance with the FDA GLP requirements. The final report was dated 1987.

Material Tested: Z-1282, Lot No. 23 dissolved in water at concentrations of 600 mg/ml for group dosed at 12 g/kg, and 300 mg/ml for group dosed at 6 g/kg.

Animals: Charles River CD-1 mice 5 weeks old; 5/sex/group.

Groups: A total of 19 groups in which Z-1282 was administered at doses of 300- and 600 mg/kg was administered orally; cyclophosamide 50 mg/kg intraperitoneally served as positive control.

Methodology: Mice were killed at 24, 48, and 72 hours after the treatment. The bone marrows of both femora were taken in a centrifuge tube containing about 7 ml of fetal calf serum. The cells were spread on glass slides; 3 slides for each animal were prepared and the slides were stained by May-Gruenwald solution and counterstained by Giemsa stain. The slides were examined and one thousand polychromatic erythrocytes (PCE) per animal were scored for the incidence of micronuclei. The ratio of PCE to normochromatic erythrocytes was determined for each animal.

Results: One high-dose animals was found dead

- The positive control induced a high frequency of micronucleated PCEs' in comparison with the negative controls in both sexes.

- Animals exposed to Z-1282 showed no significant differences in micronucleus frequency at any dose level or killing time and the corresponding control values.

Conclusions: Z-1282 was considered non active in this assay.

PHARMACOLOGY:

Pharmacologic effects of fosfomycin tromethamine (Z-1282) on various organ systems and functions as well as drug interactions, as tabulated in the NDA, are reproduced below:

ORGAN SYSTEMS:

2.6.1.1 EFFECT OF Z-1282 ON THE CENTRAL NERVOUS SYSTEM (Ref. 1)

Study Parameter	Test Model	Route of Administration	Dose (mg/kg)	Effect on Parameter
General Behavior	Mouse	Oral	10,30,100,300,1000	No effect
	Mouse	Intraperitoneal	10,30,100,300,1000	Slight effect on spontaneous movement and alertness; ptosis -- at 300 & 1000 mg/kg with peak effect 1-2 hours after treatment
Body Temperature	Mouse	Oral	10,30,100,300,1000	No effect
	Mouse	Intraperitoneal	10,30,100,300,1000	No effect
Hexobarbital-induced Hypnosis	Mouse	Oral	3,10,30,100,300	No effect
Motor Coordination	Mouse	Oral	3,10,30,100,300	No effect
	Mouse	Intraperitoneal	3,10,30,100,300	No effect
Spontaneous Motility	Mouse	Oral	30,300	No effect
Pain Threshold: Acetic Acid Writhing	Mouse	Oral	10,30,100,300	No analgesic effect
Hot Plate	Mouse	Oral	300	No analgesic effect

2 6 1 2 EFFECT OF Z-1282 ON CARDIOVASCULAR AND RESPIRATORY SYSTEMS (Ref 1)

Study Parameter	Test Model	Route of Administration	Dose (mg/kg)	Effect on Parameter
Cardiovascular Function	Rat (anesthetized)	Intravenous	1000 -- infused at 17 mg/kg/minute for 60 minutes at a rate of 0 1 mL/minute	No effect on heart rate, systolic pressure, or ECG, slight increase in diastolic pressure at end of infusion
	Rabbit (anesthetized)	Intravenous	1000 -- infused at 17 mg/kg/minute for 60 minutes at a rate of 1 0 mL/minute	No effect on heart rate, systolic and diastolic pressures, or ECG, no effect on arterial blood pO_2, pCO_2, and pH
Respiratory Function	Rat (anesthetized)	Intravenous	1000 -- infused at 17 mg/kg/minute for 60 minutes at a rate of 0 1 mL/minute	No effect on respiratory frequency, tidal volume, minute volume, including inspiratory time (T_i) and expiratory time (T_e)
	Rabbit (anesthetized)	Intravenous	1000 -- infused at 17 mg/kg/minute for 60 minutes at a rate of 1 0 mL/minute	No effect on respiratory frequency, tidal volume, minute volume, including inspiratory time (T_i) and expiratory time (T_e)

2 6 1 3 EFFECT OF Z-1282 ON THE GASTROINTESTINAL SYSTEM (Ref 1)

Study Parameter	Test Model	Route of Administration	Dose (mg/kg)	Effect on Parameter
Intestinal Motility (Charcoal Propulsion)	Mouse	Oral	3,10,30,100,300	No stimulant or inhibitory effect by all oral doses on intestinal propulsion of charcoal
Intestinal Motility (Charcoal Propulsion)	Rat	Oral	30,300	No stimulant or inhibitory effect by both oral doses on intestinal propulsion of charcoal
Bile Secretion	Rat	Oral	100,300	No effect at either dose on bile volume secretion
Spontaneous fecal output	Rat	Oral	100,300	At both doses, a slight and transient, decreased fecal output observed first two hours after dosing, effect not dose-related
Intestinal Contraction Forskolin Tromethamine	In vitro	Organ Bath -- (G.Pig ileum)	2×10^{-5} M	No relaxant or contracting activity on smooth muscle
Acetylcholine-induced	In vitro	Organ Bath -- (G.Pig ileum)	2×10^{-5} M	No interference with action of acetylcholine
Histamine-induced	In vitro	Organ Bath -- (G.Pig ileum)	2×10^{-5} M	No interference with action of histamine
Serotonin-induced	In vitro	Organ Bath -- (G.Pig ileum)	2×10^{-5} M	No interference with action of serotonin
Calcium-induced	In vitro	Organ Bath -- (G.Pig ileum)	1×10^{-4} M to 5×10^{-4} M	No interference with action of calcium ions

MUSCULAR SYSTEM:

2.6.1.4.1 EFFECT ON SMOOTH MUSCLE (GUINEA PIG TRACHEA)

Study Parameter	Test Model	Route of Administration	Dose (concentration)	Effect on Parameter
Muscle Contraction: Fosfomycin Tromethamine	In vitro	Organ Bath -- (Tracheal Spirals)	2×10^{-3} M	No relaxant or contracting activity on smooth muscle
Acetylcholine-induced	In vitro	Organ Bath -- (Tracheal Spirals)	2×10^{-3} M	No interference with action of acetylcholine
Histamine-induced	In vitro	Organ Bath -- (Tracheal Spirals)	2×10^{-3} M	No interference with action of histamine
Calcium-induced	In vitro	Organ Bath -- (Tracheal Spirals)	1×10^{-4} M to 5×10^{-1} M	No interference with action of calcium ions

2.6.1.4.2 EFFECT OF Z-1282 ON STRIATED MUSCLE (RAT DIAPHRAGM)

Study Parameter	Test Model	Route of Administration	Dose Concentration	Effect on Parameter
Neuromuscular Transmission (Phrenic nerve-Diaphragm): Fosfomycin Tromethamine	In vitro	Organ Bath	1×10^{-4} M to 2×10^{-3} M	No inhibitory effect on transmission of nerve impulse or on blocking action at neuromuscular junction (receptor level)

SECONDARY PHARMACOLOGIC ACTION:

2.6.1.5.1 EFFECT ON PYREXIA

Study Parameter	Test Model	Route of Administration	Dose (mg/kg)	Effect on Parameter
Pyrexia (Yeast-induced)	Rat	Oral	30,300	No antipyretic effect observed in fevered rats at either dose

2.6.1.5.2 EFFECT ON DIURESIS AND KIDNEY FUNCTION

Study Parameter	Test Model	Route of Administration	Dose (mg/kg)	Effect on Parameter
Diuresis	Rat	Oral	30,100,300	At 30 and 100 mg/kg, no significant change in diuresis; at 300 mg/kg, a slight transient inhibition of urine output 60 minutes after dosing. Effect disappeared within 120 minutes after administration. Urine pH was not affected.
Kidney Function	Rat	Oral	250,500,1000 (4 & 15 days)	No changes in volume of urine output, specific gravity or composition of urine either on day 4 or on day 15. No effect on kidney structure and function.

2.6.1.5.3 EFFECT ON PLATELET AGGREGATION

Study Parameter	Test Model	Route of Administration	Dose (mg/kg)	Effect on Parameter
Platelet Aggregation (Aggregometry)	Rat (Ex vivo)	Oral	100,300	No modifying effect on aggregation of platelets even when obtained from rats previously treated at either dose level. Platelet aggregation induced in vitro by either arachidonic acid or collagen.
	In vitro	Platelet-rich plasma in test drug solutions	10^{-4} M, 10^{-3} M, 10^{-2} M	No modifying effect on aggregation of platelets induced in vitro by either arachidonic acid or collagen.

DRUG INTERACTION (ANIMALS)

2.6.1.6.1 EFFECT OF Z-1282 ON COMMONLY USED DRUGS (Ref. 2)

Drug Interaction Study	Test Model	Route of Administration	Dose (mg/kg)	Influence of each dose of Fosfomycin Tromethamine
Morphine (analgesic)	Mouse	Oral	3,10,30,100,300	No interaction demonstrated; did not modify analgesic effect of morphine
Diazepam (anticonvulsant)	Mouse	Oral	30,300	No interaction demonstrated; did not modify anticonvulsant activity of diazepam
Aminophylline (bronchodilator)	Rat	Oral	300	No interaction demonstrated; did not modify the bronchodilating response of aminophylline
Acetaminophen (antipyretic)	Rat	Oral	30,300	No interaction demonstrated; did not affect acetaminophen antipyretic activity
Hydrochlorothiazide (diuretic)	Rat	Oral	30,100,300	No interaction demonstrated; did not affect the diuretic effect induced by hydrochlorothiazide
Butylscopolamine (spasmolytic)	In vitro	Organ Bath -- (G.Pig ileum)	2×10^{-4} M	No interaction demonstrated; did not modify the effect of butylscopolamine on induced contractions of guinea pig ileum

2.6.1.6.2 EFFECT OF COMMONLY USED DRUGS ON Z-1282 (Ref. 3)

Drug Interaction Study	Test Model	Bacterial Strains	Influence on Effectiveness of Fosfomycin Tromethamine
Morphine (analgesic)	Mouse Septicemia	Staphylococcus aureus or Escherichia coli	No negative interaction apparent; antibiotic effectiveness retained
Diazepam (anticonvulsant)	Mouse Septicemia	Staphylococcus aureus or Escherichia coli	No negative interaction apparent; antibiotic effectiveness retained
Aminophylline (bronchodilator)	Mouse Septicemia	Staphylococcus aureus or Escherichia coli	No negative interaction apparent; antibiotic effectiveness retained
Acetaminophen (antipyretic)	Mouse Septicemia	Staphylococcus aureus or Escherichia coli	No negative interaction apparent; antibiotic effectiveness retained
Hydrochlorothiazide (diuretic)	Mouse Septicemia	Staphylococcus aureus or Escherichia coli	No negative interaction apparent; antibiotic effectiveness retained
Butylscopolamine (spasmolytic)	Mouse Septicemia	Staphylococcus aureus or Escherichia coli	No negative interaction apparent; antibiotic effectiveness retained
Ciprofloxacin (antibacterial)	Mouse Septicemia	Staphylococcus aureus or Escherichia coli	No negative interaction apparent
Cefonicid (antibacterial)	Mouse Septicemia	Staphylococcus aureus or Escherichia coli	Escherichia coli: No negative interaction; Staphylococcus aureus: Synergistic effect evident
Nitrofurantoin (antibacterial)	Mouse Septicemia	Staphylococcus aureus or Escherichia coli	No negative interaction apparent
Cotrimoxazole (antibacterial)	Mouse Septicemia	Staphylococcus aureus or Escherichia coli	No negative interaction apparent
Morphine	In vitro	21 Urinary + 2 Standard	Potentiation effect on Proteus sp and on Klebsiella sp
Diazepam	In vitro	19 Urinary + 2 Standard	Potentiation effect on Proteus sp. and on E. coli
Aminophylline	In vitro	21 Urinary + 2 Standard	No negative interaction
Acetaminophen	In vitro	21 Urinary + 2 Standard	No negative interaction
Hydrochlorothiazide	In vitro	16 Urinary + 2 Standard	No negative interaction
Butylscopolamine	In vitro	21 Urinary + 2 Standard	No negative interaction
Ciprofloxacin	In vitro	44 Urinary + 3 Standard	Additive effect on majority
Cefonicid	In vitro	44 Urinary + 3 Standard	Additive effect on majority
Nitrofurantoin	In vitro	44 Urinary + 3 Standard	Additive effect on majority
Cotrimoxazole	In vitro	44 Urinary + 3 Standard	Additive effect on majority

Absorption, Distribution, Metabolism & Excretion:

1. **The MOUSE:** **Ref. # 39**

Swiss albino female mice (total of 70) were administered fosfomycin tromethamine at a single dose of 30 mg/kg orally (gavage) and 10 mice/time interval were sacrificed at 15, 30, 60, 120, 240, and 360 minutes after drug administration.

Results:

Peak serum concentration of fosfomycin tromethamine was reached in mice within 15 minutes following dose. Recovery in urine was 28% for the first 6 hours, 55.8% after 24 hours.

C_{max} 8.65 ± 2.57 µg/mL

T_{max} 15 minutes

Urine Recovery: 6 hours: 27.8%
24 hours: 55.8%

2. **The RAT:** **Ref. # 40**

Sprague-Dawley female rats were administered fosfomycin tromethamine at a single dose of 50 mg/kg orally (gavage) and 6 rats/time interval were sacrificed at 0.5, 1, 2, 4, 8 hours after drug administration.

Results:

Peak serum concentration in rats occurred one hour after dose administration. Recovery in urine for the first 8 hours was 36.5%; after 24 hours 49.2%.

C_{max} 16.6 ± 3.55 µg/mL

T_{max} 1 hour

Urine Recovery: 8 hours: 36.5%
24 hours: 49.2%

3. **The DOG:** **Ref. # 41**

Group 1: Six Beagle male dogs were administered fosfomycin tromethamine at dose of 50 mg/kg in cachets orally once weekly over a period of 4 weeks.

Group 2: Six Beagle male dogs were administered fosfomycin tromethamine at dose of 500 mg/kg in cachets orally once weekly over a period of 2 weeks.

Blood samples were collected at 1/2, 1, 2, 3, 4, 6, 8 and 24 hours after dosing. Urine samples were collected at 6 and 24 hours after dosing.

Results:

Group 1: Peak serum concentration in dogs was observed at 2 hours after dosing (50 mg/kg). The urine recovery rate at 6 hours was 52.2%; after 24 hours 62%.

Group 2: After a single dose of 500 mg/kg, the peak serum concentration was observed at 2 hours. Urinary recovery was 22.9% of the dose during the first 6 hours; at 24 hours 41.6%

C_{max}	for 50 mg/kg dose	39.61 ± 12.78 µg/mL
C_{max}	for 500 mg/kg dose	91.33 ± 12.50 µg/mL
T_{max}	for both groups	2 hours

Urine Recovery:	50/6 hours:	52.2%
	500/6 hours:	22.9%
	50/24 hours:	62.0%
	500/24 hours:	41.6%

4. **Tissue Distribution and Mass Balance:** **Ref. # 43**

Male rats were administered a single oral (gavage) dose of fosfomycin tromethamine @ 50 mg/kg. Blood and plasma peak concentrations were achieved 1 hour after drug administration. In all organs (e.g. brain, thymus, adrenals, stomach, small intestine, bladder, kidneys, lungs, liver, spleen and heart) analyzed by mass spectroscopy/gas chromatography the peak concentrations were always obtained 1 hour after dosing. **The kidney was the target organ.** The highest C_{max} for all tissues analyzed was found in the kidney. The level of fosfomycin in kidney was about 5-times the concentration in plasma and about 7-times the concentration in blood at 1 hour post dosage. The next highest drug concentration was found in the lung and was 7-times less than in kidney.

Twenty-four hours after drug administration, fosfomycin was below limit of detection in blood and most tissues.

Forty-eight hours after drug administration, 89% of the dosage was recovered in urine and about 9% in feces as unchanged fosfomycin.

T_{max}	1 hour	
C_{max}	11.20 ± 1.60 μ mL (Plasma) 14.31 ± 3.46 μ mL (Blood)	
Urine Recovery:	0-8 hours:	56%
	8-24 hours:	0.3%
	0-24 hours:	79%
	0-48 hours:	88.5%
Feces Recovery:	24 hours:	10.5%
	48 hours:	11.6%

Tissue concentration (at T_{max})

Brain:	0.35 ± 0.33
Thymus:	3.64 ± 2.18
Adrenals:	4.67 ± 3.02
Stomach:	8.11 ± 3.83
Small Intestine:	149.93 ± 32.94
Bladder:	17.81
Kidneys:	74.86 ± 23.29
Lungs:	10.21 ± 4.96
Liver:	7.63 ± 2.90
Spleen:	4.51 ± 1.30
Heart:	8.50 ± 4.13

5. **Placental Transfer in Pregnant Rats:** **Ref. # 44**

Placental transfer of fosfomycin was determined in pregnant rats on gestational days 14 and 19 after giving a single oral (gavage) dose of 50 mg/kg.

Maternal Tissues: In maternal kidneys, liver and plasma, the highest levels of fosfomycin was found 2 hours after drug administration at gestation day 14 and 19. The concentrations of fosfomycin in the kidney were always higher than in liver or in plasma when compared at the same time interval. Fosfomycin concentrations at T_{max} were 12 and 8.5 times greater in maternal kidneys than in maternal liver at gestation day 14 and 19, respectively. Kidney concentrations of fosfomycin were 2.9 - 3.8 times greater than plasma concentrations when measured at 2, 4, 6 and 24 hours after dosing on gestation day 19. The levels of fosfomycin were below the level of detection in plasma, kidneys and liver 24 hours post dosing on gestation day 14. However, the levels of fosfomycin were still detectable in plasma, kidneys and placenta 24 hour post dosing on gestation day 19.

Fetal Tissues: **Fosfomycin readily crossed the placenta.** Fosfomycin was detectable in the fetus pool at gestation day 14 and in fetal kidney and liver up to 6 hours after dosing on gestation day 19. The fetal kidney, as in the case of maternal kidney, was the major site of accumulation of fosfomycin. Maximal accumulation of fosfomycin either in the fetal pool or in fetal kidney and liver was between 2-4 hours post dosage. In contrast, maximal accumulation in amniotic fluid occurred between 2-4 hours post dosage. At gestation day 14 the levels of fosfomycin in the fetal pool were below the level of detection 24 hours post dosage. At gestation day 19 fosfomycin was detectable only in amniotic fluid.

6. **Toxicology of Degradation Products of Fosfomycin Tromethamine:** Ref. # 45

TOPKAT Toxicity Estimation Report for Forest Laboratories dated 8 August 1994. This report was written by **Ref. # 45.**

Background: During the conduct of stability studies of Fosfomycin Tromethamine under various conditions, four degradants were identified as: [for structures, see NDA vol. 12, pp 2-00233-234]

Degradant A: 1-Hydroxy-2-trometamoyloxy-n-propyl Phosphonic Acid.
Degradant B: Trometamol Phosphate Ester.
Degradant C: Trometamoyloxy Fosfomycin Dimer
Degradant D: 1,2-Dihydroxypropylphosphonate

This report is based on computations of a computer software program called The report states:

Reviewer's Comment: I have included this report to identify the degradants of fosfomycin tromethamine. This is neither an in vitro nor in vivo study. I find difficult to evaluate this report.

Comments:

1. Fosfomycin tromethamine was developed by Zambon Group, S.p.a. Italy.

2. The applicant's proposed use is a single oral dose of 3 gram of Fosfomycin tromethamine. This would be equivalent to a single exposure @ 60 mg/kg in a 50 kg person.

3. Preclinical toxicology studies of up to 12-13 week in the rat and 4 to 26 weeks in the dog were submitted and reviewed.

   The **lowest** No-adverse effect level(NOAEL) of 100 mg/kg/day reported in the 4-week dog study is 1.67 times the human dose. However, the actual safety margin would be larger since the comparison was based upon a subchronic toxicology study whereas human exposure is based upon single dosage use. [In other subchronic studies the NOAEL was generally 1,000 mg/kg/day or about 10.7 times the human dose.]

4. Fosfomycin tromethamine was first approved in Italy in 1986. Since then it has been marketed abroad, e.g. since 1992 as MONURIL in U.K. Thus, the drug has a history of human exposure abroad.

5. Increased abortions, fetal resorptions and reduced fetal body weights, noted in the teratology study in the rabbit, were associated with the antibiotic action on intestinal microflora in dams. This was due to unique susceptibility of the rabbit to antibiotics; generally rabbit is not considered a choice species for terata studies for antibiotics.

   The applicant' proposed Pregnancy Category [no terata effects] should be changed to Pregnancy Category The terata effects noted were: wavy ribs and delayed/retarded ossification of bones in the rat; increased abortions, fetal resorptions and reduced fetal body weights in the rabbit.

Recommendation:

I see no objection from the safety standpoint to the approval of this NDA; however, the Pregnancy Category should be changed from in the labelling.

1/6/95

S.R. Joshi, D.V.M., Ph.D.

cc:
Orig. NDA
HFD-340
HFD-520
HFD-520/Pharm/Joshi
HFD-520/MO/Screth
HFD-520/Chem/Roy
HFD-520/CSO/Dillon-Parker
HFD-520 /rd init. by REOsterberg
R/D/11/14/94/FT/1/6/95/SRJ
N-50-717.FOS

Concurrence Only
HFD-520/Dep.Dir/L.Gavrilovich
HFD-520/SPharm/REOsterberg

1/5/95

1/18/95

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation & Research

Date: August 4, 1996

To: NDA 50-717 Files, Monuril™ (fosfomycin tromethamine) Sachet

From: Pharmacology Team Leader, Division of Anti-infective Drug Products, HFD-520 8/4/96

Subject: NDA 50-717 (NDA Original Amendment dated 6-28-96); Pharmacology Amendment

Through: Lillian Gavrilovich, M.D., Deputy Director, Division of Anti-Infective Drug Products, HFD-520 8/12/96

The sponsor's submission argues that fosfomycin's pregnancy category should be Category and the submission provides additional analysis to support their claim. The sponsor claims that the incidences of wavy ribs and delayed ossification of the pelvis, ischia and sternal centra of rats were the consequence of the high dose (1000 mg/kg/day) in producing maternal toxicity. It has been the position of the pharmacology group to view wavy ribs and delays in ossification in foeti at doses which are maternally toxic as consequences of maternal toxicity and **not** as a direct effect upon the foeti. Thus, I can support the sponsor's claim for a Pregnancy Category in this case.

In the rabbit, increased abortions, fetal resorptions and reduced fetal body weights were produced by the drug. However, both Dr. Joshi and I agree that since rabbits appear to be an inappropriate specie for the evaluation of the fetotoxic potential of an antimicrobial, the results reported for the rabbit study are also due to perturbations in the intestinal flora and subsequent nutritional changes in the dams. Thus these fetal changes have **not been directly** induced by the drug. This information also supports the sponsor's contention that Monuril™ be given a Pregnancy Category

cc:
NDA Files
HFD-520 (Joshi)
HFD-520 (Feigal)
HFD-520 (Soreth)
HFD-520 (DeBellas)

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

Date CDER Received: 06/28/96
Date Assigned: 07/12/96
Date Review Started: 07/17/96
Date 1st. Draft Completed: 07/30/96
Date Review Accepted by Team Leader: 08/01/96

NDA # 50-717 (NDA Orig. Amendment dated 6/28/96)

Number of Volumes: One

Drug: **Monuril™ (fosfomycin tromethamine) Sachets**

Sponsor: **Zambon Corporation, East Rutherford, NJ.**

U.S. Agent: **Forest Laboratories, Inc., New York, NY**
Contact Person: **Michael M. Rosen, Ph.D. 212/421-7850**

Category: Antibiotic.

Human Dosage: A single dose of 3-grams powder dissolved in 4 oz.
(proposed) of tap water.

Indication: Urinary tract infection (uncomplicated)

Review Objective:

In my review dated 1/18/95 of the original NDA, I had recommended that the pregnancy category should be changed from

In this amendment the applicant has submitted a write-up on the [reproductive] developmental toxicity in the rat and the rabbit to support their proposed Pregnancy Category [rather than the recommended Pregnancy Category

The applicant suggests that because of maternal toxicity and/or the injury during dosing on day 15, the terata noted in 8 pups of rat be excluded from the results.

Review & Comments:

I have reviewed again the rat teratology study conducted by . I have prepared a Table (see attached) specifically with regard to skeletal abnormalities in all high dose rats and after excluding rat

Please note the following:

- the incidence of wavy ribs was not affected;

- The incidences of abnormalities in the pelvis and ischia of litters were still statistically highly significant ($p > 0.01$).

- The incidence of abnormalities in sternal centra were numerically very close; 28.6% and 25.0% (litters) and 4.4% and 3.4% (fetuses) in all rats and after excluding rat

Increased abortions, fetal resorptions and reduced fetal body weights, noted in the teratology study in the rabbit, were associated with the antibiotic action on intestinal microflora in dams. This was due to unique susceptibility of the rabbit to antibiotics; generally rabbit is not considered a choice species for terata studies for antibiotics.

Recommendation:

The drug is approvable; Pregnancy category should remain

8/1/96

S.R. Joshi, D.V.M., Ph.D.

cc:
Orig.IND
HFD-340
HFD-520
HFD-520/Pharm/Joshi
HFD-520/MO/Soreth
HFD-520/Chem/Timper
HFD-520/Micro/Dionne
HFD-520/CSO/Debellas
HFD-520 /rd init. by REOsterberg
R/D/7/30/96/FT/8/1/96/SRJ
N-50-717.003
HFD-520/FONGAL

Concurrence Only
HFD-520/L.Gavrilovich
HFD-5200/TLPharm/REOsterberg

see Team Leader's memo attached 8/4/96

Table: Skeletal Abnormalities in Rats Treated with Fosfomycin

Skeletal Abnormality	Controls-All		High Dose (1000 mg/kg)			
			All (Prior to Exclusion)		After Exclusion*	
	Litter (n=21)	Fetuses (n=150)	Litter (n=21)	Fetuses (n=157)	Litter (n=20)	Fetuses (n=149)
Wavy Ribs	1 (4.8)	2 (1.3)	3 (14.3)	4 (2.5)	3 (15.0)	4 (2.7)
Sternal Centra - Summarization	1 (4.3)	1 (0.7)	6 (28.6)**	7 (4.4)**	5 (25.0)	5 (3.4)
Pelvis-Summarization	2 (9.5)	3 (2.0)	9 (42.8)**	15 (9.6)**	8 (40.0)**	9 (6.0)
Pubes-Incompletely Ossified	2 (9.5)	3 (2.0)	7 (33.3)**	13 (8.3)**	6 (30.0)	7 (4.7)
Ischia-Incompletely Ossified	2 (9.5)	3 (2.0)	6 (28.6)**	10 (6.4)**	5 (25.0)**	5 (3.4)
Pubes- Not Ossified	0	0	1 (4.8)	1 (0.6)	1 (5.0)	1 (0.7)

* After excluding litter of Rat
** P >0.01

stat

STATISTICAL REVIEW AND EVALUATION

NDA:	50-717
Generic Drug Name:	fosfomycin tromethamine
Drug Trade Name:	MONUROL™
Formulation:	oral powder in 3 gram sachet
Drug Class:	1S
Applicant:	Zambon Corporation, Division of Zambon Group, SpA

DEC 17 1996

Indications: uncomplicated urinary tract infections (acute cystitis)

Documents Reviewed: NDA Volumes 1, 8, 9, 10, 11, 12 dated May 17, 1996 submitted as original amendment for NDA 50-717.
NDA Volume 1 dated June 28, 1996 submitted as original amendment for NDA 50-717.
Electronic submission of data for study MON-US-03 dated July 25, 1996.
Statistical Review and Evaluation for NDA 50-717 dated August 18, 1995.
Medical Officer's reviews of Protocol MON-US-01 and MON-US-02.

Type of Review: Clinical/Statistical

Medical Officer:	Janice Soreth, M.D., HFD-520
Statistical Reviewer:	B. Sue Bell, Ph.D., HFD-725
Project Manager:	B. Duvall-Miller, HFD-520

I. Executive Summary

The applicant requests approval of a single 3 gm dose of fosfomycin tromethamine (MONUROL™) for the treatment of uncomplicated urinary tract infections (UTI) in women. To support the UTI indication, the applicant has submitted data from three domestic, randomized, parallel group, double-blind, double dummy studies which compare the safety and efficacy of a single 3 gm dose of fosfomycin tromethamine (FT) to one of the following: a 7 day course of ciprofloxacin (CP) 250 mg q. 12 h. (protocol MON-US-01), a 10 day course of trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 mg q. 12 h. (protocol MON-US-02), or a 7 day course of nitrofurantoin monohydrate/macrocrystals (NF) 100 mg q. 12 h.

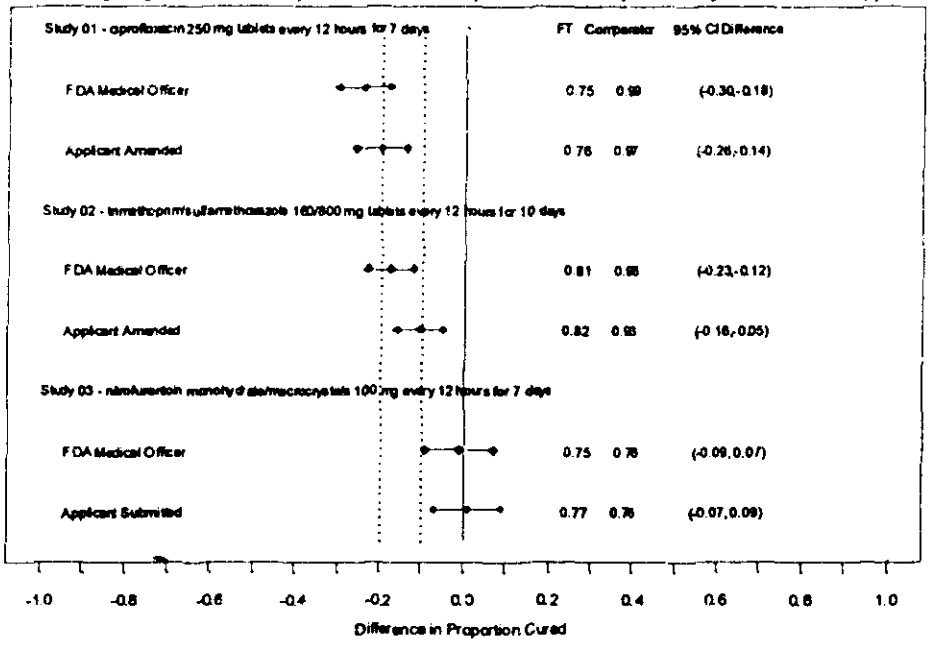
The primary efficacy variable is the rate of all bacteriologic eradication at 5-11 days after the longer course of treatment in the medical officer's evaluable patient group. Consistent with DAIDP's Points to Consider, the statistical comparison is based upon the two-sided 95% confidence interval of the difference in fosfomycin tromethamine rate minus the comparator's rate. The confidence intervals are reported as n_t, n_c (95% CI) p_t, p_c where n_t is the number in the test group, n_c is the number in the control group, p_t is the percent cured in the test group, and p_c is the percent cured in the control group.

The applicant's original request was based upon studies MON-US-01 and MON-US-02 and was not approved because these studies failed to show that FT was therapeutically equivalent in efficacy to either the CP or the TMP/SMX treatments for this indication. The 95% confidence intervals for these studies were $_{260,222}$ (-30% , -18%) $_{75\%,99\%}$ and $_{249,197}$ (-23% , -12%) $_{81\%,98\%}$ comparing FT to CP and FT to TMP/SMX, respectively. Since the efficacy percent of both comparator treatments is greater than 90%, DAIDP's Points to Consider requires that the confidence interval cross zero and that the lower bound be greater than -10%.

This amended application is based upon study MON-US-03 that shows FT is comparable to NF which is an approved drug for uncomplicated UTI. The 95% confidence interval for this study comparing FT to NF is $_{262,238}$ (-9% , 7%) $_{75\%,76\%}$. Since the efficacy percent of both treatments is in the range of 70% to 79%, DAIDP's Points to Consider requires that the confidence interval cross zero and that the lower bound be greater than -20% to establish equivalence of two treatments.

Included in the amended application was a revised analysis of the results of the first two studies performed by the applicant. In this analysis the applicant sought to follow the guidance provided in response to the original application. Figure 1 graphically compares the results of the applicant's and the medical officer's analysis of the data from each study. Even in the applicant's reanalysis, FT is still shown to be inferior to CP and TMP/SMX in the treatment of uncomplicated UTI in women.

Figure 1: 95% Confidence Intervals of Differences in Bacteriologic Eradication Rates of Single 3 gm Dose of Fosfomycin vs Multi-Dose Comparators at 5-11 Days after Longer Course of Therapy



Note: Per DAIDP's Points to Consider, in order to establish statistical equivalence the 95% CI must cross zero and remain within a lower bound of -0.10 when the effectiveness endpoint is greater than .80 or within -0.15 when .80-.89 effective or within -0.20 when .70-.79 effective.

Statistical evaluation of safety is based upon the Fisher's exact test comparing the rates of at least one adverse event in each of the treatment groups. A single dose of FT is not statistically different in safety from either CP (p=0.46) or NF (p=0.61). FT is statistically superior in safety to TMP/SMX (p=0.02). In all three studies, FT has a statistically significantly higher rate of diarrhea than its comparator with p-values of 0.04, <0.01, and 0.005 for CP, TMP/SMX, and NF, respectively.

II. Background

As discussed in the Executive Summary above, this application was not approved based upon the original submission. In this amendment, the applicant has provided an additional study MON-US-03, a revised analysis of the two earlier studies MON-US-01 and MON-US-02, and revised integrated summaries of efficacy and safety.

The focus of this review is study MON-US-03 and the updated integrated summaries of efficacy and safety. Refer to the Statistical Review and Evaluation dated August 18, 1995 for a detail review and analysis of studies MON-US-01 and MON-US-02.

III. Protocol MON-US-03

III.A. Study Design

The primary objective of the study was to compare the efficacy of a single dose of fosfomycin tromethamine (FT) (3 gm dose sachet) to nitrofurantoin monohydrate/macrocrystals (NF), 100 mg every 12 hours for seven days, in female patients with uncomplicated urinary tract infection. The secondary objective was to compare the safety profile of FT with that of NF. This study was designed as a prospective, parallel, active-controlled, multicenter trial with patients randomly allocated to either FT or NF. The primary efficacy endpoint was bacteriological cure. The total study period was seven weeks consisting of seven days of therapy plus 4-6 weeks follow-up. Patients assigned to the FT group received a 3 gm single dose of FT followed by placebo NF capsules every 12 hours for seven days. The patients who were assigned to the NF group were treated with the fosfomycin placebo sachet at the start of therapy, followed by NF capsules 100 mg every 12 hours for seven days.

Investigative sites through the United States were pre-qualified and then 27 appropriate centers were selected for study participation. Of these 27 centers, 26 actually enrolled patients. There was a target of 20 patients per center but 17 of the 26 centers failed to meet this goal with 8 centers enrolling less that 10 patients.

REVIEWER COMMENT: Investigators Costantini at study site 81 and Iravani at study site 87 were also participants in protocols MON-US-01 and MON-US-02. Further, these two investigators contributed a large proportion of the applicant's evaluable patients contributing 19%, 21% and 22% of protocols MON-US-01, MON-US-02, and MON-US-03, respectively. This raises a question as to the independence of these three studies. Investigators Harnack and Ginsburg participated in 2 of the 3 studies.

Although the application shows that investigator Liotti at study site 88 enrolled one patient who was randomized to receive NF (volume 1, page 10-01747), no data was provided for this patient in this center in the SAS datasets provided by the applicant.

Investigator Ginsburg was a participant in both protocols MON-US-02 and MON-US-03. Refer to the medical officer's report for MON-US-02 for a discussion of reasons why this investigator's data was excluded from analysis of MON-US-02's efficacy results. In MON-US-03, the bacteriologic cure rates for Ginsburg's site was 75% (12/16) for FT and 83% (10/12) for NF. Ginsburg's center was not excluded from the analysis of MON-US-03 since the cure rates were basically consistent with those observed at other sites and, unlike in MON-US-02 where it was the largest contributor of patients, this center contributed less than 6% and was ranked sixth of the 25 centers in MON-US-03. The applicant stated that the laboratory problems experienced in the previous study were addressed during the conduct of this study by changing laboratories (volume 1, page 10-01755). However, 35 of the 51 patients enrolled at this site had already been processed using the in-house laboratory. The applicant performed an analysis excluding this site and found that it did not affect the conclusions.

Non-pregnant, non-lactating females of age 12 or older with clinical signs and/or symptoms of uncomplicated UTI were eligible for enrollment. Patients with recurrent UTI or evidence of factors predisposing to the development of UTI were excluded. Also excluded were patients with onset of symptoms for this UTI episode > 96 hours earlier, symptoms suggestive of upper UTI, and patients with known or suspected hypersensitivity to either FT or NF.

Patients who met the inclusion/exclusion criteria (see medical officer's review for further details) were randomized and began receiving treatment before baseline urine culture results were known.

***REVIEWER COMMENT**: Although the protocol permitted the inclusion of females 12-17, only three 17-year-olds and one 15-year-old were included in the evaluable group. Two additional 17-year-olds were excluded as screening failures.*

The initial baseline visit occurred on study day 0 when interested and qualified patients reviewed and signed the informed consent document, took a pre-therapy pregnancy test, had their medical history documented, and received a physical examination including vital sign measurements. Clinical laboratory evaluation, urinalysis and a quantitative urine culture and susceptibility test of the isolated uropathogens were also done as part of the baseline evaluations. After randomization, a sachet of either placebo or study medication was administered in the office and patients were sent home with the appropriate NF or placebo capsules.

At two to four days after the first dose of study medication, patients were contacted by telephone to determine their medical status. Only patients with continuing or worsening symptoms were immediately evaluated in the clinic. Three follow-up visits to the clinic were required: Visit 2 (5-9 days after first dose), Visit 3 (11-15 days after first dose), and Visit 4 (4-6 weeks after last dose). At all clinic visits, vital signs were recorded, a clinical evaluation was made, a urine sample was obtained, analyzed and cultured, and adverse events were elicited. An exit physical examination was performed at Visit 4.

III.B. Efficacy

The primary efficacy endpoint was bacteriological cure and secondary endpoints included assessments of superinfection, recurrence or new infection and clinical response. A successful overall clinical response required both a bacteriological cure and the absence of UTI symptomatology. The applicant's primary bacteriological evaluation windows were study days 5 to 11 for FT and study days 11 to 17 for NF. The medical officer used study days 11 to 17 for both FT and NF. The applicant made four assessments of bacteriological response in three temporal windows. The assessments made were: Day 5-11 (Visit 2), Day 11-17 (Visit 3), After Day 17 (with respect to original uropathogen only), After Day 17 (taking into consideration not only the original uropathogen but also the incidence of new infection and recurrence). To distinguish between the two assessments made after Day 17, the evaluation that takes into consideration new infection/recurrence is hereafter called the "Final Visit" evaluation.

***REVIEWER COMMENT**: For this review, the bacteriological cure at the final visit 4-6 weeks after the last dose is based upon the medical officer's "all sustained eradication" from the statistical review of MON-US-01 and MON-US-02 and the applicant's reporting of "Final Visit" bacteriological results in the amended application.*

Bacteriological evaluations were based upon urine specimens obtained by the midstream clean catch technique. The baseline was based upon urine collected within 96 hours prior to starting treatment. The urine cultures were performed by the local laboratory associated with the clinical site. Bacteriological cure and failure rates were calculated for the evaluable population that included all patients who had $\geq 10^5$ CFU/mL of a known uropathogen on baseline culture and who either completed the study or were discontinued due to treatment failure or failure-related reasons.

Table 1 provides an accounting of the patients included in the ITT, the modified ITT, and the evaluable populations for both the applicant's and the medical officer's analysis. There is little difference between the applicant's and medical officer's evaluable groups. The medical officer reviewed the CRFs for those patients whom the applicant had discontinued and returned two FT treated patients and one NF treated patient to the evaluable populations.

Table 1: Applicant's and Medical Officer's accounting of patients enrolled in protocol MON-US-03.

	fosfomycin		nitrofurantoin		
	N	% of Total	N	% of Total	Total
Applicant's Analysis Groups					
Patients randomized (ITT)	375	50%	374	50%	749
Patients without 10^5 CFU/mL of a known uropathogen at baseline.	103	48%	113	52%	216
Patients with a baseline pathogen (MITT)	272	51%	261	49%	533
Patients excluded for reasons such as lost to follow-up or protocol violations.	12	33%	24	67%	36
Evaluable patient population	260	52%	237	48%	497
Medical Officer's Analysis Groups					
Patients randomized (ITT)	375	50%	374	50%	749
Patients without 10^5 CFU/mL of a known uropathogen at baseline.	103	48%	113	52%	216
Patients with a baseline pathogen (MITT)	272	51%	261	49%	533
Patients excluded for reasons such as lost to follow-up or protocol violations.	10	30%	23	70%	33
Evaluable patient population	262	52%	238	48%	500

***REVIEWER COMMENT**: In the NDA, the applicant used the term ITT to refer to the population that is normally referred to as the modified ITT population and used the term modified ITT for what is normally referred to as the evaluable or per protocol population. For consistency with the statistical reviews of the other two protocols included in this NDA and with other DAIDP reviews, the more conventional use of these terms will be used rather than the applicant's. Basically, the ITT population includes all randomized patients, the modified ITT population is a subset of the ITT population that includes those who were randomized and who have a baseline pathogen, and the evaluable population is a subset of the modified ITT population that excludes patients with protocol violations that are not related to treatment failure.*

***REVIEWER COMMENT**: Note that twice the patients were excluded from the NF arm as from the FT arm (12 for FT versus 24 for NF). This difference was due to NF losing more patients to follow-up and discontinuations due to adverse experience/intercurrent illness during the first few week of study drug administration.*

Bacteriological cure at a time point required that a urine culture be taken and that all of the uropathogens, found at baseline at levels $\geq 10^5$ CFU/mL, were reduced to levels $< 10^4$ CFU/mL. If more than one sample was taken within the window, the worst case was used.

***REVIEWER COMMENT**: Once a patient has been designated a bacteriological failure then that patient should be considered a bacteriological failure at all remaining visits. For 11 patients (6 in FT arm and 5 in NF arm) this did not appear to be the case. The CRFs for these patients were reviewed. Although the bacteriologic outcome at the applicant's primary assessment window did not require revision, most other assessments including the clinical outcomes and the final bacteriological outcome were reclassified from success to failure for these 11 patients.*

Table 2 summarizes the results from both the applicant's and the medical officer's primary outcome assessment which is bacteriological cure. As can be seen by the 95% confidence intervals of the difference in the percent cured by FT minus the percent cured by NF, FT is comparable to NF in bacteriological efficacy at all time points based upon the criteria established in DAIDP's Points to Consider. The confidence interval crosses zero and is within the lower bound of -20% required when the cure rate is between 70% and 80%.

Table 2: Applicant's and Medical Officer's bacteriological evaluation of the evaluable populations at three follow-up time points for protocol MON-US-03 where cured is the bacteriological eradication of the baseline pathogen.

	n cured / N evaluable	% cured	n cured / N evaluable	% cured	95% CI of difference in %
Applicant's Evaluation	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	200 / 260	77%	179 / 237	76%	(-7%, 9%)
by 5-11 days post therapy	215 / 260	83%	179 / 237	76%	(-0%, 15%)
at final visit 4-6 weeks after last dose	170 / 260	65%	147 / 237	62%	(-6%, 12%)
Medical Officer's Evaluation	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	196 / 262	75%	180 / 238	76%	(-9%, 7%)
by 5-11 days post therapy	215 / 262	82%	180 / 238	76%	(-1%, 14%)
at final visit 4-6 weeks after last dose	164 / 262	63%	143 / 238	60%	(-7%, 11%)

By pathogen cure rates based upon the medical officer's evaluable population are provided in Table 3. This table includes those pathogens that the applicant included in the Indications and Usage section of their proposed label.

The assessment of UTI symptomatology was evaluated using a four point scoring system for six key UTI symptoms. The six UTI symptoms evaluated were the following: flank tenderness, suprapubic tenderness, dysuria, urinary urgency, urinary burning, and urinary frequency. The following scores were used: 0 for absent or normal, 1 for very mild or slight, 2 for moderate, and 3 for severe. A patient was classified as a cure if the six UTI symptoms assessed were all scored as 0 and no concomitant antibiotic for UTI was taken in the period from baseline evaluation to the relevant assessment. Table 4 presents both the applicant's assessment and the medical officer's assessment of clinical cure based upon symptomatalogy.

***REVIEWER COMMENT**: In reviewing the applicant's data, patients were found who had moderate to severe symptoms at a visit but who were classified as symptomatic successes at that visit. For consistency with the protocol, such patients were reclassified as failures for the medical officer's evaluation.*

Note that the applicant's clinical success rates for FT improves over time from 69% to 75% for the visit 5-11 days after the 1-day FT therapy and the visit 5-11 days after end of the 7-day NF therapy, respectively. This is because some patients were failures at the visit during study days 5-11 but were free of symptoms at the visit during study days 11-17. In the medical officer's assessment, these failures should be carried forward as failures. When considered in conjunction with other misclassifications, the result is that the medical officer's clinical success rates are 68% and 63% for the visit 5-11 days after the end of the 1-day FT therapy and the visit 5-11 days after the and of the 7-day NF therapy, respectively.

The applicant also included an outcome of "overall clinical assessment" which was derived from requiring both a bacteriological success and a clinical success. However, the focus of this review is on the bacteriological outcome and the clinical symptomalogical outcome considered independently rather than in a derived combination.

Table 4: Applicant's and Medical Officer's evaluation of clinical symptoms in the evaluable populations at three follow-up time points for protocol MON-US-03 where clinical cure requires relief of UTI symptoms.

	n cured / N evaluable	% cured	n cured / N evaluable	% cured	95% CI of difference in %
Applicant's Evaluation	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	196 / 260	75%	182 / 237	77%	(-9%, 6%)
by 5-11 days post therapy	180 / 260	69%	182 / 237	77%	(-16%, 1%)
at final visit 4-6 weeks after last dose	183 / 260	70%	156 / 237	66%	(-4%, 13%)
Medical Officer's Evaluation	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	164 / 262	63%	183 / 238	77%	(-23%,-6%)
by 5-11 days post therapy	177 / 262	68%	183 / 238	77%	(-18%,-1%)
at final visit 4-6 weeks after last dose	144 / 262	55%	154 / 238	65%	(-19%, -1%)

Subgroup analysis for age, race, and weight was performed on the key bacteriological and clinical outcomes. Table 5 below presents the results for the subgroup analysis at 5-11 days post therapy in the applicant's evaluable group based upon the bacteriological cure rates. As can be noted by the p-values of the statistical tests, there were no differences between the levels in any of the subgroups. This was also the case for the clinical outcome as well as at the 4-6 week follow-up visit.

Table 5: Analysis of bacteriological efficacy by subgroup based upon rate of bacteriologic cure at 5-11 days post therapy in the applicant's evaluable group for protocol MON-US-03.

Subgroup	n cured / N evaluable	% cured	n cured / N evaluable	% cured	p-value Fisher's Exact	p-value Breslow-Day
	fosfomycin		**nitrofurantoin**			
< 45	188 / 220	85%	158 / 194	81%	0.29	0.557
45-65	18 / 25	72%	17 / 32	53%	0.18	
>65	9 / 15	60%	4 / 11	36%	0.43	
caucasian	180 / 221	81%	156 / 203	77%	0.28	0.184
black	22 / 24	92%	19 / 27	70%	0.08	
other	13 / 15	87%	4 / 7	57%	0.27	
< 110 pounds	14 / 16	88%	13 / 14	93%	1.00	0.539
110-150 pounds	139 / 168	83%	107 / 147	73%	0.04	
> 150 pounds	62 / 76	82%	59 / 76	78%	0.69	

III.C. Safety

In this clinical study, 192 of 375 (51%) FT-treated patients and 184 of 374 (49%) NF-treated patients reported at least one adverse event during the study period. A total of 417 adverse events were reported by FT-treated patients and 392 events were reported by NF-treated patients. The majority of these adverse events were considered to be mild to moderate in severity. Table 6 presents the adverse events experienced by greater than 1% of the patients by body system. Significantly more FT-treated patients reported diarrhea (14.7% versus 8%) and significantly more NF-treated patients reported pruritus (1.6% versus 0%). Seven patients in the FT group and 16 in the NF group were discontinued from the study due to an adverse event or intercurrent illness. No patient experienced a serious adverse event.

Table 6: Occurrence of Adverse Events in 1.0% or more of patients enrolled in protocol MON-US-03

Body System	Adverse Events	FT (N = 375) Number of Patients	FT (N = 375) % of Patients	NF (N = 374) Number of Patients	NF (N = 374) % of Patients	p-value Fisher's Exact
Body as a whole	headache	38	1.0	45	12.0	0.418
Body as a whole	pain	15	4.0	16	4.3	0.857
Body as a whole	back pain	13	3.5	11	2.9	0.836
Body as a whole	abdominal pain	12	3.2	5	1.3	0.139
Body as a whole	asthenia	3	0.8	6	1.6	0.340
Body as a whole	fever	2	0.5	5	1.3	0.286
Body as a whole	flu syndrome	2	0.5	4	1.1	0.451
Digestive	diarrhea	55	14.7	30	8.0	**0.005**
Digestive	nausea	25	6.7	32	8.6	0.339
Digestive	dyspepsia	8	2.1	12	3.2	0.376
Digestive	vomiting	2	0.5	8	2.1	0.063
Digestive	flatulence	2	0.5	4	1.1	0.451
Nervous	dizziness	13	3.5	10	2.7	0.673
Nervous	somnolence	4	1.1	0	0.0	0.124
Respiratory	rhinitis	16	4.3	22	5.9	0.324
Respiratory	pharyngitis	15	4.0	11	2.9	0.550
Respiratory	sinusitis	8	2.1	6	1.6	0.789
Respiratory	bronchitis	5	1.3	3	0.8	0.725
Respiratory	cough increased	5	1.3	0	0.0	0.062
Skin and skin structures	rash	2	0.5	7	1.9	0.107
Skin and skin structures	pruritus	0	0.0	6	1.6	**0.015**
Urogenital	vaginal moniliasis	18	4.8	17	4.5	1.000
Urogenital	vaginitis	14	3.7	13	3.5	1.000
Urogenital	dysmenorrhea	8	2.1	8	2.1	1.000
Urogenital	urinary frequency	6	1.6	4	1.1	0.752
Urogenital	dysuria	5	1.3	6	1.6	0.773
Urogenital	Urine abnormalitities	0	0.0	4	1.1	0.062

IV. Integrated Summaries of Efficacy and Safety

IV.A. Efficacy

Table 7 presents the medical officer's bacteriological evaluations of all three clinical trials that have been submitted in support of this NDA. The medical officer's test of cure is at the time point that is 5-11 days after the longer treatment arm. The applicant's primary assessment point was at 5-11 days after end of therapy. A long term follow-up was captured at 4-6 weeks after the end of therapy.

***REVIEWER COMMENT**: In the NDA, the applicant suggested making the test of cure window at 5-11 days after the start of therapy. Use of this time point implies that test for cure for the longer treatment arms be made while patients are still on therapy which is unacceptable. For the NDA submission, the applicant used as their test of cure a window 5-11 days after the end of therapy. This required an additional visit so that patients came in at what would have been 5-11 days after the end of each treatment arm. This was consistent with the choice of a primary efficacy window by the statistical reviewer of the first two studies. However, the medical officer's primary efficacy window is 5-11 days after the end of the longer therapy. The sponsor will be sensitive to the medical officer's choice of a test of cure window because it reduces their efficacy by 3%, 4%, and 7% for studies MON-US-01, MON-US-02, and MON-US-03 respectively. This reduction in apparent efficacy is most likely due to the potential for self-reinfection during the additional week of therapy required for the comparator arms At 4-6 weeks the efficacy of FT drops by 14% in the pooled studies in contrast with a drop of 10%, 11% and 16% for ciprofloxacin, TMP/SMX, and nitrofurantoin, respectively.*

Table 7: Medical Officer's bacteriological evaluation of the evaluable population for each of the three UTI studies where cured is the bacteriological eradication of the baseline pathogen.

	n cured / N evaluable	% cured	n cured / N evaluable	% cured	95% CI of difference in %
Pooled Studies	**fosfomycin**				
by 5-11 days after longer therapy	591 / 771	77%			
by 5-11 days post therapy	630 / 771	82%			
at final visit 4-6 weeks after last dose	483 / 771	63%			
Study MON-US-01	**fosfomycin**		**ciprofloxacin**		
by 5-11 days after longer therapy	194 / 260	75%	219 / 222	99%	(-30%, -18%)
by 5-11 days post therapy	203 / 260	78%	219 / 222	99%	(-26%, -15%)
at final visit 4-6 weeks after last dose	158 / 260	61%	197 / 222	89%	(-36%, -20%)
Study MON-US-02	**fosfomycin**		**TMP/SMX**		
by 5-11 days after longer therapy	201 / 249	81%	194 / 197	98%	(-23%, -12%)
by 5-11 days post therapy	212 / 249	85%	194 / 197	98%	(-19%, -8%)
at final visit 4-6 weeks after last dose	161 / 249	65%	172 / 197	87%	(-31%, -15%)
Study MON-US-03	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	196 / 262	75%	180 / 238	76%	(-9%, 7%)
by 5-11 days post therapy	215 / 262	82%	180 / 238	76%	(-1%, 14%)
at final visit 4-6 weeks after last dose	164 / 262	63%	143 / 238	60%	(-7%, 11%)

Table 8 presents the applicant's bacteriological evaluations of all three clinical trials that have been submitted in support of this NDA. The source of this information was the NDA original amendment volume 1 of 1 stamped June 28, 1996. In this amendment, the applicant reanalyzed the first two studies, MON-US-01 and MON-US-02, to be consistent with the process used in the original medical and statistical reviews of these studies. By comparing with the above table of the medical officer's results, it can be seen that there are no striking differences in the two analyses. The applicant's results are biased slightly in their favor but not sufficient to change the conclusions from those that resulted from the medical officer's original analysis.

Table 8: Applicant's bacteriological evaluation of the evaluable population for each of the three UTI studies where cured is the bacteriological eradication of the baseline pathogen.

	n cured / N evaluable	% cured	n cured / N evaluable	% cured	95% CI of difference in %
Pooled Studies	**fosfomycin**				
by 5-11 days after longer therapy	629 / 801	78%			
by 5-11 days post therapy	673 / 801	84%			
at final visit 4-6 weeks after last dose	514 / 801	64%			
Study MON-US-01	**fosfomycin**		**ciprofloxacin**		
by 5-11 days after longer therapy	205 / 268	76%	237 / 245	97%	(-26%, -14%)
by 5-11 days post therapy	222 / 268	83%	237 / 245	97%	(-19%, -8%)
at final visit 4-6 weeks after last dose	164 / 268	61%	206 / 245	84%	(-31%, -15%)
Study MON-US-02	**fosfomycin**		**TMP/SMX**		
by 5-11 days after longer therapy	224 / 273	82%	222 / 239	93%	(-16%, -5%)
by 5-11 days post therapy	236 / 273	86%	222 / 239	93%	(-12%, -1%)
at final visit 4-6 weeks after last dose	180 / 273	66%	184 / 239	77%	(-19%, -3%)
Study MON-US-03	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	200 / 260	77%	179 / 237	76%	(-7%, 9%)
by 5-11 days post therapy	215 / 260	83%	179 / 237	76%	(-0%, 15%)
at final visit 4-6 weeks after last dose	170 / 260	65%	147 / 237	62%	(-6%, 12%)

Table 9 provides cure rates for those pathogens that the applicant included in the Indications and Usage section of the proposed label. Fosfomycin data has been pooled across the three studies. The data is reported for 5-11 days after the longer course of therapy, 5-11 days post-treatment, and 4-6 weeks post-treatment.

Table 10 provides both the medical officer's and the applicant's analysis of clinical efficacy for each of the three studies at each of the three follow-up time points. Also included is an a summary of fosfomycin's clinical efficacy pooled across the studies.

Table 10: Clinical evaluation by both the medical officer and the applicant for each of the three UTI studies where clinical success requires relief of symptoms.

	n cured / N evaluable	% cured	n cured / N evaluable	% cured	95% CI of difference in %
Medical Officer's Evaluable Population					
Pooled Studies	**fosfomycin**				
by 5-11 days after longer therapy	542 / 771	70%			
by 5-11 days post therapy	575 / 771	75%			
at final visit 4-6 weeks after last dose	461 / 771	60%			
Study MON-US-01	**fosfomycin**		**ciprofloxacin**		
by 5-11 days after longer therapy	189 / 260	73%	213 / 222	96%	(-30%, -17%)
by 5-11 days post therapy	199 / 260	77%	213 / 222	96%	(-26%, -13%)
at final visit 4-6 weeks after last dose	153 / 260	59%	196 / 222	88%	(-37%, -22%)
Study MON-US-02	**fosfomycin**		**TMP/SMX**		
by 5-11 days after longer therapy	189 / 249	76%	186 / 197	94%	(-25%, -12%)
by 5-11 days post therapy	199 / 249	80%	186 / 197	94%	(-21%, -8%)
at final visit 4-6 weeks after last dose	164 / 249	66%	173 / 197	88%	(-30%, -14%)
Study MON-US-03	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	164 / 262	63%	183 / 238	77%	(-23%, -6%)
by 5-11 days post therapy	177 / 262	68%	183 / 238	77%	(-18%, -1%)
at final visit 4-6 weeks after last dose	144 / 262	55%	154 / 238	65%	(-19%,-1%)
Applicant's Evaluable Population					
Pooled Studies	**fosfomycin**				
by 5-11 days after longer therapy	623 / 801	77%			
by 5-11 days post therapy	584 / 801	73%			
at final visit 4-6 weeks after last dose	580 / 801	72%			
Study MON-US-01	**fosfomycin**		**ciprofloxacin**		
by 5-11 days after longer therapy	208 / 268	78%	220 / 245	90%	(-19%, -6%)
by 5-11 days post therapy	205 / 268	76%	220 / 245	90%	(-20%, -7%)
at final visit 4-6 weeks after last dose	189 / 268	71%	211 / 245	86%	(-23%, -8%)
Study MON-US-02	**fosfomycin**		**TMP/SMX**		
by 5-11 days after longer therapy	219 / 273	80%	204 / 239	85%	(-12%, 2%)
by 5-11 days post therapy	199 / 273	73%	204 / 239	85%	(-20%, -5%)
at final visit 4-6 weeks after last dose	208 / 273	76%	199 / 239	83%	(-14%, 0%)
Study MON-US-03	**fosfomycin**		**nitrofurantoin**		
by 5-11 days after longer therapy	196 / 260	75%	182 / 237	77%	(-9%, 6%)
by 5-11 days post therapy	180 / 260	69%	182 / 237	77%	(-16%, 1%)
at final visit 4-6 weeks after last dose	183 / 260	70%	156 / 237	66%	(-4%, 13%)

IV.B. Safety

The applicant maintains that FT shows a more favorable safety profile when compared to TMP/SMX, an equal or better profile when compared to NF, and an equal profile when compared to CIPRO." Table 11 summarizes the adverse events for the three clinical trials conducted under protocols MON-US-01, MON-US-02, and MON-US-03. Statistical evaluation of safety is based upon the Fisher's exact test comparing the rates of at least one adverse event in each of the treatment groups. A single dose of FT is not statistically different in safety from either CP (p=0.46) or NF (p=0.61). FT is statistically superior in safety to TMP/SMX (p=0.02).

Table 11: Summary of adverse events in FT and comparator treatment groups in the ITT populations of MON-US-01, MON-US-02, and MON-US-03.

	FT (N=1233)		CP (N=445)		TMP/SMX (N=428)		NF (N=374)	
Category	n	%	n	%	n	%	n	%
Patients with AEs	567	46.0%	193	43.4%	212	49.5%	184	49.2%
Patients with Probably or Definitely Related AEs	81	6.6%	28	6.3%	45	10.5%	21	5.6%
Patients with Severe AEs	53	4.3%	18	4.0%	27	6.3%	21	5.6%
Patients with Serious AEs	3	0.2%	1	0.2%	5	1.2%	0	0.0%
Patients Discontinued due to all AEs	20	1.6%	6	1.3%	18	4.2%	15	4.0%
Patients Discontinued due to AEs Related to Drug	12	1.0%	5	1.1%	18	4.2%	11	2.9%

Table 12 provides a listing of the adverse events reported by 0.5% or more of the FT-treated ITT population. The number and percent reporting the adverse event in the comparator arms is also included in the table for comparison. In each of the three studies, FT has a statistically significantly higher rate of diarrhea than its comparator with p-values based upon a Fisher's exact test of 0.04, <0.01, and 0.005 for CP, TMP/SMX, and NF, respectively.

Table 12: Number and percentage of patients experiencing an adverse reaction in descending order by percent reporting the event in the FT-treated population

		FT (N=1233)		CP (N=445)		TMP/SMX (N=428)		NF (N=374)	
Body System	Adverse Events	n	%	n	%	n	%	n	%
Digestive	diarrhea	128	10.4%	19	4.3%	11	2.6%	30	8.0%
Body	headache	127	10.3%	42	9.4%	46	10.7%	45	12.0%
Digestive	nausea	64	5.2%	21	4.7%	43	10.0%	32	8.6%
Respiratory	rhinitis	55	4.5%	19	4.3%	13	3.0%	22	5.9%
Urogenital	vaginitis	52	4.2%	21	4.7%	17	4.0%	13	3.5%
Urogenital	vaginal moniliasis	42	3.4%	20	4.5%	9	2.1%	17	4.5%
Body	back pain	37	3.0%	13	2.9%	5	1.2%	11	2.9%
Urogenital	dysmenorrhea	32	2.6%	7	1.6%	5	1.2%	8	2.1%
Respiratory	pharyngitis	31	2.5%	7	1.6%	9	2.1%	11	2.9%
Nervous	dizziness	28	2.3%	14	3.1%	16	3.7%	10	2.7%
Body	abdominal pain	27	2.2%	5	1.1%	2	0.5%	5	1.3%
Body	pain	27	2.2%	6	1.3%	11	2.6%	16	4.3%
Digestive	dyspepsia	22	1.8%	7	1.6%	7	1.6%	12	3.2%
Body	asthenia	21	1.7%	2	0.4%	9	2.1%	6	1.6%
Skin and skin structures	rash	17	1.4%	5	1.1%	22	5.1%	7	1.9%
Respiratory	sinusitis	15	1.2%	5	1.1%	5	1.2%	6	1.6%
Respiratory	bronchitis	13	1.1%	1	0.2%	0	0.0%	3	0.8%
Body	flu syndrome	11	0.9%	4	0.9%	5	1.2%	4	1.1%
Urogenital	urinary tract infection	11	0.9%	4	0.9%	0	0.0%	2	0.5%
Digestive	vomiting	11	0.9%	2	0.4%	12	2.8%	8	2.1%
Respiratory	cough increased	10	0.8%	6	1.3%	4	0.9%	0	0.0%
Body	infection	10	0.8%	2	0.4%	4	0.9%	0	0.0%
Digestive	abnormal stools	9	0.7%	0	0.0%	0	0.0%	0	0.0%
Body	fever	7	0.6%	1	0.2%	6	1.4%	5	1.3%
Digestive	flatulence	7	0.6%	1	0.2%	4	0.9%	4	1.1%
Urogenital	urinary frequency	8	0.6%	1	0.2%	0	0.0%	4	1.1%
Urogenital	dysuria	6	0.5%	0	0.0%	1	0.2%	6	1.6%
Cardiovascular	migraine	6	0.5%	2	0.4%	1	0.2%	2	0.5%
Musculoskeletal	myalgia	6	0.5%	2	0.4%	0	0.0%	2	0.5%
Skin and skin structures	pruritus	6	0.5%	5	1.1%	9	2.1%	6	1.6%
Nervous	somnolence	6	0.5%	0	0.0%	2	0.5%	0	0.0%

V. Summary and Conclusions

Efficacy

Statistical evaluation of efficacy is based upon the two-sided 95% confidence interval of the fosfomycin tromethamine minus comparator difference in the rate of all bacteriologic eradication rate at 5-11 days after the end of the longer treatment arm in the medical officer's evaluable patient group. The confidence intervals are reported as n_t , n_c (95% CI) p_t , p_c where n_t is the number in the test group, n_c is the number in the control group, p_t is the percent cured in the test group, and p_c is the percent cured in the control group.

In study MON-US-01, the 95% confidence interval is $_{260\,,\,222}$ (-30% , -18%) $_{75\%,\,99\%}$ which demonstrates that a single dose of 3 gm fosfomycin tromethamine is therapeutically inferior in efficacy to 7 days of ciprofloxacin 250 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women.

In study MON-US-02, the 95% confidence interval is $_{249\,,\,197}$ (-23% , -12%) $_{81\%,\,98\%}$ which demonstrates that a single dose of 3 gm fosfomycin tromethamine is therapeutically inferior in efficacy to 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women.

In study MON-US-03, the 95% confidence interval is $_{262\,,\,238}$ (-9% , 7%) $_{75\%\,,\,76\%}$ which demonstrates that a single dose of 3 gm fosfomycin tromethamine is therapeutically equivalent in efficacy to 7 days of nitrofurantoin monohydrate/macrocrystals 100 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women.

Safety

Statistical evaluation of safety is based upon the Fisher's exact test comparing the rates of at least one adverse event in each of the treatment groups.

A single dose of 3 gm fosfomycin tromethamine is not statistically significantly different in safety from either 7 days of ciprofloxacin 250 mg q. 12 hr. or 7 days of nitrofurantoin monohydrate/macrocrystals 100 mg q. 12h.. In study MON-US-01, the rate of at least one adverse event is 46% (199/432) for fosfomycin tromethamine and 43% (193/445) for ciprofloxacin which produces a Fisher's exact p-value of 0.46. In study MON-US-03, the rate of at least one adverse event is 51% (192/375) for fosfomycin tromethamine and 49% (184/374) for nitrofurantoin which produces a Fisher's exact p-value of 0.61.

A single dose of 3 gm fosfomycin tromethamine is statistically superior in safety to 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12 h. In study MON-US-02, the rate of at least one adverse event is 41% (176/426) for fosfomycin tromethamine and 50% (212/428) for trimethoprim/sulfamethoxazole which produces a Fisher's exact p-value of 0.02.

In all three studies, fosfomycin tromethamine has a statistically significantly higher rate of diarrhea than its comparators. This is the only adverse even where the direction of the effect was consistent across all three studies. In study MON-US-01, the rate of diarrhea is 8% (33/432) and 4% (19/445) for fosfomycin tromethamine and ciprofloxacin, respectively (p=0.04). In study MON-US-02, the rate of diarrhea is 9% (40/426) and 3% (11/428) for fosfomycin tromethamine and trimethoprim/sulfamethoxazole, respectively (p<0.01). In study MON-US-03, the rate of diarrhea is 14.7% (55/375) and 8% (30/374) for fosfomycin tromethamine and for nitrofurantoin, monohydrate/macrocrystals respectively (p=0.005).

Subgroup analyses by age (18-44,45-65, and >65) and race (white, black, and other) did not reveal any noteworthy subgroup differen with respect to efficacy or safety.

Conclusion

A single dose of 3 gm fosfomycin tromethamine meets DAIDP's guidelines for establishing therapeutical equivalence in efficacy to 7 days of nitrofurantoin monohydrate/macrocrystals 100 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women. However, the label should indicate that this treatment is therapeutically inferior to treatments of either 7 days of ciprofloxacin 250 mg q. 12h. or 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12h. for this indication.

12/16/96

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12/17/96

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Archival: NDA 50-717
HFD-520
HFD-520/D. Feigal
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HFD-520/Project Manager/C. Debellas
HFD-725/BioStat/S. Bell
HFD-344/M. Thomas
Chron
This review contains 17 pages

STATISTICAL REVIEW AND EVALUATION

NDA: 50-717

AUG 18 1995

Applicant: Zambon Corporation/ Forest Laboratories, Inc.

Name of Drug: fosfomycin tromethamine (MONUROL™)

Documents Reviewed: NDA volumes 1.66-1.73, stamp dated Se[illegible]ber 29, 1994
Statistical Amendment (electronic data s[illegible]ion), dated January 5, 1995
Additional electronic data submitted by [illegible]t on May 18,1995
Medical Officer's electronic data (Study 01), received June 14, 1995
Medical Officer's electronic data (Study 02), received June 29, 1995
Draft Medical Officer's Review (Study 02), received July 5, 1995
Draft Medical Officer's Review (Study 01), received July 6, 1995

Indication: uncomplicated urinary tract infections (acute cystitis)

Medical Input: Janice Soreth, M.D., HFD-520

I. ABSTRACT

The applicant requests approval of a single 3 gm dose of fosfomycin tromethamine (MONUROL™) for the treatment of uncomplicated urinary tract infections. To support their indication, the applicant has submitted data from two domestic, randomized, parallel group, double-blind, double dummy studies which compare the safety and efficacy of a single 3 gm dose of fosfomycin tromethamine (FT) to either a 7 day course of ciprofloxacin (CP) 250 mg q. 12 h. (protocol MON-US-01) or a 10 day course of trimethoprim/sulfamethoxazole (TS) 160/800 mg q. 12 h. (protocol MON-US-02) in the treatment of women with uncomplicated urinary tract infections. The primary efficacy variable is the rate of all bacteriologic eradication at 5-11 days post treatment in the medical officer's evaluable patient group. In study 01, the eradication rate is 78% (203/260) for FT versus 99% (219/222) for CP [95% C.I.:(-26%, -15%)]. In study 02, the eradication rate is 85% (212/249) for FT versus 98% (194/197) for TS [95% C.I.:(-19%, -8%)]. The overall rate of adverse events is similar across treatments in study 01 [46% (199/432) for FT versus 43% (193/445) for CP, p=0.46], and lower for FT in study 02 [41% (176/426) FT versus 50% (212/428) for TS, p=0.02]. In both studies, FT had a higher rate of diarrhea than its comparator [study 01: 8% (33/432) versus 4% (19/445), p=0.04; study 02: 9% (40/426) versus 3% (11/428), p<0.01]. Compared to a 7 day course of ciprofloxacin 250 mg q. 12 h. or a 10 day course of trimethoprim/sulfamethoxazole 160/800 mg q. 12 h., a single 3 gm dose of fosfomycin tromethamine is inferior in efficacy, and does not have a substantial safety advantage for the treatment of uncomplicated urinary tract infections in women.

II. INTRODUCTION

The applicant requests the following indication in the **Indications and Usage** section of the proposed label:

The following treatment regimen is suggested in the **Dosage and Administration** section of the proposed label:

III. EVALUATION

III.A. STUDY DESIGN

MON-US-01 and MON-US-02 were domestic, randomized (1:1 ratio), parallel-group, active-controlled, double-blind, double-dummy, multicenter trials. Patients received either a 3 gm single oral dose of fosfomycin tromethamine packaged in a sachet, ciprofloxacin 250 mg tablets every 12 hours for seven days (study 01) or trimethoprim/sulfamethoxazole 160/800 mg tablets every 12 hours for ten days (study 02). To maintain the study blind, FT patients received 7 days (study 01) or 10 days (study 02) of placebo tablets, and CP or TS patients received a placebo sachet on the first day of therapy.

Non-pregnant, non-lactating females of age 18 or older with clinical signs and/or symptoms of uncomplicated UTI were eligible for enrollment. Patients who met the inclusion/exclusion criteria (see medical officer's review for details) were randomized to treatment before baseline urine culture results were known. According to protocol, if the baseline culture did not isolate an organism or an organism was isolated at insufficient quantities ($<10^5$ CFU) the patient was to be removed from the trial and treated according to the investigator's discretion.

By protocol convention, the baseline visit was designated as Visit 1. Four additional follow-up contacts (designated as Visits 1A, 2, 3, and 4) were required. The timing of these contacts in relation to study day is presented in Table 1. By convention, the first day of therapy was designated as study day 0, and all subsequent study days were defined in terms of the number of days after the first day of therapy. Note that due to the double-blind nature of the studies, all patients received either 7 days (study 01) or 10 days (study 02) of therapy. However, in reality, the FT patients only received one day of active therapy. Therefore, Table 1 also presents descriptions of the visit timing from both blinded and unblinded perspectives.

TABLE 1: Protocol Defined Visit Schedule

Visit	Study Day		Study Timepoint (treatment blinded)	Study Timepoint (treatment unblinded)
	MON-US-01	MON-US-02		
1	0	0	baseline assessment first day of therapy	FT: first day of therapy CP: first day of therapy TS : first day of therapy
1A	2-4	2-4	48-96 hrs after first dose of therapy	FT: 2-4 days post therapy CP: days 3-5 on therapy TS: days 3-5 on therapy
2	5-9	5-9	5-9 days after first dose of therapy	FT: 5-9 days post therapy CP: days 6-7 on therapy or 1-3 days post therapy TS: days 6-10 on therapy
3	11-15	14-18	5-9 days after last dose of therapy	FT: 11-15 days post therapy (Study 01) 14-18 days post therapy (Study 02) CP: 5-9 days post therapy TS: 5-9 days post therapy
4	34-48	37-51	4-6 weeks after last dose of therapy	FT: 5-7 weeks post therapy CP: 4-6 weeks post therapy TS: 4-6 weeks post therapy

The procedures performed at each visit are presented in Table 2. Note that Visit 1A was an optional clinic visit. However, a telephone contact was required. The noted evaluations for Visit 1A were performed only if the patient was symptomatic.

***REVIEWER COMMENT**: Laboratory parameters (hematology and blood chemistry) were not measured when FT patients were on therapy The earliest post baseline laboratory measurements for FT were taken at 5-9 days post therapy.*

TABLE 2: Protocol Defined Study Procedures

Assessment/Observation	Visit				
	1	1A[a]	2	3	4
Inclusion/Exclusion	✓				
Informed Consent	✓				
Randomization/Administration of Treatment[b]	✓				
Medical History	✓				
Physical Examination	✓				✓
Vital Signs	✓	✓	✓	✓	✓
Clinical Evaluation	✓	✓	✓	✓	✓
Pregnancy Test	✓				
Bacteriology (Urine Culture and Susceptibility)	✓	✓	✓	✓	✓
Urinalysis	✓	✓	✓	✓	✓
Hematology	✓		✓	✓	
Chemistry	✓		✓	✓	
Adverse Events	✓	✓	✓	✓	✓

[a] Visit 1A was an optional clinic visit. A telephone contact was required.

[b] The sachet and first tablet were administered under the observation of the investigator.

III.B. OUTCOME DEFINITIONS

III.B.1. BACTERIOLOGIC EFFICACY

III.B.1.a. APPLICANT

According to section 10.1 of the applicant's protocols, bacteriologic outcomes were defined as follows:

At early post therapy visit (Visit 2 for FT, Visit 3 for CP and TS) :

Cure: All initially susceptible pathogens ($\geq 10^5$ CFU) are reduced to $\leq 10^4$ CFU 5-9 days after the last dose of study medication.

Failure: Persistence of $\geq 10^5$ CFU of the initially susceptible pathogen. it will be considered a bacteriologic failure if the pathogen is present at levels $\geq 10^5$ CFU at 48-96 hours after the first dose of therapy or if the pathogen is initially eliminated at 48-96 hours after the first dose of therapy and is re-isolated at 5-9 days post therapy.

Superinfection: Growth of $\geq 10^5$ CFU of a different pathogen during therapy.

Impossible to Evaluate: A bacteriologic evaluation of cure or failure cannot be made due to, but not limited to such reasons as no bacterial pathogen isolated pretherapy, urine specimens not obtained at protocol specified time intervals, concomitant antimicrobial administration interfered with analysis, etc.

At late post therapy visit (Visit 4 for all treatments):

Recurrence: Growth of $\geq 10^5$ CFU of an initially susceptible pathogen at 4-6 weeks post therapy after demonstration of a bacteriologic cure.

New Infection: Growth of $\geq 10^5$ CFU of a different new pathogen at 4-6 weeks post therapy.

***REVIEWER COMMENTS**: These bacteriologic outcomes were assigned by the applicant's medical monitor. By design, the CRF collected information on each urine culture, but did not collect the investigator's interpretation of the urine culture information.*

By definition, the outcome of superinfection can occur only for CP or TS patients.

The outcomes of superinfection, recurrence, and new infection were evaluated individually in terms of yes/no responses. The applicant did not assign outcomes which account for all patients at 4-6 weeks post therapy. If a patient is a bacteriologic failure at 5-9 days post therapy, he/she should be designated as such at 4-6 weeks post therapy. If a patient is a bacteriologic cure at both time points, this should be reflected at the 4-6 week assessment. The outcome of new infection is mutually exclusive of the outcome of the initial infection; i.e., a patient may have eradication of the original infection with a new infection.

This reviewer performed an analysis of the applicant's data which accounts for all patients at the late post therapy visit using the following conventions:

Sustained Cure: bacteriologic cure at the early post therapy visit with documentation of no new infection or no recurrence at the late post therapy visit.

Sustained Cure with New Infection: bacteriologic cure at the early post therapy visit with documentation of a new infection at any time post therapy (timing of new infections was not available on the applicant's database) and with documentation of no recurrence at the late post therapy visit.

Recurrence: bacteriologic cure at the early post therapy visit with documentation of recurrence at the late post therapy visit.

Early Bacteriologic Failure: bacteriologic failure at the early post therapy visit

No Evaluation: no outcome recorded on the database for the early post therapy visit or for the late post therapy visit

Note that by protocol, visit timing was part of the definitions of the applicant's bacteriologic outcome. In section 3.8.3.1 of the study reports, the applicant extended the visit windows "In an effort to capture and analyze all available and appropriate data." The applicant's extended visit windows are presented in Table 3.

The fact that visit timing was linked to bacteriologic outcome is a major flaw in the applicant's analyses of the data. According to the applicant's definitions, a bacteriologic assessment had to be made exactly within the specified time window (see Table 3), or the medical monitor would assign patient's outcome as "Impossible

to Evaluate" or "No Evaluation". Clearly, this is an inappropriate way to handle treatment failures or recurrences, since these outcomes tend to occur at unscheduled visits. Furthermore, it is misleading to assign the outcome of "Impossible to Evaluate" or "No Evaluation" to patients who actually had assessments made, but were not within the specified time window. When the applicant assigned the outcome of "Impossible to Evaluate" or "No Evaluation" the reason for this outcome was not provided.

TABLE 3: Applicant's Window of Days for Bacteriological and Clinical Evaluations			
	TIME WINDOW (in terms of study day)		
Evaluation	FT	CP	TS
Pre-Primary (Used for superinfection)[a]	N/A	1-6	1-9
Pre-Primary (Used for new infection)	1-4	7-10	10-13
Primary (Used for primary efficacy evaluations and determination of new infection)	5-11	11-17	14-20
Post-Primary (Used for the determination of recurrence and new infection)	≥12	≥ 18	≥ 21

[a] Superinfection was not a possible outcome for patients in the FT group

III.B.1.b. MEDICAL OFFICER

The medical officer assigned bacteriologic outcomes as follows:

At early post therapy visit (Visit 2 for FT, Visit 3 for CP and TS):

Eradication: All pathogens with $\geq 10^5$ CFU at baseline are reduced to $<10^4$ CFU.

Eradication with New Infection: All pathogens with $\geq 10^5$ CFU at baseline are reduced to $<10^4$ CFU, with presence of a new pathogen at levels $\geq 10^5$ CFU during early post therapy period

Persistence: Any pathogen with $\geq 10^5$ CFU at baseline is present at $\geq 10^4$ CFU at least 48-96 hours after the first dose of therapy.

Presumed Persistence: Presence of clinical symptoms during the early post therapy period, but a urine culture was not taken at the same time as the clinical assessment.

At late post therapy visit (Visit 4 for all treatments):

Sustained eradication: All pathogens with $\geq 10^5$ CFU at baseline are reduced to $<10^4$ CFU during early post therapy and remain at $<10^4$ CFU during late post therapy.

Sustained Eradication with New Infection: All pathogens with $\geq 10^5$ CFU at baseline are reduced to $<10^4$ CFU during early post therapy and remain at $<10^4$ CFU during late post therapy, with presence of a new pathogen at levels $\geq 10^5$ CFU during late post therapy period.

Recurrence: Growth of $\geq 10^4$ CFU of an initially susceptible pathogen during late post therapy after demonstration of bacteriologic eradication during early post therapy.

Presumed Recurrence: Presence of clinical symptoms during the late post therapy period after demonstration of bacteriologic eradication during early post therapy, but a urine culture was not taken at the same time as the clinical assessment.

Early Bacteriologic Eradication/Clinical Failure With Concomitant Antibiotic: Patients who were clinical failure/bacteriologic eradication at early post therapy who were given a concomitant antibiotic for clinical symptoms, thus precluding a late post therapy bacteriologic assessment.

Early Persistence: Persistence or presumed persistence of pathogen during early post therapy period.

Early New Infection: Presence of new infection during early post therapy period.

***REVIEWER COMMENT**: By study protocol, FT patients had 3 post therapy visits (5-9 days, 11-15 days or 14-18 days, and 5-7 weeks post treatment) where as CP or TS patients had only 2 post therapy visits (5-9 days and 4-6 weeks post treatment). To make use of this extra piece of information for the FT group, the medical officer made the distinction between "early recurrence" and "late recurrence" only for FT patients. A FT recurrence was defined as "early" if it occurred on study day 12-17 (study 01) or study day 12-20 (study 02). A FT recurrence was defined as "late" if it occurred on study day ≥18 (study 01) or study day ≥21 (study 02).*

III.B.2. CLINICAL EFFICACY

III.B.2.a. APPLICANT

According to section 10.2 of the applicant's protocols, clinical outcomes were defined as follows:

At early post therapy visit (Visit 2 for FT, Visit 3 for CP and TS):

Cure: All pre-therapy signs and symptoms have subsided in a reasonable period of time with no evidence of their resurgence at the follow up visit 5-9 days post therapy.

Improvement: Most but not all pre-therapy signs and symptoms have subsided in a reasonable period of time without complete resolution at the follow up visit 5-9 days post therapy.

Failure: No apparent response to therapy. Persistence of all pre-therapy signs and symptoms at 5-9 days post therapy.

Unassessable: A clinical judgement of cure, improvement, or failure cannot be made due to, but not limited to such reasons as improper dose or length of therapy, concomitant antimicrobial therapy, no pathogen isolated, therapy discontinued due to adverse reactions, inadequate colony count, inadequate or no follow up cultures. The investigator will be required to state the circumstances which cause the case to be rated as non-evaluable.

***REVIEWER COMMENTS**: These clinical outcomes were assigned by the study investigators.*

Although the clinical signs and symptoms at each visit (flank tenderness, suprapubic tenderness, frequency, dysuria, burning, urgency) were assessed individually on a 4 point scale (0=absent/normal, 1=mild, 2=moderate, 3=severe), the overall clinical evaluation was not directly derived from these individual symptom scores.

By protocol and CRF design, the investigator did not make an overall clinical evaluation at the late post therapy visit (Visit 4). Therefore, the applicant did not make any assessments of clinical outcome at the late post therapy visit.

There was no space on the CRF for the investigator to state the circumstances which caused the patient to have a clinical evaluation of "unassessable".

Since the clinical and bacteriologic assessments were supposed to be independent, bacteriologic circumstances should not have made a patient clinically "unassessable".

Note that by protocol, visit timing was part of the definitions of the applicant's clinical outcome. In section 3.8.3.1 of the study reports, the applicant extended the visit windows "In an effort to capture and analyze all available and appropriate data." The applicant's extended visit windows are presented in Table 3 above. See additional comments in section II.B.1.a. above.

II.B.2.b. MEDICAL OFFICER

The medical officer assigned clinical outcomes as follows:

At early post therapy visit (Visit 2 for FT, Visit 3 for CP and TS):

Cure: All or nearly all pre-therapy signs and symptoms are eliminated. One sign/symptom of a mild nature was accepted as a cure.

Failure: Persistence of pre-therapy signs and symptoms. One or more signs/symptoms of a moderate nature or two or more signs/symptoms of a mild nature were considered failures.

At late post therapy visit (Visit 4 for all treatments):

Sustained Cure: All or nearly all pre-therapy signs and symptoms eliminated during early post therapy without resurgence during late post therapy.

Relapse: All or nearly all pre-therapy signs and symptoms eliminated during early post therapy with resurgence of one or more signs/symptoms during late post therapy.

Early Clinical Cure/Bacteriologic Persistence With Concomitant Antibiotic: Patients who were bacteriologic persistence/clinical cure at early post therapy who were given a concomitant antibiotic for the persistent organism, thus precluding a late post therapy clinical assessment.

Early Failure: Presence of clinical signs/symptoms during early post therapy period.

***REVIEWER COMMENT**: By study protocol, FT patients had 3 post therapy visits (5-9 days, 11-15 days or 14-18 days, and 5-7 weeks post treatment) where as CP or TS patients had only 2 post therapy visits (5-9 days and 4-6 weeks post treatment). To make use of this extra piece of information for the FT group, the medical officer made the distinction between "early relapse" and "late relapse" only for FT patients. A FT relapse was defined as "early" if it occurred on study day 12-17 (study 01) or study day 12-20 (study 02). A FT relapse was defined as "late" if it occurred on study day ≥18 (study 01) or study day ≥21 (study 02).*

II.B.3. SAFETY

According the applicant's protocols attribution of clinical adverse events was assigned by the investigator as follows:

Definitely related:	Relationship has been confirmed by dechallenge and rechallenge; remission and recurrence follow a reasonable temporal sequence.
Probably related:	Strong suspicion of drug association when type, time course, and relationship to dosing and/or dechallenge are considered.
Possibly related:	As suggested by type, time, course, relationship to taking of medication and external events; may follow a known response pattern to suspected drug but could have been produced by patient's clinical state and/or other therapy.
Unlikely:	Drug relationship very unlikely; no clear external cause; does not follow a known response pattern to drug.
Not related:	Clearly pre-existing or caused by a specific extraneous event; not worsened by the study treatment; not a known response pattern.

Clinical adverse events were also graded on the following scale:

Mild:	Discomfort without disruption of daily activity.
Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
Severe:	Incapacitating with inability to work or perform normal daily activity.

III.C. EXCLUSION CRITERIA FOR PATIENT ANALYSIS GROUPS

III.C.1. MODIFIED INTENT TO TREAT PATIENTS

III.C.1.a. APPLICANT

According to section 3.8.3.5 of the study reports, a patient is excluded from the applicant's modified intent to treat group if she did not have a positive urine culture ($\geq 10^5$ CFU of a least one pathogen) at baseline (study day -2 to 0).

III.C.1.b. MEDICAL OFFICER

The medical officer did not define or evaluate patients for a modified intent to treat population.

III.C.2. EVALUABLE PATIENTS

III.C.2.a. APPLICANT

According to section 3.8.3.5 of the study reports, a patient is excluded from the applicant's evaluable group if she did not have a positive urine culture ($\geq 10^5$ CFU of a least one pathogen) at baseline (study day -2 to 0), if the isolated baseline pathogen was not susceptible to both study antibiotics or susceptibility testing was not

done, if the patient was not compliant with taking the study medication (took <10 tablets in study 01 or <14 tablets in study 02) or compliance was unknown, or if the medical monitor did not deem the patient appropriate for analysis.

***REVIEWER COMMENTS**: The study reports state that the medical monitor review of patients was performed prior to breaking the study blind. However, the exclusion criteria used by the applicant's medical monitor was not documented in the study reports. Most patients who were excluded by the medical monitor were given the exclusion reason "other". The applicant provided more information on this "other" group via facsimile transmission on May 25, 1999. According to the applicant, the medical monitor excluded patients based upon a review of past medical history, past history of illness, and past surgical history, however, no specific or consistently applied criteria were given.*

The reader should note that according to the applicant's evaluability criteria, a FT patient could be excluded for not taking the appropriate number of placebo tablets.

The reader should also note that the timing of patient post-baseline visits was not a criterion for exclusion from the applicant's patient analysis groups. If an otherwise evaluable patient did not have a visit within the specified visit windows, the patient was deemed evaluable for analysis, but given the outcome "No Evaluation". See additional comments in section II.B.1.a.

III.C.2.b. MEDICAL OFFICER

A patient is excluded from the medical officer's evaluable patient group if there is no baseline pathogen with $\geq 10^5$ CFU, if there is no visit at 5-11 days post therapy (does not apply to bacteriologic persistence or clinical failure), if there is no visit at ≥21 days post therapy (does not apply to bacteriologic recurrence or clinical relapse), if the patient took <10 tablets (CP patients only) or <14 tablets (TS patients only) or tablet compliance unknown (does not apply to FT patients), if the patient had an intercurrent illness, if a concomitant antimicrobial was given for another illness, or if the patient had a protocol violation with respect to disease diagnosis.

***REVIEWER COMMENT**: Due to data inconsistencies, the medical officer also excluded all patients from investigator Ginsberg of study 02. See the medical officer's review for details.*

III.D. ANALYTICAL METHODS

III.D.1. APPLICANT METHODS

According to section 3.10 of the study reports, the applicant compared treatment groups with respect to baseline demographic variables using a t-test for quantitative variables, and a Chi-square contingency table analysis or Fisher's exact test for qualitative variables.

The applicant compared treatment groups with respect to bacteriological and clinical cure rates (on the patient level) using a Fisher's exact test. One sided 95% confidence intervals for the treatment difference in cure rate (comparator minus fosfomycin) were also computed using a normal approximation to the binomial distribution. When computing cure rates, all patients with outcomes of "no evaluation" were excluded.

The applicant did not perform center-adjusted analysis because approximately two-thirds of the centers had fewer than ten patients in one or both of the treatment groups. However, descriptive analyses by center were provided.

The applicant did not perform statistical tests of bacteriologic cure rates on the pathogen level. However, descriptive analyses by pathogen were provided.

With respect to categorical safety outcomes, the applicant compared treatments using Fisher's exact test. For quantitative safety variables such as vital sign measurements, serum chemistry and hematology results, the applicant compared treatment groups at baseline using a two sample t-test. At each post-baseline visit, the treatment groups were compared with respect to the mean change from baseline using a two sample t-test. Within each treatment group, the significance of the mean change from baseline was determined using a paired t-test.

For all tests of hypotheses, the applicant declared statistical significance if the two-sided p-value was ≤ 0.05.

***REVIEWER COMMENTS**: The applicant's primary efficacy variable was not specified in the protocol or study report.*

The applicant's method for computing confidence intervals is not appropriate for demonstrating efficacy equivalence. According to the DAIDP "Points to Consider" document, two-sided 95% confidence intervals of the FT minus comparator difference in cure rates should be used.

III.D.2. REVIEWER METHODS

Treatment group comparisons with respect to baseline demographic characteristics, baseline disease characteristics, and inclusion into the patient analysis groups were performed using the Fisher's exact test, chi-square test, two sample t-test or Wilcoxon rank sum test where appropriate.

The treatment groups were compared for efficacy equivalence using two sided 95% confidence intervals of the FT minus comparator difference in "success" rate of each efficacy variable of interest. The confidence intervals were computed using a normal approximation to the binomial distribution and incorporated a continuity correction. The confidence intervals were interpreted using the guideline outlined on page 20 of the draft DAIDP "Points to Consider" document. Efficacy equivalence analyses were performed for the following variables:

- all bacteriologic eradication at 5-11 days post treatment (includes eradication/cure, eradication/cure with superinfection, and eradication/cure with new infection)
- bacteriologic eradication/cure at 5-11 days post treatment
- all bacteriologic eradication by the end of the longer course of therapy (day 17 for study 01 and day 20 for study 02; includes eradication and eradication with new infection; computed for MO data only)
- bacteriologic eradication by the end of the longer course of therapy (MO data only)
- all sustained eradication at 4-6 weeks post therapy (includes sustained eradication/cure and sustained eradication/cure with new infection)
- sustained bacteriologic eradication at 4-6 weeks post therapy
- bacteriologic eradication of *E. coli* isolates at 5-11 days post treatment (MO data only)
- bacteriologic eradication of *E. coli* isolates by the end of the longer course of therapy (MO data only)
- bacteriologic eradication of *E. coli* isolates at 4-6 weeks post treatment (MO data only)
- clinical cure or improvement at 5-11 days post treatment
- clinical cure at 5-11 days post treatment
- clinical cure at the end of the longer course of therapy (MO data only)
- sustained clinical cure at 4-6 weeks post therapy (MO data only)
- "overall success" at 5-11 days post treatment (overall success defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure; computed for MO data only)
- "complete success" at 5-11 days post treatment (complete success defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure and no adverse event; computed for MO data only)

This reviewer considers the rate of all bacteriologic eradication at 5-11 days post treatment in the medical officer's evaluable patient group to be the primary efficacy variable. All other efficacy variables are considered secondary.

Subset efficacy analyses by age (≤65 versus >65) and race (white, black, other) were performed for the primary efficacy variable.

Treatment group comparisons of adverse event rates were performed using Fisher's exact test. Comparisons were made for the following variables:

- patients with at least one adverse event
- patients with at least one adverse event by body system
- patients with at least one adverse event by each type of event
- patients with at least one severe adverse event
- patients discontinued due to an adverse event

Subset safety analyses by age (≤65 versus >65) and race (white, black, other) were performed for the rateof at least one adverse event. All patients who took at least one dose of study medication are included in the safety analyses.

Unless otherwise stated, all tests are two sided, and the level of significance is 0.05.

All tabulated data presented in this review were obtained from the applicant's study reports, the applicant's SAS data sets, the medical officer's draft reviews dated 7/6/95 (study 01) and 7/5/95 (study 02), and the medical officer's Paradox data bases dated 6/14/95 (study 01) and 6/29/95 (study 02).

REVIEWER NOTE: *When the medical officer's analysis group exclusion criteria as stated in section II.C.2.b. were applied to the medical officer's data bases, the resultant groups of evaluable patients differed from those presented in the medical officer' s draft reviews. However, the inconsistencies did not grossly impact study conclusions. In this review, the medical officer's evaluable patient groups as presented in the medical officer's draft reviews of 7/6/95 (study 01) and 7/5/95 (study 02) are used in all efficacy analyses.*

III.E. RESULTS

REVIEWER NOTE: *Three investigators (Harnack, Costantini, and Iravani) participated in both studies. These centers enrolled 17% (147/877) and 21% (179/854) of the patients in protocols MON-US-01 and MON-US-02, respectively. The independence of these trials is questionable.*

III.E.1. PROTOCOL MON-US-01

A total of 877 patients were enrolled across 32 centers. Enrollment by center ranged from 1 to 74. By randomization, 432 and 445 patients were allocated to receive FT and CP, respectively.

The number of patients included in each analysis group is displayed in Table 4. In each analysis group, the percentage of included FT patients is numerically greater than the percentage of included CP patients. However, the treatment difference is significant only in the MO evaluable group. The treatment difference in the percentage of patients included in this analysis group is mainly due to an imbalance with regard to the number of patients without a pathogen at baseline [148 (34%) for FT versus 180 (40%) for CP]. An imbalance also exists with regard to the number of patients excluded by the MO for a missing or late 5-11 day post therapy visit [5 (1%) for FT versus 11(3%) for CP, see medical officer's review]. This phenomenon is directly linked to treatment efficacy, since a "cure" outside the 5-11 day window would be excluded from the analysis, but a "failure" outside of the window would not be excluded from the analysis.

TABLE 4: Study 01 Patients Included in Analysis Groups

analysis group	FT (N=432)		CP (N=445)		p-value[1]
	included	(%)	included	(%)	
applicant modified ITT	283	(66)	265	(60)	0.070
applicant evaluable	231	(53)	212	(48)	0.091
MO evaluable	260	(60)	222	(50)	0.002

[1] P-value from Fisher's exact test.

Within the analysis groups, the treatments did not differ significantly with respect to baseline demographic characteristics or baseline disease characteristics. In general, patients studied were young, white females.

Only 10 of the 32 centers had at least 10 patients per treatment included in any of the analysis groups. Since enrollment by center was generally small, meaningful by center analyses could not be performed.

Bacteriologic results at 5-11 days post treatment are presented in Table 5. The rate of all eradication for FT is 83%, 84%, and 78% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. For CP, the rate of all eradication is 99% in all analysis groups. The rates for eradication/cure are similar. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of all eradication, and a significantly lower rate of eradication/cure than CP.

TABLE 5: Study 01 Bacteriologic Outcomes at Early Post Therapy Visit (5 to 11 days post treatment) (study day 5-11 for FT, study day 11-17 for CP)

outcome	modified ITT				evaluable							
	applicant				applicant				MO			
	FT (N=283)		CP (N=265)		FT (N=231)		CP (N=212)		FT (N=260)		CP (N=222)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
all eradication	**225**	**(83)**	**231**	**(99)**	**189**	**(84)**	**187**	**(99)**	**203**	**(78)**	**219**	**(99)**
eradication/cure	225	(83)	231	(99)	189	(84)	187	(99)	196	(75)	218	(98)
cure with superinfection (applicant outcome only)	-		0	(0)	-		0	(0)	-		-	
eradication with new infection (MO outcome only)	-		-		-		-		7	(3)	1	(<1)
all persistence	**45**	**(17)**	**2**	**(1)**	**35**	**(16)**	**1**	**(<1)**	**57**	**(22)**	**3**	**(1)**
persistence/failure	45	(17)	2	(1)	35	(16)	1	(<1)	54	(21)	2	(1)
presumed persistence	-		-		-		-		3	(1)	1	(<1)
applicant "no evaluation"[a]	**13**		**32**		**7**		**24**		**-**		**-**	
denominator excluding applicant "no evaluation"	**270**		**233**		**224**		**188**		**260**		**222**	
95% C.I.[b]: all eradication	**(-21, -11)**				**(-20, -10)**				**(-26, -15)**			
eradication/cure only	**(-21, -11)**				**(-20, -10)**				**(-29, -17)**			

[a] This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.
[b] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Bacteriologic results at the end of the longer course of therapy (study day 17) for the MO evaluable analysis group are presented in Table 6. The rate of all eradication is 75% for FT compared to 99% for CP. The rates for eradication only are similar. The confidence interval results show that at the end of the longer course of therapy, FT has a significantly lower rate of all eradication, and a significantly lower rate of eradication than CP.

TABLE 6: Study 01 Medical Officer Bacteriologic Outcomes By Study Day 17 (5-17 days post therapy for FT, 5-11 days post therapy for CP)

outcome	MO evaluable patients			
	FT (N=260)		CP (N=222)	
	n	(%)	n	(%)
all eradication	**194**	**(75)**	**219**	**(99)**
eradication	187	(72)	218	(98)
eradication with new infection	7	(3)	1	(<1)
all persistence/early recurrence	**66**	**(25)**	**3**	**(1)**
MO early recurrence (study day 12-17 for FT only)	9	(3)	-	-
persistence	54	(21)	2	(1)
presumed persistence	3	(1)	1	(<1)
95% C.I.[a]: **all eradication**	**(-30, -18)**			
eradication only	**(-32, -20)**			

[a] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Bacteriologic results at 4-6 weeks post treatment are presented in Table 7. The rate of all sustained eradication for FT is 71%, 71%, and 61% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of all sustained eradication for CP is 95%, 96%, and 89% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 4-6 weeks post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of all sustained eradication than CP.

The rate of sustained eradication/cure for FT is 64%, 65%, and 57% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of sustained eradication/cure for CP is 91%, 92%, and 86% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 4-6 weeks post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of sustained eradication/cure than CP.

Bacteriologic results for *E. coli* isolates in the MO evaluable analysis group are presented in Table 8. The rate of *E. coli* eradication for FT is 81%, 77%, and 69% at 5-11 days post treatment, by study day 17, and at 4-6 weeks post treatment, respectively. The rate of *E. coli* eradication for CP is 98%, 98%, and 90% at 5-11 days post treatment, by study day 17, and at 4-6 weeks post treatment, respectively. As demonstrated by the 95% confidence interval results, FT has a significantly lower rate of *E. coli* eradication than CP at all time points. Due to small numbers of isolates, meaningful analyses of other urinary pathogens could not be performed.

TABLE 7 : Study 01 Bacteriologic Outcomes at Late Post Therapy Visit (approximately 4-8 weeks post treatment)
(study day ≥12 for FT, study day ≥18 for CP)

outcome	modified ITT				evaluable							
	applicant (computed by reviewer)				applicant (computed by reviewer)				MO			
	FT (N=283)		CP (N=265)		FT (N=231)		CP (N=212)		FT (N=260)		CP (N=222)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
all sustained eradication	**183**	**(71)**	**210**	**(95)**	**153**	**(71)**	**173**	**(96)**	**158**	**(61)**	**197**	**(89)**
sustained eradication/cure	166	(64)	201	(91)	141	(65)	166	(92)	148	(57)	192	(86)
sustained erad./cure with new infection	17	(7)	9	(4)	12	(6)	7	(4)	10	(4)	5	(2)
all recurrence/persistence	**75**	**(29)**	**10**	**(5)**	**63**	**(29)**	**8**	**(4)**	**87**	**(33)**	**20**	**(9)**
applicant recurrence (regardless of timing)	30	(12)	8	(4)	28	(13)	7	(4)	-	-	-	-
MO early recurrence (study day 12-17 for FT only)	-	-	-	-	-	-	-	-	9	(3)	-	-
MO late recurrence (study day ≥18)	-	-	-	-	-	-	-	-	19	(7)	11	(5)
MO presumed late recurrence (study day ≥18)	-	-	-	-	-	-	-	-	2	(1)	6	(3)
early persistence/fail (documented or presumed)	45	(17)	2	(1)	35	(16)	1	(<1)	57	(22)	3	(1)
MO patients without long term bacteriologic follow up[@]	-	-	-		-	-	-	-	**15**	**(6)**	**5**	**(2)**
early bact. erad./ clinical failure with concomitant antibiotic	-	-	-		-	-	-	-	8	(3)	4	(2)
early eradication with new infection	-	-	-		-	-	-	-	7	(3)	1	(<1)
applicant "no evaluation"[*]	**25**		**45**		**15**		**31**		-		-	
applicant "no evaluation" at early visit	13		32		7		24		-		-	
applicant "no evaluation" at late visit	12		13		8		7		-		-	
denominator excluding applicant "no evaluation"	**258**		**220**		**216**		**181**		**260**		**222**	
95% C.I.[#]: all sustained eradication	**(-31, -18)**				**(-32, -17)**				**(-36, -20)**			
sustained eradication/cure	**(-34, -20)**				**(-34, -18)**				**(-37, -22)**			

[@] As a worst case analysis, these patients have been included in the medical officer analyses as bacteriologic failures. According to the medical officer, most of these patients received a concomitant antibiotic after the early post therapy visit.

[*] This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.

[#] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 8: Study 01 95% C.I. of the FT minus CP Difference in Bacteriologic Eradication Rate for *E. Coli* Isolates According to Medical Officer Evaluable Group					
study time	eradication rate				95% C.I.*
	FT (N=216)		CP (N=187)		
	n	(%)	n	(%)	
early post therapy visit (5-11 days post therapy)	175	(81)	184	(98)	(-23, -11)
by study day 17 (5-17 days post therapy for FT; 5-11 days post therapy for CP)	167	(77)	184	(98)	(-27, -15)
late post therapy visit (approximately 4-6 weeks post therapy)	149	(69)	168	(90)	(-29, -13)

* Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Clinical results at 5-11 days post treatment are presented in Table 9. The rate of cure or improvement for FT is 96%, 83%, and 77% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of cure or improvement for CP is 100%, 95%, and 96% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of cure or improvement than CP.

The cure rate for FT is 81%, 83%, and 77% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The cure rate for CP is 94%, 95%, and 96% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower cure rate than CP.

Tables 10 and 11 display clinical results at the end of the longer course of therapy (study day 17) and at 4-6 weeks post therapy, respectively, for the MO evaluable analysis group. At study day 17, the cure rate is 73% for FT compared to 96% for CP. At 4-6 weeks post therapy, the sustained cure rate is 59% for FT compared to 88% for CP. The confidence interval results show that FT has a significantly lower cure rate than CP at both time points.

At 5-11 days post treatment, the rate of "overall success" (defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure) in the MO evaluable analysis group is 67% (174/260) for FT and 95% (211/222) for CP. The 95% confidence interval of the FT minus CP difference in overall success rate is (-35%, -21%), which shows that FT has a significantly lower rate of overall success than CP.

At 5-11 days post treatment, the rate of "complete success" (defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure and no adverse event) in the MO evaluable analysis group is 37% (95/260) for FT and 50% (112/222) for CP. The 95% confidence interval of the FT minus CP difference in complete success rate is (-23%, -5%), which shows that FT has a significantly lower rate of complete success than CP.

***REVIEWER COMMENT**: In the MO evaluable analysis group, 54% (141/260) of FT patients and 55% (121/222) of CP patients did not have an adverse event. The 95% confidence interval of the FT minus CP difference in the rate of no adverse event is (-10%, 9%), which shows that the treatments are similar with respect to the rate of no adverse events.*

TABLE 9: Study 01 Clinical Outcomes at Early Post Therapy Visit (5 to 11 days post treatment)
(study day 5-11 for FT, study day 11-17 for CP)

outcome	modified ITT				evaluable							
	applicant				applicant				MO			
	FT (N=283)		CP (N=265)		FT (N=231)		CP (N=212)		FT (N=260)		CP (N=222)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
cure or improvement	**247**	**(96)**	**230**	**(100)**	**177**	**(83)**	**178**	**(95)**	**199**	**(77)**	**213**	**(96)**
cure	207	(81)	217	(94)	177	(83)	178	(95)	199	(77)	213	(96)
improvement	40	(16)	13	(6)	0	(0)	0	(0)	-	-	-	-
failure	**9**	**(4)**	**0**	**(0)**	**37**	**(17)**	**10**	**(5)**	**61**	**(23)**	**9**	**(4)**
applicant "no evaluation"[a]	**27**		**35**		**17**		**24**		-		-	
denominator excluding applicant "no evaluation"	**256**		**230**		**214**		**188**		**260**		**222**	
95% C.I.[b]: cure or improvement	**(-6, -1)**				**(-18, -5)**				**(-26, -13)**			
cure	**(-20, -7)**				**(-18, -5)**				**(-26, -13)**			

[a] This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.
[b] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 10: Study 01 Medical Officer Clinical Outcomes By Study Day 17 (5-17 days post therapy for FT, 5-11 days post therapy for CP)				
outcome	MO evaluable patients			
	FT (N=260)		CP (N=222)	
	n	(%)	n	(%)
cure	**189**	**(73)**	**213**	**(96)**
all failure	**71**	**(27)**	**9**	**(4)**
MO early relapse (study day 12-17 for FT only)	10	(4)	-	-
early failure	61	(23)	9	(4)
95% C.I.[a]: cure	**(-30, -17)**			

[a] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 11: Study 01 Medical Officer Clinical Outcomes At the Late Post Therapy Visit (approximately 4-6 weeks post treatment) (study day ≥12 for FT, study day ≥18 for CP)				
outcome	MO evaluable patients			
	FT (N=260)		CP (N=222)	
	n	(%)	n	(%)
sustained cure	**153**	**(59)**	**196**	**(88)**
all failure	**87**	**(33)**	**24**	**(11)**
MO early relapse (study day 12-17 for FT only)	10	(4)	-	-
MO late relapse (study day ≥18)	16	(6)	15	(7)
early failure	61	(23)	9	(4)
patients without long term clinical follow up[b]	**20**	**(8)**	**2**	**(1)**
early bacteriologic failure/clinical cure with concomitant antibiotic	20	(8)	2	(1)
95% C.I.[a]: sustained cure	**(-37, -22)**			

[a] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.
[b] As a worst case analysis, these patients have been included clinical "failures", since they received a concomitant antibiotic.

Subset efficacy analyses by age (<65, >65) and race (white, black, other) for the rate of all bacteriologic eradication at 5-11 days post treatment in the medical officer's evaluable group are presented in Table 12. Confidence interval results were performed only for those subsets with ≥10 patients per treatment group. Efficacy results were consistent across the subgroups.

TABLE 12: Study 01 Subgroup Efficacy Analysis of Rate of All Bacteriologic Eradication At 5-11 Days Post Treatment According to Medical Officer Evaluable Group					
subgroup	eradication rate				95% C.I.[a]
	FT		CP		
	n/N	(%)	n/N	(%)	
age ≤65	188/240	(78)	210/213	(99)	(-26, -14)
age >65	15/20	(75)	9/9	(100)	-
race white	179/229	(78)	200/202	(99)	(-27, -15)
race black	13/18	(72)	12/13	(92)	(-52, 12)
race other	11/13	(85)	7/7	(100)	-

[a] Two sided 95% confidence intervals of the FT minus CP difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction. Confidence intervals are presented only for those subgroups with at least 10 patients per treatment group.

A summary of safety outcomes as reported in the applicant's study report is presented in Table 13. FT and CP are similar with respect to the rates of at least one adverse event, at least one treatment related adverse event, at least one severe adverse event, and discontinuation due to an adverse event. FT has significantly higher rates of at least one metabolic and nutritional system adverse event, at least one diarrhea adverse event, and at least one rash adverse event.

***REVIEWER COMMENT**: Using the applicant's SAS data sets, this reviewer could not exactly reproduce some of the applicant's tabulations of adverse events presented in the study report. However, the discrepancies are minor and do not impact study conclusions.*

TABLE 13: Study 01 Summary of Safety Outcomes[1]						
outcome	FT (N=432)		CP (N=145)		p-value[2]	95% C.I.[3]
	n	(%)	n	(%)		
at least one adverse event (AE)	199	(46)	193	(43)	0.46	(-4, 10)
at least one treatment related (definitely or probably) AE	36	(8)	28	(6)	0.30	(-2, 6)
at least one severe AE	14	(3)	18	(4)	0.59	(-4, 2)
discontinued due to an AE	6	(1)	6	(1)	>0.99	(-2, 2)
at least one metabolic and nutritional system AE	9	(2)	2	(<1)	0.04	(0, 3)
at least one diarrhea AE	33	(8)	19	(4)	0.04	(0, 7)
at least one rash AE	10	(2)	3	(1)	0.05	(0, 3)

[1] Numbers were obtained from the applicant's study report tables. Outcomes are presented only for those body system and individual events with a statistically significant treatment difference (0.05 level).
[2] Two sided p-value from Fisher's exact test.
[3] Two sided 95% confidence intervals of the FT minus CP difference in event rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Subset safety analyses by age (≤65, >65) and race (white, black, other) for the rate of at least one adverse event are presented in Table 14. No noteworthy subgroup differences were observed.

TABLE 14: Study 01 Subgroup Safety Analysis of Rate of At Least One Adverse Event [1]

subgroup	adverse event rate				p-value[2]	95% C.I.[3]
	FT		CP			
	n/N	(%)	n/N	(%)		
all patients	193/432	(45)	198/445	(45)	>0.99	(-7, 7)
age ≤65	178/397	(45)	194/425	(46)	0.83	(-8, 6)
age >65	15/35	(43)	4/20	(20)	0.14	(-5, 51)
race white	172/374	(46)	177/398	(44)	0.71	(-6, 9)
race black	14/41	(34)	14/28	(50)	0.22	(-42, 11)
race other	7/17	(41)	7/19	(37)	>0.99	(-33, 42)

[1] Numbers were obtained from reviewer analyses of the applicant's SAS data sets.
[2] Two sided p-value from Fisher's exact test.
[3] Two sided 95% confidence intervals of the FT minus CP difference in event rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

III.E.2. PROTOCOL MON-US-02

A total of 854 patients were enrolled across 30 centers. Enrollment by center ranged from 3 to 78. By randomization, 426 and 428 patients were allocated to receive FT and TS, respectively.

The number of patients included in each analysis group is displayed in Table 15. In each analysis group, the percentage of included FT patients is numerically greater than the percentage of included CP patients. However, the treatment difference is significant only in the MO evaluable group. The treatment difference in the percentage of patients included in this analysis group is mainly due to an imbalance with regard to the number of patients without a pathogen at baseline [115 (27%) for FT versus 146 (34%) for TS]. An imbalance also exists with regard to the number of patients excluded by the MO for a missing or late 5-11 day post therapy visit [1 (<1%) for FT versus 11(3%) for TS, see medical officer's review]. This phenomenon is directly linked to treatment efficacy, since a "cure" outside the 5-11 day window would be excluded from the analysis, but a "failure" outside of the window would not be excluded from the analysis.

TABLE 15: Study 02 patients included in Analysis Groups

analysis group	FT (N=426)		TS (N=428)		p-value[1]
	included	(%)	included	(%)	
applicant modified ITT	291	(68)	266	(62)	0.081
applicant evaluable	213	(50)	193	(45)	0.171
MO evaluable	249	(58)	197	(46)	<0.001

[1] P-value from Fisher's exact test.

Within the analysis groups, the treatments did not differ significantly with respect to baseline demographic characteristics or baseline disease characteristics. In general, patients studied were young, white females.

Only 7 of the 30 centers had at least 10 patients per treatment included in any of the analysis groups. Since enrollment by center was generally small, meaningful by center analyses could not be performed.

Bacteriologic results at 5-11 days post treatment are presented in Table 16. The rate of all eradication for FT is 89%, 90%, and 85% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. For TS, the rate of all eradication is 98% in all analysis groups. The rates for eradication/cure are similar. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of all eradication, and a significantly lower rate of eradication/cure than TS.

Bacteriologic results at the end of the longer course of therapy (study day 20) for the MO evaluable analysis group are presented in Table 17. The rate of all eradication is 81% for FT compared to 98% for TS. The rates for eradication only are similar. The confidence interval results show that at the end of the longer course of therapy, FT has a significantly lower rate of all eradication, and a significantly lower rate of eradication than TS.

TABLE 16: Study 02 Bacteriologic Outcomes at Early Post Therapy Visit (5 to 11 days post treatment) (study day 5-11 for FT, study day 14-20 for TS)

outcome	modified ITT				evaluable							
	applicant				applicant				MO			
	FT (N=291)		TS (N=266)		FT (N=213)		TS (N=193)		FT (N=249)		TS (N=197)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
all eradication	**246**	**(89)**	**207**	**(98)**	**187**	**(90)**	**166**	**(88)**	**212**	**(85)**	**194**	**(98)**
eradication/cure	246	(89)	206	(98)	187	(90)	165	(88)	204	(82)	190	(96)
cure with superinfection (applicant outcome only)	-		1	(<1)	-		1	(<1)	-		-	
eradication with new infection (MO outcome only)	-		-		-		-		8	(3)	4	(2)
all persistence	**30**	**(11)**	**4**	**(2)**	**21**	**(10)**	**3**	**(2)**	**37**	**(15)**	**3**	**(2)**
persistence/failure	30	(11)	4	(2)	21	(10)	3	(2)	37	(15)	37	(2)
presumed persistence	-		-		-		-		-		-	
applicant "no evaluation"[a]	**15**		**55**		**5**		**24**		-	-	-	-
denominator excluding applicant "no evaluation"	**276**		**211**		**208**		**169**		**249**		**197**	
95% C.I.[b]: all eradication	**(-13, -4]**				**(-13, -3)**				**(-19, -8)**			
eradication/cure	**(-13, -4]**				**(-13, -3)**				**(-20, -9)**			

[a] This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.
[b] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 17: Study 02 Medical Officer Bacteriologic Outcomes By Study Day 20 (5-20 days post therapy for FT, 5-11 days post therapy for TS)

outcome	MO evaluable patients			
	FT (N=249)		TS (N=197)	
	n	(%)	n	(%)
all eradication	**201**	**(81)**	**194**	**(98)**
eradication	190	(76)	190	(96)
eradication with new infection	11	(4)	4	(2)
all persistence/early recurrence	**48**	**(19)**	**3**	**(2)**
MO early recurrence (study day 12-20 for FT only)	11	(4)	-	-
persistence	37	(15)	3	(2)
presumed persistence	-		-	-
95% C.I.*: all eradication	(-23, -12)			
eradication/cure	(-26, -14)			

* Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Bacteriologic results at 4-6 weeks post treatment are presented in Table 18. The rate of all sustained eradication for FT is 79%, 81%, and 85% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of all sustained eradication for TS is 92%, 92%, and 87% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 4-6 weeks post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of all sustained eradication than TS.

The rate of sustained eradication/cure for FT is 74%, 75%, and 84% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of sustained eradication/cure for TS is 88%, 87%, and 84% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 4-6 weeks post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of sustained eradication/cure than TS.

Bacteriologic results for *E. coli* isolates in the MO evaluable analysis group are presented in Table 19. The rate of *E. coli* eradication for FT is 86% and 70% at 5-11 days post treatment and at 4-6 weeks post treatment, respectively. The rate of *E. coli* eradication for TS is 98% and 90% at 5-11 days post treatment and at 4-6 weeks post treatment, respectively. As demonstrated by the 95% confidence interval results, FT has a significantly lower rate of *E. coli* eradication than TS at both time points. *E. coli* eradication rates by study day 20 were not provided in the medical officer's review. Due to small numbers of isolates, meaningful analyses of other urinary pathogens could not be performed.

Clinical results at 5-11 days post treatment are presented in Table 20. The rate of cure or improvement for FT is 99%, 76%, and 80% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The rate of cure or improvement for TS is 100%, 93%, and 94% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower rate of cure or improvement than TS.

The cure rate for FT is 77%, 76%, and 80% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. The cure rate for TS is 93%, 93%, and 94% in the applicant modified ITT, applicant evaluable, and MO evaluable groups, respectively. At 5-11 days post treatment in all analysis groups, the 95% confidence intervals show that FT has a significantly lower cure rate than TS.

TABLE 18 : Study 02 Bacteriologic Outcomes at Late Post Therapy Visit (approximately 4-6 weeks post treatment) (study day ≥12 for FT, study day ≥21 for TS)

outcome	modified ITT				evaluable							
	applicant (computed by reviewer)				applicant (computed by reviewer)				MO			
	FT (N=291)		TS (N=266)		FT (N=213)		TS (N=193)		FT (N=249)		TS (N=197)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
all sustained eradication	**209**	**(79)**	**190**	**(92)**	**164**	**(81)**	**155**	**(92)**	**161**	**(65)**	**172**	**(87)**
sustained eradication/cure	196	(74)	181	(88)	152	(75)	147	(87)	159	(64)	165	(84)
sustained erad./cure with new infection	13	(5)	9	(4)	12	(6)	8	(5)	2	(1)	7	(4)
all recurrence/persistence	**66**	**(21)**	**16**	**(8)**	**39**	**(19)**	**13**	**(8)**	**75**	**(30)**	**17**	**(9)**
applicant recurrence (regardless of timing)	25	(9)	12	(6)	18	(9)	10	(6)	-	-	-	-
MO early recurrence (study day 12-20 for FT only)	-	-	-	-	-		-	-	11	(4)	-	-
MO late recurrence (study day ≥21)	-	-	-	-	-		-	-	27	(11)	14	(7)
MO presumed late recurrence (study day ≥21)	-	-	-	-	-		-	-	-	-	-	-
early persistence/fail (documented or presumed)	30	(11)	4	(2)	21	(10)	3	(2)	37	(15)	3	(2)
MO patients without long term bacteriologic follow up[@]	-	-	-	-	-	-	-	-	**13**	**(5)**	**8**	**(4)**
early bact. erad./ clinical failure with concomitant antibiotic	-	-	-	-	-	-	-	-	2	(1)	4	(2)
early eradication with new infection	-	-	-	-	-	-	-	-	11	(4)	4	(2)
applicant "no evaluation"[*]	**27**		**60**		**10**		**25**		-		-	
applicant "no evaluation" at early visit	12		5		5		24		-		-	
applicant "no evaluation" at late visit	15		55		5		1		-		-	
denominator excluding applicant "no evaluation"	**264**		**206**		**203**		**168**		**249**		**197**	
95% C.I.[$]: all sustained eradication	**(-20, -7)**				**(-19, -4)**				**(-31, -15)**			
sustained eradication/cure	**(-21, -6)**				**(-21, -4)**				**(-28, -12)**			

[@] As a worst case analysis, these patients have been included in the medical officer analyses as bacteriologic failures. According to the medical officer, most of these patients received a concomitant antibiotic after the early post therapy visit.

[*] This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.

[$] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 19: Study 02 95% C.I. of the FT minus TS Difference in Bacteriologic Eradication Rate for *E. Coli* Isolates According to Medical Officer Evaluable Group

study time	eradication rate				95% C.I.
	FT (N=207)		TS (N=174)		
	n	(%)	n	(%)	
early post therapy visit (5-11 days post therapy)	179	(86)	171	(98)	(-17, -8)
by study day 20 (5-20 days post therapy for FT, 5-11 days post therapy for TS)	not given		not given		-
late post therapy visit (approximately 4-6 weeks post therapy)	145	(70)	157	(90)	(-28, -12)

[a] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 20: Study 02 Clinical Outcomes at Early Post Therapy Visit (5 to 11 days post treatment) (study day 5-11 for FT, study day 14-20 for TS)

outcome	modified ITT				evaluable							
	applicant				applicant				MO			
	FT (N=291)		TS (N=266)		FT (N=213)		TS (N=193)		FT (N=249)		TS (N=197)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
cure or improvement	**262**	**(99)**	**209**	**(100)**	**156**	**(76)**	**158**	**(93)**	**199**	**(80)**	**186**	**(94)**
cure	205	(77)	195	(93)	156	(76)	158	(93)	199	(80)	186	(94)
improvement	57	(22)	14	(7)	-		-		-		-	
failure	**3**	**(1)**	**0**	**(0)**	**48**	**(24)**	**11**	**(7)**	**50**	**(20)**	**11**	**(6)**
applicant "no evaluation"[a]	**26**		**57**		**9**		**24**		**-**		**-**	
denominator excluding applicant "no evaluation"	**265**		**209**		**204**		**169**		**249**		**197**	
95% C.I.[b]: cure or improvement	**(-3, -1)**				**(-24, -10)**				**(-21, -8)**			
cure	**(-22, -9)**				**(-24, -10)**				**(-21, -8)**			

[a] This category is excluded from the applicant analyses. The reasons for "no evaluation" were not provided by the applicant.
[b] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

Tables 21 and 22 display clinical results at the end of the longer course of therapy (study day 20) and at 4-6 weeks post therapy, respectively, for the MO evaluable analysis group. At study day 20, the cure rate is 76% for FT compared to 94% for TS. At 4-6 weeks post therapy, the sustained cure rate is 66% for FT compared to 88% for TS. The confidence interval results show that FT has a significantly lower cure rate than TS at both time points.

TABLE 21: Study 02 Medical Officer Clinical Outcomes By Study Day 20
(5-20 days post therapy for FT, 5-11 days post therapy for TS)

outcome	MO evaluable patients			
	FT (N=249)		TS (N=197)	
	n	(%)	n	(%)
cure	**189**	**(76)**	**186**	**(94)**
all failure	**60**	**(24)**	**11**	**(6)**
MO early relapse (study day 12-20 for FT only)	10	(4)	-	-
early failure	50	(20)	11	(6)
95% C.I.[a]: cure	**(-25, -12)**			

[a] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 22: Study 02 Medical Officer Clinical Outcomes At the Late Post Therapy Visit
(approximately 4-6 weeks post treatment)
(study day ≥12 for FT, study day ≥21 for TS)

outcome	MO evaluable patients			
	FT (N=249)		TS (N=197)	
	n	(%)	n	(%)
sustained cure	**164**	**(66)**	**173**	**(88)**
all failure	**76**	**(30)**	**22**	**(11)**
MO early relapse (study day 12-20 for FT only)	10	(4)	-	-
MO late relapse (study day ≥21)	16	(6)	11	(6)
early failure	50	(20)	11	(6)
patients without long term clinical follow up[b]	**9**	**(4)**	**2**	**(1)**
early bacteriologic failure/clinical cure with concomitant antibiotic	9	(4)	2	(1)
95% C.I.[a]: sustained cure	**(-30, -14)**			

[a] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.
[b] As a worst case analysis, these patients have been included clinical "failures", since they received a concomitant antibiotic.

At 5-11 days post treatment, the rate of "overall success" (defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure) in the MO evaluable analysis group is 76% (188/249) for FT and 94% (185/197) for TS. The 95% confidence interval of the FT minus TS difference in overall success rate is (-25%, -12%), which shows that FT has a significantly lower rate of overall success than TS.

At 5-11 days post treatment, the rate of "complete success" (defined as a bacteriologic eradication or bacteriologic eradication with new infection and clinical cure and no adverse event) in the MO evaluable analysis group is 41% (103/249) for FT and 43% (85/197) for TS. The 95% confidence interval of the FT minus TS difference in complete success rate is (-11%, 8%), which shows that FT and TS are comparable with respect to the rate of complete success.

REVIEWER COMMENT: In the MO evaluable analysis group, 54% (134/249) of FT patients and 46% (90/197) of TS patients did not have an adverse event. The 95% confidence interval of the FT minus TS difference in the rate of no adverse event is (-2%, 18%). Although the confidence interval includes zero, the direction of the interval highlights FT's lower rate of adverse events compared to TS.

Subset efficacy analyses by age (≤65, >65) and race (white, black, other) for the rate of all bacteriologic eradication at 5-11 days post treatment in the medical officer's evaluable group are presented in Table 23. Confidence interval results were performed only for those subsets with ≥10 patients per treatment group. Efficacy results were consistent across the subgroups.

TABLE 23: Study 02 Subgroup Efficacy Analysis of Rate of All Bacteriologic Eradication at 5-11 Days Post Treatment According to Medical Officer Evaluable Group

subgroup	eradication rate				95% C.I.[a]
	FT		TS		
	n/N	(%)	n/N	(%)	
age ≤65	195/228	(86)	177/180	(98)	(-18, -7)
age >65	17/21	(81)	17/17	(100)	(-41, 3)
race white	175/209	(84)	169/172	(98)	(-20, -9)
race black	27/29	(93)	14/14	(100)	(-21, 8)
race other	10/11	(91)	11/11	(100)	(-35, 17)

[a] Two sided 95% confidence intervals of the FT minus TS difference in "success" rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction. Confidence intervals are presented only for those subgroups with at least 10 patients per treatment group.

A summary of safety outcomes as reported in the applicant's study report is presented in Table 24. FT and TS are similar with respect to the rate of at least one severe adverse event. Compared to TS, FT has a significantly lower rate of at least one adverse event, at least one treatment related adverse event and discontinuation due to an adverse event. FT also has significantly lower rates of at least one nervous system adverse event, at least one skin and skin structure system adverse event, at least one nausea adverse event, at least one constipation adverse event, at least one dizziness adverse event, and at least one rash adverse event than TS. However, FT has significantly higher rates of at least one diarrhea adverse event and at least one abnormal stool adverse event.

REVIEWER COMMENT: Using the applicant's SAS data sets, this reviewer could not exactly reproduce some of the applicant's tabulations of adverse events presented in the study report. However, the discrepancies are minor and do not impact study conclusions.

Subset safety analyses by age (≤65, >65) and race (white, black, other) for the rate of at least one adverse event are presented in Table 25. No noteworthy subgroup differences were observed.

TABLE 24: Study 02 Summary of Safety Outcomes[1]						
outcome	FT (N=426)		TS (N=428)		p-value[2]	95% C.I.[3]
	n	(%)	n	(%)		
at least one adverse event (AE)	176	(41)	212	(50)	0.02	(-15, -1)
at least one treatment related (definitely or probably) AE	25	(6)	45	(11)	0.02	(-9, -1)
at least one severe AE	20	(5)	27	(6)	0.37	(-5, 2)
discontinued due to an AE	7	(2)	18	(4)	0.04	(-5, 0)
at least one nervous system AE	12	(3)	30	(7)	<0.01	(-7, -1)
at least one skin and skin structure system AE	12	(3)	41	(10)	<0.01	(-10, -3)
at least one nausea AE	21	(5)	43	(10)	<0.01	(-9, -1)
at least one diarrhea AE	40	(9)	11	(3)	<0.01	(3, 10)
at least one constipation AE	0	(0)	8	(2)	<0.01	(-3, 0)
at least one abnormal stool AE	5	(1)	0	(0)	0.03	(0, 2)
at least one dizziness AE	5	(1)	15	(4)	0.04	(-5, 0)
at least one rash AE	3	(1)	22	(5)	<0.01	(-7, -2)

[1] Numbers were obtained from the applicant's study report tables. Outcomes are presented only for those body system and individual events with a statistically significant treatment difference (0.05 level).
[2] Two sided p-value from Fisher's exact test.
[3] Two sided 95% confidence intervals of the FT minus TS difference in event rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

TABLE 25: Study 02 Subgroup Safety Analysis of Rate of at Least One Adverse Event [1]						
subgroup	adverse event rate				p-value[2]	95% C.I.[3]
	FT		TS			
	n/N	(%)	n/N	(%)		
all patients	176/426	(41)	208/428	(49)	0.03	(-14, 0)
age ≤65	163/397	(41)	194/394	(49)	0.02	(-15, -1)
age >65	13/29	(45)	14/34	(41)	0.80	(-24, 31)
race white	152/361	(42)	180/369	(49)	0.08	(-14, 1)
race black	16/46	(35)	17/36	(47)	0.27	(-36, 11)
race other	8/19	(42)	11/23	(49)	0.76	(-41, 29)

[1] Numbers were obtained from the applicant's SAS data sets.
[2] Two sided p-value from Fisher's exact test.
[3] Two sided 95% confidence intervals of the FT minus TS difference in event rate computed by the reviewer using a normal approximation to the binomial and incorporating a continuity correction.

IV. SUMMARY AND CONCLUSIONS
(Which May be Conveyed to the Sponsor)

Statistical evaluation of efficacy is based upon the two-sided 95% confidence interval of the fosfomycin tromethamine minus comparator difference in the rate of all bacteriologic eradication rate at 5-11 days post treatment in the medical officer's evaluable patient group.

Statistical evaluation of safety is primarily based upon the two-sided Fisher's exact test treatment comparison of the rate of at least one adverse event in the safety analysis group. Treatment comparisons of rates of individual adverse events are also considered.

1. In study MON-US-01, the 95% confidence interval is $_{280, 222}$ (-26%, -15%) $_{75\%, 85\%}$, which demonstrates that a single dose of 3 gm fosfomycin tromethamine is inferior in efficacy to 7 days of ciprofloxacin 250 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women.

2. In study MON-US-02, the 95% confidence interval is $_{249, 167}$ (-19%, -8%) $_{85\%, 85\%}$, which demonstrates that a single dose of 3 gm fosfomycin tromethamine is inferior in efficacy to 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12 h. in the treatment of uncomplicated urinary tract infections in women.

3. In study MON-US-01, the rate of at least one adverse event is 46% (199/432) for fosfomycin tromethamine and 43% (193/445) for ciprofloxacin. The Fisher's exact test p-value is 0.46, which indicates that a single dose of 3 gm fosfomycin tromethamine is not significantly different in safety from 7 days of ciprofloxacin 250 mg q. 12h. in the treatment of uncomplicated urinary tract infections in women.

4. In study MON-US-02, the rate of at least one adverse event is 41% (176/428) for fosfomycin tromethamine and 50% (212/428) for trimethoprim/sulfamethoxazole. The Fisher's exact test p-value is 0.02, which indicates that a single dose of 3 gm fosfomycin tromethamine superior in safety to 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12 h. in the treatment of uncomplicated urinary tract infections in women.

5. In both studies, fosfomycin tromethamine has a significantly higher rate of diarrhea than its comparator. This is the only adverse event where the direction of the effect was consistent across the two studies. In study MON-US-01, the rate of diarrhea is 8% (33/432) and 4% (19/445) for fosfomycin tromethamine and ciprofloxacin, respectively (p=0.04). In study MON-US-02, the rate of diarrhea is 9% (40/428) and 3% (11/428) for fosfomycin tromethamine and trimethoprim/sulfamethoxazole, respectively (p<0.01).

6. Subgroup analyses by age (≤65 and >65) and race (white, black, and other) did not reveal any noteworthy subgroup differences with respect to efficacy or safety.

REVIEWER CONCLUSIONS: ***From a statistical standpoint, the applicant has failed to provide two independent, adequate and well controlled trials which demonstrate that a single dose of 3 gm fosfomycin tromethamine is therapeutically equivalent in efficacy to an approved comparator for the treatment of uncomplicated urinary tract infections in women.***

While a single dose of 3 gm fosfomycin tromethamine may have a slight safety advantage over 10 days of trimethoprim/sulfamethoxazole 160/800 mg q. 12 h., the observed differences are not substantial enough to compensate for the lack of efficacy.

RECOMMENDED REGULATORY ACTION: ***This reviewer does not recommend approval of a single dose of 3 gm fosfomycin tromethamine for the treatment of uncomplicated urinary tract infections in women.***

Elizabeth A. Turney 8/16/95

Elizabeth A. Turney, M.S.
Biomedical Statistician, Group 7

Ralph Harkins Ph D

Concur: Ralph Harkins, Ph.D.
Supervisory Statistician, Group 7

Ralph Harkins Ph D 8/18/95

for Satya D. Dubey, Ph.D.
Branch Chief, SERB

cc:
~~Orig. NDA 50-717~~
HFD-520
HFD-520/Dillon-Parker
HFD-520/Fanning
HFD-520/Albrecht
HFD-520/Soreth
HFD-713/Dubey [File: DRU 1.3.2]
HFD-713/Harkins
HFD-713/Turney
HFD-344/Lisook
Chron.
This review contains 30 pages and 25 tables.
WordPerfect 6.0/NDA50717.wpd/8-15-95

Clin. Micro

JUL

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Clinical Microbiological Review

NDA #: 50-717 **REVIEW #:** #1 **REVIEW DATE:** 23-MAR-95

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	29-SEP-94	29-SEP-94	03-FEB-95

NAME & ADDRESS OF APPLICANT:

ZAMBON CORPORATION
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DRUG PRODUCT NAME

Proprietary:	MONURAL™
Nonproprietary/USAN:	Fosfomycin Tromethamine
Code Names/#'s:	Z1282
Chemical Type/ Therapeutic Class:	1 S

ANDA Suitability Petition/DESI/Patent Status:

Patent 4,863,308 expires 2/23/2005--method of UTI treatment with fosfomycin tromethamine; Patent 5,162,309 expires 11/10/2009--relates to solid fosfomycin tromethamine physico-chemical characteristics; Patent 5,191,094 expires 3/2/2010--relates to process of preparation of fosfomycin tromethamine. All patents held by Zambon Group, Vincenza, Italy.

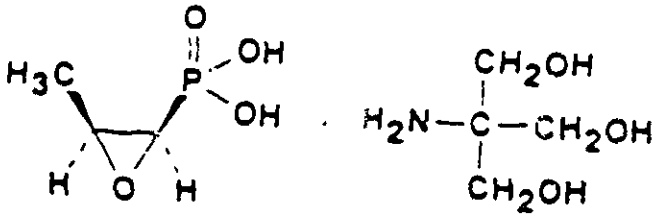
PHARMACOLOGICAL CATEGORY/INDICATION: Antibiotic/single dose treatment of uncomplicated UTI

DOSAGE FORM: Powder (Sachets)
STRENGTHS: 3 grams
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name: Mono-(2-ammonium-2-hydroxymethyl-1,3-propanediol)-(2R-cis)-(3-methyloxiranyl)phosphonate-(2R-cis)-(3-methyloxiranyl)phosphonic acid, compd. with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Chemical Structure:



Molecular Formula: $C_7H_{18}NO_7P$

Molecular Weight: 259.2

SUPPORTING DOCUMENTS: DMF
Manufacturing site for alternate packager and labeler. DMF
for drug product. DMF
for drug substance. DMF
Fosfomycin Tromethamine (drug substance). DMF
DMF

RELATED DOCUMENTS: IND 35,546--fosfomycin tromethamine.

CONSULTS: None

REMARKS/COMMENTS:

Since this is a non-sterile oral product there is no microbiology involved in the Chemistry, Manufacturing, and Controls of the product, except for a total Microbial Count performed on the purified water used. The water meets European Pharmacopeia standards since the product is made in Switzerland. The limits on microbial testing are NMT cfu/mL and no coliforms or *Pseudomonas aeruginosa* present. These limits meet the standard for EPA drinking water and are satisfactory.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 507 of the Act when changes are made in the MICROBIOLOGY section of the package insert. The final decision on susceptiblity breakpoints will be made after this drug is present to the Advisory Committee.

The changes needed should be sent to the sponsor. These revisions are listed as notification to the sponsor at the end of this review on pages 97-101.

MICROBIOLOGICAL REVIEW

TABLE OF CONTENTS

INTRODUCTION

Fosfomycin tromethamol is a phosphonic acid derivative and is the mono-acid salt of fosfomycin with tromethamine. The antibacterial activity of fosfomycin tromethamine is due to fosfomycin. This activity is due to inhibition of cell wall synthesis.

The sponsor wishes to be approved for single three gram dose treatment of uncomplicated urinary tract infections due to susceptible strains of *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis, Enterobacter* species, and *Staphylococcus saprophyticus.*

PRECLINICAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

Fosfomycin exerts its inhibitory action on one of the first steps of peptidoglycan biosynthesis. Fosfomycin has a molecular structure that resembles p-enolpyruvate. Since its structure resembles that of p-enolpyruvate it is able to bind with enolpyruvyl transferase and irreversibly block the condensation of uridine diphosphate-N-acetyl-glucosamine with p-enolpyruvate.

All procaryotic cell walls have one common chemical denominator: presence of mureins. The mureins constitute the principle strengthening and shape-determining constituents of the wall. In gram-positive bacteria murein content is usually greater than 50% of the cell wall. Mureins have two amino sugars; N-Acetylglucosamine and N-Acetylmuramic acid in a ratio of 1:1. They also contain L-alanine, D-glutamic acid, meso-diaminopimelic acid or LL-diaminopimelic acid or L-lysine, and D-alanine. In all mureins the composition of the poly(amino sugar) moiety is the same; it consists of alternating N-acetylmuramyl and N-acetylglycosaminyl residues, attached by β-1,4 linkages. There is variation, however, in the composition of the peptide side chain attached to this structure. The main difference is in the nature of the diamino acid at position 3 in the peptide chain and in the presence and nature of supplementary amino acids, which serve as a peptide bridge between cross-linked peptide chains. Gram-negative bacteria have meso-diaminopimelic acid in the third position of the side chain and a peptide bond links the terminal carboxyl group of D-alanine on one chain with the amino group of diaminopimelic of the next chain. Gram-positive bacteria usually have amino acids in peptide bridges between the tetrapeptide chains. These bridges are usually made up of L-alanine of glycine amino acids.

The first step in the synthesis of the murein structure

The steps involved in this synthesis are

Listed below are the steps involved in the synthesis

In the second stage of cell wall synthesis

Kahan et al (1) did an extensive study on the mode of action of fosfomycin. The first indication that fosfomycin inhibited cell wall biosynthesis was the observation that bacteria exposed to inhibitory concentrations in media of high osmolarity formed spheroplasts. The authors showed that fosfomycin blocked the incorporation of diamino[^{14}C]pimelic acid into cell walls but did not block the incorporation of leucine into protein. They tried to determine the stage of cell wall synthesis that was blocked by analyzing the N-acetylamino sugar ester pool of fosfomycin treated cells. All known inhibitors of cell wall synthesis induce the accumulation of these compounds. The composition of the attached peptide chain is diagnostic of the site of inhibition. Fosfomycin failed to induce the accumulation of such sugar esters. Penicillin, however, is less effective in inducing the accumulation of these sugar esters in cells first exposed to fosfomycin. Since penicillins act on the later stages of cell wall synthesis, fosfomycin must act at an earlier stage. A survey of the sensitivity to fosfomycin of enzymes concerned with the incorporation of alanine into cell wall precursors proved negative. The authors found that enolpyruvyl transferase activity could be completely inhibited by fosfomycin. The percentage inhibition increases with time of incubation, which suggested to them that the enzyme becomes progressively inactivated. Increases in the amount of substrate (UDP-N-acetylglucosamine) had little effect upon the degree of inhibition. The degree of inhibition decreased markedly as the concentration of phosphoenolpyruvate in the reaction mixture increased. It appears that fosfomycin inactivates the transferase by serving as a phosphoenolpyruvate analog. When no phosphoenolpyruvate was present, fosfomycin showed maximum sensitivity for the enzyme. Enzyme activity could not be restored even by prolonged dialysis. UDP-N-acetyglucosamine was needed for inactivation of the enzyme by fosfomycin. Using radioactivity labeled fosfomycin, the authors were able to show covalent binding of fosfomycin to enzyme.

The sponsor has also provided another reference (2) in which the authors state that fosfomycin appears to inhibit synthesis of penicillin binding protein involved in the final stage of cell wall synthesis. In this study *Enterococcus faecium* bacteria treated with fosfomycin showed alteration in penicillin-binding protein. PBP1 and PBP6 showed a decrease inversely proportional to drug concentration. It was shown that fosfomycin did not

compete with penicillin for binding PBPs and it did not inhibit carboxypeptidase activity. The sponsor wants to state in the labelling for fosfomycin that the drug also inhibits synthesis of penicillin binding proteins involved in the final stage of peptidoglycan polymerization. Since this is the only reference on this mode of action and it appears that there is no explanation of why fosfomycin decreases PBPs, this statement should not be in the label. This may be a secondary effect caused by the fact that since the first step in cell wall synthesis has been blocked the cell has no need for the enzymes (PBPs) needed in the final stage of cell wall synthesis and may just not be producing them.

This submission contains two papers that show that fosfomycin reduces the adherence of bacteria to uroepithelial cells. Albini et al (3) evaluated the effect of fosfomycin on the adhesion of *Escherichia coli* and *Proteus mirabilis* to human uroepithelial cells. A mixture of bacteria and epithelial cells were mixed in human urine at pH 6 and incubated for three hours. Fosfomycin was subsequently added to a concentration of 1,000 μg/mL. At 0,1,2,4,6 and 24 hours samples were taken and the numbers of adhering bacteria and colony-forming units were determined. They found that one hour of exposure caused an almost complete inhibition of adhesiveness. Carlone et al (4) studied the adhesion of the same two organisms to human uroepithelial cells. Bacteria and cells were allowed to incubate for one hour in phosphate-buffered saline. Fosfomycin at 1/4 and 1/8 the MIC (MIC value was 32 μg/mL for both organisms) for the organisms was added at the beginning of the incubation. A control without drug was also run. Unattached bacteria were then eliminated by filtering the suspension through a 5 μm membrane filter. After repeated washings the cells were placed on a microscope slide, air-dried, fixed and stained. The number of bacteria attached to 40 ureoepithelial cells were counted. The authors found that adhesion was approximately 55% of the control when using 1/8 the MIC and approximately 44% of the control when using 1/4 the MIC for both organisms.

Since the enzyme that is the target of fosfomycin is inside the cell, the drug must gain entry before it can exert its effect. There are two pathways that can be used to get the drug into the cell: 1) the constitutive L-α-glycerophosphate transport system, or 2) the inducible hexose phosphate pathway. Phosphate ions inhibit uptake via the L-α-glycerophosphate system. Culture media containing phosphate buffers inhibit the uptake of fosfomycin into cells. The alternative hexose phosphate pathway operates only under conditions of induction by hexose phosphates. Bacteria with this inducible pathway show lower MIC values when glucose-6-phosphate is added to the media.

Kalan et al (1) found that there was wide variation in intrinsic sensitivity to fosfomycin from one bacterial species to the next. No major differences were found in either the content of pyruvyl transferase or in the enzymes's sensitivity to fosfomycin in extracts from five species that covered a range of *in vivo* susceptibilities. Differences were also not found between extracts of a sensitive strain and of a resistant isolate derived from it. Because no evidence could be found for metabolic inactivation of fosfomycin, the authors concluded that sensitivity was determined primarily by permeability of the bacterium by the drug. They also showed that certain highly sensitive strains had accumulation of fosfomycin in the cell much higher than that in the medium. Since fosfomycin and L-*α*-glycerophosphate have similar structures the authors investigated the role of the L-*α*-glycerophosphate transport system. They found that all strains that exhibit sensitivity to fosfomycin possess an ability to metabolize L-*α*-glycerophosphate and almost all strains acquiring resistance to fosfomycin, except *Klebsiella/Aerobacter* species, show virtually no metabolism of L-*α*-glycerophosphate. If L-*α*-glycerophosphate is incorporated into the growth medium at 1 mM the uptake of labeled fosfomycin is blocked, presumely by competing with fosfomycin for the enzymes needed for uptake. Phosphate ions, which inhibits L-*α*-glycerophosphate transport also blocks fosfomycin's action on the bacterium. *E. coli* mutants that lack the genes (*glpT*) for this transport system were resistant to fosfomycin.

Kalan et al (1) discovered an alternate transport pathway for fosfomycin. This was discovered when cells showed an enhanced sensitivity to fosfomycin when grown on media with small proportions of blood. The authors were able to isolate this potentiator from lysed red blood cells and determined it to be a mixture of glucose-6-phosphate, fructose-6-phosphate, and glucose-1-phosphate. Erythrocyte enzymes liberated by hemolysis acted on broth constituents to produce these compounds. The authors associated this potentiating effect with another known bacterial transport system, the hexose phosphate uptake system (genetic designation *uhp*). This uptake systems only works in the presence of a competent inducer. If no inducer was present then fosfomycin was not transported into the cell. This uptake system is also not found in every species of bacterium. It seems to be confined to the *Enterobacteriaceae* (excluding *Proteus* species) and to *Staphylococcus* species. Isomerization of fructose-6-phosphate and mannose-6-phosphate is needed before they can activate the uptake system. Isomerization of glucose-1-phosphate is also needed. Just as with the L-*α*-glycerophosphate uptake pathway the connection between fosfomycin activity and hexose-phosphate uptake could be seen. Resistant organisms isolated from media that contained both glucose-6-phosphate and fosfomycin (at concentrations below the level inhibitory when *glpT* alone

provides transport) were invariably found to be uhp and high levels of glucose-6-phosphate antagonized the action of fosfomycin when induced cells were tested for sensitivity, presumably due to competition for the *uhp* binding sites. The authors showed that the expression of the *glpT* and *uhp* systems correlates both with the susceptibility of strains to fosfomycin and with their ability to allow entry and accumulation of fosfomycin. In the absence of inducers, the wild-type *glpT* $^{+}$, *uhp* $^{+}$ cell merely equilibrates with the external levels of radioactive fosfomycin, whereas the *glT* $^{-}$ *uhp* $^{+}$ mutant forbids entry of the drug. After growth in glycerol, which induces full expression of the *glT* system, the *glT* $^{+}$ strain showed a slight accumulation of fosfomycin and became more sensitive, whereas the *glT* $^{-}$ strain was uninfluenced. When the strains were cultured on glucose-6-phosphate and resuspended in fresh, unsupplemented medium (to minimize competition by unutilized glucose-6-phosphate for the transport system), both strains showed a fivefold accumulation of fosfomycin within the cells over external concentrations. The resistant strain now demonstrated a high susceptibility that approximated that of the parent strain.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Since fosfomycin has been used in Europe and Japan for a number of years there are many studies from these countries on its *in vitro* activity. In order to document fosfomycin's activity against isolates from the United States against uropathogens from a large geographical distribution and to confirm the drug's activity using NCCLS methods, the sponsor contracted for two studies. In the initial pre-clinical study, Barry et al (5) determined the *in vitro* activity of fosfomycin against 352 isolates. The organisms, obtained from a wide variety of geographic locations throughout the United States, represented 25 species often found in urinary tract infections. The authors performed both agar dilution and broth microdilution susceptibility tests using NCCLS procedures. The authors did test both with and without added glucose-6-phosphate (G-6-P). Concentrations of G-6-P from μg/mL were tested. The investigators found that there was no advantage to concentrations higher than 25 μg/mL, and that MICs were much higher for many isolates if no G-6-P was added. They also showed that results were almost identical when tests were performed in G-6-P augmented Mueller-Hinton broth (MHB) or Mueller Hinton agar (MHA). Fosfomycin inhibited 83.5% (294/352) of the isolates tested at ≤64 μg/mL and 91.2% (321/352) of the isolates tested at ≤128 μg/mL. As will be seen in almost all studies there was a wide range in the MIC values within the species. MIC values often ranged from the lowest to the highest tested value (usually between μg/mL and μg/mL). It appears that in almost every population there are some resistant isolates. The results of this and all other studies will be given in summary tables of results for each species at the end of the discussion of *in vitro* activity.

In the second study, Barry (6) obtained agar dilution MICs from 3,167 United States isolates using NCCLS methods with Mueller-Hinton agar supplemented with 25 μg/mL of glucose-6-phosphate. Among 1597 *Escherichia coli* isolates all strains had MIC values of ≤128 μg/mL and only two had MICs of 128 μg/mL. *Morganella morganii* and *Enterobacter agglomerans* were more resistant than the other *Enterobacteriaceae*. *Staphylococcus saprophyticus* showed the most variation in results. Only 52% of 128 strains were susceptible to 64 μg/mL, 12% had MICs of 128 μg/mL, and 36% had MIC values of ≥256 μg/mL.

Other studies were performed mostly outside the United States. Given below by species are Tables which give a summary of the *in vitro* activity of fosfomycin.

GRAM-POSITIVE AEROBES

ENTEROCOCCI

Table 1
***In vitro* activity of fosfomycin against *Enterococcus* species**

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	41			32	64
					32	64
					32	64
					32	64
					32	64
					32	64
					32	64
King (8)	UK	25			32	64
Wise (9)	UK	47			16	16
Naber (10)	Germany	9			32	64
Ravizzola (13)	Spain	94			32	64
					32	64

Enterococcus durans

Table 2
In vitro* activity of fosfomycin against *Enterococcus durans

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	5			32	512
					32	>512
Barry (6)	USA	6			32	>512

The MIC_{90} value in both studies is high and not enough isolates were tested.

Enterococcus faecalis

Table 3
In vitro* activity of fosfomycin against *Enterococcus faecalis

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	25			32	32
					32	32
Pinasi (12)	Italy	21			32	64
Gismando (14)	Spain	30			3.12	50
					25	200
Barry (6)	USA	196			32	64

The MIC_{90} value in all studies was 64 μg/mL or below, two studies were performed in the United States and a sufficient number of isolates were tested.

Enterococcus faecium

Table 4
In vitro* activity of fosfomycin against *Enterococcus faecium

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	10			64	64
					64	64
Barry (6)	USA	33			32	64

The MIC_{90} value in all studies was 64 µg/mL. Although there were only two studies that speciated this organism and only 43 isolates were tested, it appears that the activity of fosfomycin against this species corresponds to that shown when the genus was not speciated. There were many isolates tested as just *Enterococcus* species and almost all studies had an MIC_{90} value of 64 µg/mL. Since it is unlikely that *Enterococcus* will be speciated if found in an uncomplicated urinary tract infection and it appears that fosfomycin has the same *in vitro* activity against both *Enterococcus faecalis* and *Enterococcus faecium*

STAPHYLOCOCCI

Staphylococcus aureus

Table 5
In vitro* activity of fosfomycin against *Staphylococcus aureus

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
King (8)	UK	40			4	8
Wise (9)	UK	20			2	2
Ravizzola (13)	Spain	158			32	>256
					4	>256
Gismondo (14)	Italy	93			6.25	12.5
					25	50

Although the MIC_{90} value in many studies was below 64 μg/mL, this organisms is not an usual urinary tract pathogen. No studies were performed in the United States.

Staphylococcus epidermidis

Table 6
In vitro* activity of fosfomycin against *Staphylococcus epidermidis

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
King (8)	UK	20			4	64
Wise (9)	UK	19			8	128

This organism is not an usual urinary tract pathogen. No studies were performed in the United States.

Staphylococcus saprophyticus

Table 7
In vitro* activity of fosfomycin against *Staphylococcus saprophyticus

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	30			128	512
					64	512
					128	>256
					64	256
					64	512
					64	256
					64	256
Wise (9)	UK	42			64	>128
Pinasi (12)	Italy	19 species			4	64
Barry (6)	USA	128			64	>512

The MIC_{90} value in all studies, except for the Pinasi study in which all species of *Staphylococcus* were included, were >128 µg/mL. This organism is a major pathogen in urinary tract infections and may be included in the clinical efficacy section of the package insert if the Medical Officer determines that infections caused by it are cured. This organism will also probably be the one that determines the resistant breakpoint for this drug since it is the only major urinary pathogen with MICs that are high enough to be resistant and not cured.

SUMMARY OF GRAM-POSITIVE ACTIVITY

The following gram-positive organisms may be included in the package insert. Other organisms may be included in the section of organisms that fosfomycin has been shown to have clinical efficacy for if the Medical Officer determines that they should be listed. Conversely, if the clinical picture or intend to treat analysis reveals that some of the genera/species that are susceptible by *in vitro* methods are not clinically cured, they will be deleted even though the *in vitro* results demonstrate otherwise. Further, if any of these genera/species are not relevant to urinary tract infections, they will be deleted.

The following gram-positive organism that the applicant has listed in the labelling should be removed unless the Medical Officer determines that fosfomycin has clinical efficacy against it:

GRAM-NEGATIVE AEROBES

ACINETOBACTER

Acinetobacter calcoaceticus enitratus

Table 8
In vitro* activity of fosfomycin against *Acinetobacter calcoaceticus

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	10			128	128
					128	128
					128	128
					128	128
					128	128
					128	128
					128	256
King (8)	UK	35			128	128
Barry (6)	USA	47 species			128	512

The MIC_{90} values were all 128 µg/mL or higher. This organism is also not an usual urinary pathogen.

CITROBACTER

***Citrobacter* species**

Table 9
***In vitro* activity of fosfomycin against *Citrobacter* species**

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	30			2	4
					≤1	2
					16	16
					8	16
					≤1	4
					2	4
					2	4
Wise (9)	UK	9			0.5	1
Pinasi (12)	Italy	18			0.5	2
Revizzola (13)	Spain	49			256	>256
					8	>256

Citrobacter diversus

Table 10
In vitro* activity of fosfomycin against *Citrobacter diversus

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	10			8	16
					≤1	2
Barry (6)	USA	50			≤2	4

Citrobacter freudii

Table 11
In vitro* activity of fosfomycin against *Citrobacter freudii

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	20			8	16
					≤1	2
King (8)	UK	20			0.5	2
Barry (6)	USA	100			≤2	≤2

Citrobacter koseri

Table 12
In vitro* activity of fosfomycin against *Citrobacter koseri

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
King (8)	UK	20			1	2

The MIC_{90} value in most studies that were performed with glucose-6-phosphate added to the medium was μg/mL. Only one study performed in the United Kingdom (no USA studies) was performed with *Citrobacter koseri* isolates and only 20 isolates were tested.

Although only 60 isolates of *Citrobacter diversus* were tested as individual species the MIC_{90} values were well below 64 μg/mL and studies performed as *Citrobacter* species which included many *C. diversus* isolates had low MIC_{90} values.

ENTEROBACTER

Enterobacter species

Table 13
***In vitro* activity of fosfomycin against *Enterobacter* species**

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	45			16	32
					32	128
					256	>256
					512	>512
					32	128
					32	256
					64	256
Wise (9)	UK	10			1	64
Pinasi (12)	Italy	14			8	16
Ravizzola (13)	Spain	51			64	>256
					2	>256
Gismando (14)	Italy	30			12.5	50
					50	200

Enterobacter aerogenes

Table 14
In vitro* activity of fosfomycin against *Enterobacter aerogenes

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	15			512	512
					16	64
King (8)	UK	30			4	8
Barry (6)	USA	102			16	64

Enterobacter agglomerans

Table 15
In vitro* activity of fosfomycin against *Enterobacter agglomerans

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	10			128	512
					16	128
Barry (6)	USA	48			16	256

Enterobacter cloacae

Table 16
In vitro* activity of fosfomycin against *Enterobacter cloacae

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	20			512	>512
					32	128
King (8)	UK	25			32	256
Barry (6)	USA	102			16	128

In most studies of individual species except for *E. aerogenes* studies the MIC_{90} value was 128 µg/mL or greater. The MIC_{90} values in the studies in which *Enterobacter aerogenes* were tested were µg/mL when glucose-6-phosphate were added.

ESCHERICHIA

Table 17

In vitro* Activity of Fosfomycin against *Escherichia coli

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	51			1	4
					2	8
					64	128
					16	64
					2	8
					2	8
					4	16
Reeves (7)	UK	56			2	4
King (8)	UK	45			2	8
Wise (9)	UK	49			1	4
Naber (10)	Germany	191			2	16
Lerner (11)	US	45 Chicago			1	16
		32 Wayne State			4	32
Pinasi (12)	Italy	73			0.5	2
Ravizzola (13)	Spain	161			8	256
					1	16
Gismando (14)	Italy	45			12.5	50
					25	200
Barry (6)	US	1597			≤2	≤2

It appears that the MIC_{90} value in most studies is between 2 and 16 μg/mL when the media is supplemented with 25 μg/mL of glucose-6-phosphate. When not supplemented with glucose-6-phosphate the MIC values are much higher. It appears that the MIC value may also be higher in urine and in nutrient broth. Since the MIC_{90} value in most studies is well below 64 μg/mL , there were a sufficient number of studies both in the United States and in other countries and a large number of isolates were tested

KLEBSIELLA

***Klebsiella* species**

Table 18
***In vitro* activity of fosfomycin against *Klebsiella* species**

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	30			16	32
					32	64
					256	>256
					512	>512
					16	64
					64	128
					64	128
King (8)	UK	45			4	32
Wise (9)	UK	51			16	64
Pinasi (12)	Italy	12			16	64
Ravizzola (13)	Spain	74			4	>256
					16	128

Klebsiella oxytoca

Table 19
In vitro* activity of fosfomycin against *Klebsiella oxytoca

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	10			512	>512
					8	32
Barry (6)	USA	51			8	32

Klebsiella pneumoniae

Table 20
In vitro* activity of fosfomycin against *Klebsiella pneumoniae

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	20			512	>512
					32	64
Lerner (11)	USA	13			32	64
Barry (6)	USA	184			16	128

In most studies performed with 25 μg/mL of glucose-6-phosphate added to the media, the MIC_{90} value was either 32 or 64 μg/mL. Most studies were performed in the United States. Although there were only 61 isolates of *K. oxytoca* tested as individual species, many were probably included and tested as *Klebsiella* species and all species seem to have approximately the same MICs. There was an adequate number of isolates of *K. pneumoniae* tested.

MORGANELLA

Morganella morganii

Table 21
In vitro* activity of fosfomycin against *Morganella morganii

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	10			128	>256
					256	512
					256	>256
					256	>512
					256	>512
					256	>512
					256	>512
King (8)	UK	20			>256	>256
Wise (9)	UK	17			>128	>128
Ravizzola (13)	Spain	58			64	>256
					64	>256
Barry (6)	USA	49			256	512

The MIC_{90} value in all studies was >256 μg/mL.

PROTEUS sp.

Proteus mirabilis

Table 22
In vitro* activity of fosfomycin against *Proteus mirabilis

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	15			2	64
					2	32
King (8)	UK	40			4	128
Wise (9)	UK	49			4	>128
Naber (10)	Germany	19			32	>128
Lerner (11)	USA	9			4	64
Pinasi (12)	Italy	22			2	64
Ravizzola (13)	Spain	64			8	128
					8	128
Gismando (14)	Italy	34			12.5	50
					50	200
Barry (6)	USA	102			≤2	32

The addition of glucose-6-phosphate does not seem to effect the *in vitro* activity of fosfomycin against *Proteus mirabilis*. The MIC_{90} value in most studies varies from μg/mL. Since there is a large number of isolates tested and the United States studies hac MIC_{30} values of 64 μg/mL or less,

Proteus vulgaris

Table 23
In vitro* activity of fosfomycin against *Proteus vulgaris

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	10			8	128
					4	128
King (8)	UK	25			8	32
Wise (9)	UK	17			16	32
Pinasi (12)	Italy	18 indole positive			128	>512
Ravizzola (13)	Spain	39			2	8
					1	8
Barry (6)	USA	49			≤2	8

The MIC_{90} values ranged from μg/mL. The >512 μg/mL value, however, was from a study in which species were classified as indole positive only so other species may have been included. The study with the 128 μg/mL value only tested ten isolates so one isolate may have caused the slightly higher than usual value. Other studies had MIC_{90} values of μg/mL.

PROVIDENCIA sp.

Providencia rettgeri

Table 24
In vitro* activity of fosfomycin against *Providencia rettgeri

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	10			8	256
					8	128
King (8)	UK	20			64	>256
Wise (9)	UK	5			16	>128
Ravizzola (13)	Spain	45			128	>256
					128	>256
Gismondo (14)	Italy	28			100	>200
					200	>200
Barry (6)	USA	41			8	64

Except for one of the Barry studies which had an MIC_{90} value of 64 μg/mL, all studies had MIC_{90} values of 128 μg/mL or higher. Many studies had MIC_{90} values greater than the highest dilution tested (i.e. >256 μg/mL).

Providencia stuartii

Table 25
In vitro* activity of fosfomycin against *Providencia stuartii

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	15			32	256
					32	128
King (8)	UK	35			64	>256
Barry (6)	USA	44			16	128

All studies had MIC_{90} values of 128 μg/mL or higher. Since it appears that the susceptible breakpoint will be 64 μg/mL.

PSEUDOMONAS sp.

***Pseudomonas* species**

Table 26
***In vitro* activity of fosfomycin against *Pseudomonas* species**

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	35			128	256
					64	256
					128	512
					64	256
					64	256
					64	256
					64	256
King (8)	UK	33			>256	>256
Ravizzola (13)	Spain	64			256	>256
					256	>256
Gismando (14)	Italy	40			50	200
					50	>200

Pseudomonas aeruginosa

Table 27
In vitro* activity of fosfomycin against *Pseudomonas aeruginosa

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	10			64	64
					64	128
King (8)	UK	35			128	256
Wise (9)	UK	48			128	>128
Pinasi (12)	Italy	34			32	256
Barry (6)	USA	100			32	64

The MIC_{90} value for *P. aeruginosa* in these studies was 64 µg/mL or higher. Many isolates had high MIC values. This organism is also not an usual urinary pathogen in uncomplicated urinary tract infections.

Pseudomonas cepacia

Table 28
In vitro* activity of fosfomycin against *Pseudomonas cepacia

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	5			64	>512
					64	>512

This organism is not an usual urinary tract pathogen, its MICs are high and not enough studies or isolates were tested.

Pseudomonas fluorescens

Table 29
In vitro* activity of fosfomycin against *Pseudomonas fluorescens

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	5			64	256
					64	256

This organism is not an usual urinary tract pathogen, its MICs are high and not enough studies or isolates were tested.

Pseudomonas putida

Table 30
In vitro* activity of fosfomycin against *Pseudomonas putida

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	5			128	256
					128	256

This organism is not an usual urinary tract pathogen, its MICs are high and not enough studies or isolates were tested.

Pseudomonas stutzeri

Table 31
In vitro* activity of fosfomycin against *Pseudomonas stutzeri

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	5			64	64
					64	64

This organism is not an usual urinary tract pathogen and not enough studies or isolates were tested.

SERRATIA sp.

Serratia marcescens

Table 32
In vitro* activity of fosfomycin against *Serratia marcescens

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	20			8	16
					16	32
					16	64
					16	64
					16	16
					16	32
					32	64
King (8)	UK	25			16	32
Wise (9)	UK	19			128	128
Pinasi (12)	Italy	14 species			16	>512
Barry (6)	USA	98			8	32

The MIC_{90} value in most studies was 32 µg/mL or below when glucose-6-phosphate was used. The addition of glucose-6-phosphate made at most a one tube dilution difference. One study had an MIC_{90} value of >512 µg/mL, but this study included other *Serratia* species. In both United States studies the MIC_{90} value was 32 µg/mL or less.

XANTHOMONAS

Xanthomonas maltophilia

Table 33
In vitro* activity of fosfomycin against *Xanthomonas maltophilia

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry (5)	USA	5			64	256
					64	256
Barry (6)	USA	49			64	128

This organism is not an usual urinary tract pathogen and not enough studies or isolates were tested. The MICs were also high.

SUMMARY OF GRAM-NEGATIVE ACTIVITY

The following gram-negative organisms may be included in the package insert. Other organisms may be included in the section of organisms that fosfomycin has been shown to have clinical efficacy for if the Medical Officer determines that they should be listed. Conversely, if the clinical picture or intend to treat analysis reveals that some of the genera/species that are susceptible by *in vitro* methods are not clinically cured, they will be deleted even though the *in vitro* results demonstrate otherwise. Further, if any of these genera/species are not relevant to urinary tract infections, they will be deleted.

The following gram-negative organisms that the applicant has listed in the labelling should be removed unless the Medical Officer determines that fosfomycin has clinical efficacy against it:

ORGANISMS ALLOWED IN THE LABEL

The following organisms will be allowed in the package insert from the microbiological (*in vitro* activity) viewpoint. These organisms will be divided between the clinical efficacy list of organisms and the *in vitro* only list after the Medical Officer has decided for which organisms fosfomycin has clinical efficacy against.

BACTERICIDAL ACTIVITY

Reeves et al (7) investigated the bactericidal activity of fosfomycin using two strains each of *Escherichia coli* and *Enterobacter cloacae* and one strain each of *Klebsiella pneumoniae, Citrobacter freundii* and *Staphylococcus aureus*. The authors used Diagnostic Sensitivity Test Agar and added μg/mL of G-6-P. Table 34 shows the results of this study. The mean 99.9% (3 log reduction; bactericidal activity) kill time at 8X MIC was 2.2 hours (range hours) and at 2X MIC was 2.9 hours (range hours) for six of the seven strains; a 99.9% kill was not achieved with *E. coli* 10418 at 2X MIC. Urine levels of fosfomycin are often greater than 8X MIC for many organisms, especially *E. coli*. Recovery was seen at the 24 hour time point for both *E. coli* strains and *Enterobacter 7* at both 2X and 8X concentrations, and at the 2X concentration for the *Klebsiella* 456 and *S. aureus* strains. These organisms were never fully eradicated even after 24 hours. No recovery was seen for the other tested organisms.

Table 34
Rate of Bacterial Killing achieved with Fosfomycin

Bacterial strain	MIC (μg/mL)	Fold MIC	Kill Time in Hours	
			90%	99.9%
S. aureus Oxford	32	2X	2.2	5.2
		8X	1.6	2.1
E. coli 10418	4	2X	2.5	NA
		8X	1.8	2.8
E. coli 333	4	2X	2.1	2.9
		8X	1.6	2.4
Klebsiella 456	16	2X	0.9	1.8
		8X	0.5	1.8
E. cloacae 7	64	2X	1.9	2.2
		8X	1.2	1.7
E. cloacae 415	2	2X	1.6	2.6
		8X	1.4	2.2
C. freundii	4	2X	1.4	2.8
		8X	1.0	2.2

Lerner et al (11) examined the bactericidal effect of fosfomycin with various strains by diluting logarithmically grown cultures to 10^7 CFU/mL in nutrient broth with μg/mL of G-6-P added. Sets of killing curves were obtained with fosfomycin against two isolates of *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. The fosfomycin MICs for these strains ranged from μg/mL. Strains were tested with fosfomycin at 1X, 4X and 20X MIC of each strain. The viable cell count of all strains declined rapidly by about three logs (definition of bactericidal) in 1-2 hours, even in the presence of only 1X MIC of drug. No evidence of recovery could be seen by the five hour time point, except for the *E. coli* 61 culture at 1X MIC concentration. The study was not carried out for longer time periods.

Pinasi et al (12) tested twelve bacterial strains with different MICs to fosfomycin. They used human urine at pH 6.5 to simulate clinical conditions. Concentrations of fosfomycin were used that simulated those present in human urine following an oral administration of a 3 gram dose. The three *E. coli* strains with MICs of 0.5, 32 and 128 μg/mL were sterilized (no growth seen) in 2, 6, and 4 hours, respectively. The urine culture of *P. aeruginosa* with an MIC of 2 μg/mL was sterilized in six hours. A strain of *K. aerogenes* with an MIC of 128 μg/mL was sterilized in 2-4 hours, while two strains of *K. pneumoniae* and a strain of *E. cloacae* with MICs of 256 μg/mL were sterilized in 6-8 hours. Two strains of *Enterococcus faecalis* with MICs of 32 and 128 μg/mL, were sterilized in 24 and 30 hours, respectively. A strain of *Proteus mirabilis* with an MIC of 0.5 μg/mL was sterilized in 6 hours. Fosfomycin was not able to sterilize a culture of *Providencia stuartii* with an MIC >512 μg/mL. All MICs were determined in Muller-Hinton agar with added glucose-6-phosphate.

Reeves' and Lerner's studies show that fosfomycin is bactericidal at concentrations fold greater than the MIC value for most organisms. Reeves' study, however, showed that growth recovered in many cases after 24 hours. Since this drug will be dosed only once, this may have clinical significance. Lerner's study only evaluated growth for 5 hours, so no information can be derived on what happens after most bacteria are killed. Both of these studies were not performed in urine which is where this drug will be used and only used doses 2 to 8 times that of the MIC. The Pinasi study more closely represents what happens in urinary tract infections and showed that a 3 gram dose (the dose given in the NDA) will sterilize cultures of the most common urinary tract pathogens in a short period of time. Cultures of *Enterococcus faecalis* were the most difficult to sterilize (a *Providencia stuartii* was not sterilized, but this pathogen is not in the Indications section). No cultures of *Staphylococcus saprophyticus* were tested. It appears that when dosed as indicated in the NDA that fosfomycin is bactericidal for most urinary tract pathogens.

FACTORS INFLUENCING *IN VITRO* ACTIVITY

The *in vitro* activity of fosfomycin varies considerably with the conditions under which it is tested. Various factors such as type of culture media, addition of urine, addition of human blood or serum, pH of the media, and inoculum size affect the antibacterial activity of fosfomycin.

TYPE OF MEDIA

In phosphate-rich media such as Mueller-Hinton agar or broth, fosfomycin MICs are greater than those obtained in less enriched media such as nutrient broth or agar. Greenwood et al (15) studied the activity of fosfomycin in different culture media in the presence and absence of glucose-6-phosphate. Results of this study are presented in Table 35. In general MICs in Mueller Hinton broth were higher than those in nutrient both or Eugonbroth, while Isosensitest broth was in between. The effect of glucose-6-phosphate was often great, but it was not uniform across all species tested. Although a four-fold or greater reduction in MIC was achieved for many strains, others appeared unaffected. *Proteus* spp., *Pseudomonas aeruginosa,* and *Serratia marcescens* appeared to be least affected by glucose-6-phosphate, while *Escherichia coli* was the most affected. The effect of glucose-6-phosphate is due to the mechanisms of uptake of fosfomycin into bacteria. The primary means of cell entry involves the enzyme that transports L-α-glycerophosphate. The efficiency of this enzyme is reduced with increasing concentrations of glucose or phosphates in the test medium. Some species have a secondary entry system which involves the inducible enzyme responsible for hexose phosphate transport; this enzyme is induced in the presence of glucose-6-phosphate. This system counteracts the inhibition of the L-α-glycerophosphate system caused by glucose and phosphates in the media.

Barry et al (5) evaluated the effect of various concentrations of glucose-6-phosphate on fosfomycin MICs in Mueller Hinton agar and broth [See tables of activity under Antimicrobial Spectrum of Activity]. They found that the addition of 25 µg/mL of G-6-P to broth or agar improved fosfomycin's activity against *E. coli, Citrobacter* spp., *Klebsiella* spp., and *Enterobacter* spp. *S. marcescens, Proteus* spp., *M. morganii, Providencia* spp., *Pseudomonas* spp., *Enterococcus* spp., and *S. saprophyticus* were not markedly influenced, probably because they lack a hexose transport system. The addition of higher concentrations of glucose-6-phosphate (up to 200 µg/mL) did not further increase fosfomycin's activity significantly.

Table 35
In vitro Activity of fosfomycin in five culture broths

Organism (n)	Mueller Hinton		Nutrient broth		Isosensitest		Eugonbroth	
	- G6P	+ G6P	- G6P	+ G6P	- 6GP	+ G6P	- 6GP	+ G6P
Staphylococci (8)	16-R	4-R	1-64	0.5-4	2-R	1-16	0.25-R	0.25-64
Enterococci (2)	4-32	4	8-16	1-32	2-8	4-8	0.5-4	0.25-0.5
Escherichia coli (14)	R	4-R	8-R	1-R	64-R	1-R	8-R	0.5-2
Proteus spp (8)	8-R	8-R	0.25-R	0.25-R	4-R	2-R	0.25-R	0.25-R
Pseudomonas aeruginosa (7)	8-R	8-R	4-R	4-R	32-R	32-R	4-R	4-R
Klebsiella/Enterobacter spp (8)	R	R	4-R	4-R	R	16-R	32-R	8-R
Serratia marcescens (4)	R	R	16-32	16-32	R	64-R	16-32	16-32
Citrobacter spp (2)	R	4-8	0.5-1	0.5-1	R	1-2	8-16	0.5-2

R = ≥ 128 µg/mL

ADDITION OF URINE

Ferrara et al (15) showed that the activity of fosfomycin, against three strains of bacteria, was decreased by the addition of 50% urine to the culture medium or by the use of urine as culture medium. The results of this experiment can be seen in Table 36.

Table 36
Effect of Urine on the *in vitro* activity of fosfomycin

Organism	MIC (μg/mL)	
	Nutrient Broth	Urine
E. coli	50	200
P. mirabilis	50	200
E. faecalis	50	200

There was a four-fold increase in the MIC of fosfomycin in all cases. An increase in the MICs of other antibiotics was also observed in the same experiment. Even with this increase the concentration of fosfomycin in urine (as high as μg/mL) is well above the MIC for many urinary pathogens.

Gismondo et al (14) compared MICs of fosfomycin in nutrient broth supplemented with 0.1% glucose with MICs in urine. These results can be seen in the tables in the Antimicrobial Spectrum of Activity section of this review. The authors found that the MICs were usually 2-4 fold higher in urine for most species tested.

These studies show that urine usually increases the MIC value for most organisms by 2 to 4-fold. This slight increase in MIC should not have an adverse effect on the clinical use of this drug for urinary tract infections since the drug is mainly excreted in the urine and concentrations are well above even these increased MIC values.

HUMAN BLOOD OR SERUM

The supplementation of media with human blood produced a minimal increase in the antibacterial activity of fosfomycin. Ferrara et al (16) reported that the addition of human blood to nutrient agar caused a 2- to 4-fold decrease of the MIC of fosfomycin for many strains. Table 37 shows that results of their study. This decrease is due to the enzymes in the red blood cells that work on the constituents in the broth to produce glucose-6-phosphate.

Table 37
Effect of Blood on the *in vitro* Activity of Fosfomycin

Organism	MIC (µg/mL)	
	Nutrient Agar	Nutrient Agar + 10% Human Blood
S. aureus	50	25
S. aureus	12.5	6.2
S. aureus	100	25
S. epidermidis	25	12.5
S. epidermidis	25	25
E. faecalis	50	12.5
E. faecalis	25	12.5
E. coli	12.5	6.2
E. coli	25	12.5
K. pneumoniae	50	50
K. pneumoniae	25	25
E. aerogenes	3.1	1.6
E. aerogenes	100	25
P. mirabilis	12.5	25
P. mirabilis	100	100
M. morganii	100	100
P. aeruginosa	50	50
P. aeruginosa	50	50

These same authors also studied the influence of human serum on the activity of fosfomycin. They used nutrient broth containing 10 and 20% heat inactivated human serum. They reported that the presence of human serum only elevated fosfomycin's MICs by a factor of They found, however, that there was a in the MIC in serum with a strain of *P. mirabilis*. These results are shown in Table 38.

Table 38
Effect of Serum on the *in vitro* Activity of Fosfomycin

Organism	MIC (µg/mL)		
	Nutrient Broth	Nutrient Broth + 10% Serum	Nutrient Broth + 20 % Serum
S. aureus	12.5	25	50
S. epidermidis	25	100	100
E. faecalis	25	100	100
E. coli	12.5	25	100
K. pneumoniae	12.5	25	25
E. aerogenes	6.2	12.5	25
P. mirabilis	6.2	100	100
M.morganii	100	100	100
P. aeruginosa	12.5	25	25

Since this drug is being used for urinary tract infections, the effect of human blood or serum should not be important.

pH OF MEDIA

Ferrara et al (16) investigated the antibacterial activity of fosfomycin by a macrodilution method in nutrient broth at pH values of 6.0, 7.4, and 8.5. The inoculum was 10^5 CFU/mL. The assay was carried out on three strains each of *S. aureus* and *E. coli*. The results are seen in Table 39. Increasing pH decreased the activity of fosfomycin.

Table 39
Influence of pH on the *in vitro* Activity of Fosfomycin

Organism	MIC (µg/mL)		
	pH 6	pH 7.4	pH 8.5
E. coli CH79	3.1	25	100
E. coli CH 64	3.1	12.5	50
E. coli CH 60	3.1	25	100
S. aureus CH 184	3.1	12.5	25
S. aureus CH 192	12.5	50	200
S. aureus CH 179	25	50	200

Wise et al (9) studied the effect of pH on the MICs of fosfomycin in urine. MICs were determined in urine at pH 5, 6, 7, and 8 against two strains each of *Escherichia coli, Klebsiella, Pro eus mirabilis* and *Pseudomonas aeruginosa*. In this study the lowest MICs were not at the lowest pH (which was pH 6) as in the study using nutrient broth, but at pH 6-7 and not at pH 5. Human urine has a pH of 6 in most instances when it is tested, which is the pH at which fosfomycin has its highest activity. Table 40 shows the results of this study.

These studies show that the drug should work its best in human urine at pHs around 6, which is the pH value of most human urine.

Table 40
Effect of pH on the *in vitro* Activity of Fosfomycin in Urine

Organism	MIC (μg/mL)			
	pH 5	pH 6	pH 7	pH 8
E. coli	32	4	8	16
E. coli	16	2	8	8
Klebsiella spp	16	16	8	64
Klebsiella spp	4	8	8	32
P. mirabilis	32	64	64	64
P. mirabilis	32	32	32	32
Ps. aeruginosa	16	≤2	8	32
Ps. aeruginosa	≤4	4	≤4	≤4

INOCULUM EFFECTS

Ferrara et al (16) studied the effect of three different inoculum sizes (10^3, 10^5, and 10^8 CFU) against *S. aureus, E. coli, Proteus mirabilis,* and *K. pneumoniae* and other bacteria. Inocula were transferred by a multipoint inoculator on nutrient agar plates, in which serial dilutions of fosfomycin were prepared. The assays were performed at different pH and in the presence and absence of glucose-6-phosphate at a concentration of 25 μg/mL. The results of this study can be seen in Table 41. The MICs of fosfomycin were not significantly affected when the inoculum size went from 10^3 to 10^5 CFU, but at 10^8 CFU the MIC usually increased by 2- to 4-fold and in a few cases by 16-fold. Urinary tract infections usually have a high number of bacteria (often as high as 10^8 CFU/mL of urine) and a pH of around 6. It appears from Table 41 that *K. pneumoniae* may be the most affected by these conditions.

Greenwood et al (17) reported that only 9% of the strains studied showed an inoculum effect when tested at pH 5.5 in the presence of glucose-6-phosphate, compared to 37% of the strains tested at pH 7.1 and 22% of the strains tested at pH 7.9. Human urine is usually closer to pH 5.5 or 6.0 than to pH 7.0, so the result at pH 5.5 is probably closer to what happens in urinary tract infections. These results are shown in Table 42.

Table 41
Effect of Inoculum Size on *In vitro* Activity of Fosfomycin

Organism (number of strains)	-Fold Increase in MIC from 10^3 to 10^8 CFU					
	pH 6		pH 7.4		pH 8.5	
	- G-6-P	+ G-6-P	- G-6-P	+ G-6-P	- G-6-P	+ G-6-P
S. aureus (4)	4.68	8.06	5.16	9.81	4.57	8.01
S. faecalis (5)	3.75	3.17	3.6	2.66	3.2	2.25
K. pneumoniae (4)	15.16	18.7	6.73	15.2	2.12	8
E. aerogenes (5)	4.0	3.76	3.11	2.67	2	1.83
P. mirabilis (4)	4.0	5	4.37	5.37	4.31	5.35
Indole-positive Proteus (4)	3.07	5.48	1.45	2.66	1.6	1.88
P. aeruginosa (4)	3.73	4	6.55	4	3.55	4.66
Serratia spp (5)	2.89	3.76	4.52	2.95	1.86	6.38

Table 42
Inoculum Effects Observed with Fosfomycin at Three pH Levels

pH	% of 53 Strains Showing an Inoculum Effect [a]	
	- G-6-P	+ G-6-P
5.5	10	9
7.1	8	37
7.9	14	22

[a] 4-fold or greater increase in MIC when inoculum raised from 10^3 to 10^5 CFU/spot

POST ANTIBIOTIC EFFECT

This submission contains one report on the post antibiotic effect of fosfomycin. The post antibiotic effect defines the time in which an antibacterial agent continues to inhibit the growth of bacteria after the concentration of drug has fallen below the MIC. A prolonged post antibiotic effect may extend the effectiveness of a drug, permitting an extension of the interval between doses.

The post antibiotic effect (PAE) is typically measured as the difference in time required for the control and test cultures to increase one $\log_{10}$ after drug removal. Albini et al (18) incubated *E. coli* in Mueller Hinton broth for one hour in the presence of 0, 10 100 and 1000 μg/mL of fosfomycin. The bacteria were then suspended in the same volume of culture medium as that used initially, without the antibiotic, and incubated. The post antibiotic effect was determined by measuring the viability of the cells by ATP production (measured as bioluminescence). The post antibiotic effect values obtained were 0.9 hours for 10 μg/mL, 2 hours for 100 μg/mL, and 3.6 hours for 1000 μg/mL.

The post antibiotic effect due to fosfomycin does not appear to be remarkable. The clinical significance of an *in vitro* post antibiotic effect is not well established. Given the fact that fosfomycin will be dosed as a single treatment any post antibiotic effect as short as 3.6 hours seems insignificant.

MECHANISM OF RESISTANCE STUDIES

There appears to be no enzymes, such as β-lactamases, that hydrolyze fosfomycin.

There are three types of mutations that have been reported that will cause a bacteria to become resistant to fosfomycin. The most common type of mutations are on the chromosomal genes *glpT* and *Uhp*, which control transport of L-α-glycerophosphate and hexose phosphate, respectively. These mutations result in impaired uptake in the transport of carbohydrates. Kahan et al (1) demonstrated after examining 24 strains, that all strains that exhibit any sensitivity to fosfomycin possess an ability to metabolize L-α-glycerophosphate. They found that the most sensitive strains displayed the higher rates of metabolism. They also found that with the exception of *Klebsiella/Aerobacter* species all of these strains upon acquiring resistance to fosfomycin by mutation also lost their ability to metabolize L-α-glycerophosphate. If L-α-glycerophosphate is added to medium the uptake of fosfomycin can be blocked, presumably as a consequence of competition for the transport system. *E. coli (glpT⁻)* mutants were found to be resistant to fosfomycin.

Just as the different sensitivities of various strains can be attributed to the level of activity of the L-α-glycerophosphate transport system, it is also possible to associate these sensitivities with another known bacterial transport system, the hexose phosphate uptake system. This system needs to be induced before it can be expressed. It also is confined to the *Enterobacteriaceae* (excluding *Proteus* species) and to *Staphylococcus*. Kahan et al (1) were able to show that resisters isolated from media that contained both glucose-6-phosphate and fosfomycin (at a concentration below the level inhibitory when *glpT* alone provides transport) were *uhp*⁻. Kadner and Winkler (19) used an *E. coli* strain that was *glpT*⁻ (so that it lacked the L-α-glycerophosphate transport system) and grew cells on medium supplemented with glucose-6-phosphate, after two cycles of growth with fosfomycin 70 to 90% of the survivors were unable to grow on medium supplemented with glucose-6-phosphate. Most of the bacteria that grew (ones resistant to fosfomycin) had a mutation that blocked the hexose phosphate transport pathway. All of these mutants exhibited wild-type growth rates with glucose as a carbon source. These bacteria could also use lactose, gluconate, mannitol, ribose, glycerol, or galactose as carbon source.

Tsuruoka and Yamada (20) selected fosfomycin resistant *E. coli* by growing the bacteria in the presence of 10 μg/mL of fosfomycin and transferring the cells that grew to fresh nutrient broth with fosfomycin at 50 μg/mL and then to 100 μg/mL. The authors found two groups of resistant cells, distinguishable by colony size on nutrient agar. One group had smaller colonies and the second group had larger colonies indistinguishable from the parent strain. Many of the smaller colony-forming isolates fell into two classes: those which seemed to be decreased in utilization of several carbohydrates including L-α-glycerophosphate, but not glucose-6-phosphate, and those which seemed to be decreased in utilization of L-α-glycerophosphate only. Most of the larger colony-formers seemed decreased in utilization of L-α-glycerophosphate only. About 50% (43/79) of the smaller colony forming isolates were decreased in the utilization of several carbohydrates and about 40% (33/79) of them were decreased in the utilization of L-α-glycerophosphate only, and the other three were not examined because they failed to grow on the indicated carbohydrates, but did grow in nutrient agar. About 90% (37/40) of large colony forming isolates were not decreased in use of several carbohydrates except L-α-glycerophosphate and the remainder were decreased in the use of several carbohydrates including L-α-glycerophosphate. The authors examined an isolate of both the smaller colony formers (FR 90) which was decreased in utilization of several carbohydrates and one of the larger colony formers (FR 95) which was decreased in the use of L-α-glycerophosphate only. When nutrient broth was used the growth of FR 90 was about 80 minutes in doubling time, while that of FR 95 was about 45 minutes (same as parent strain). FR 95 could not use L-α-glycerophosphate but grew well on glucose and glycerol. FR 90 was incapable of growth on L-α-glycerophosphate, glucose, or glycerol and other carbohydrates but grew well on glucose-6-phosphate although the onset of growth was delayed 3 to 4 hours in comparison to the that of the parent strain. Both isolates which were capable of growth in the presence of 200 μg/mL of fosfomycin were sensitized to the drug by the addition of glucose-6-phosphate in the growth medium. FR 90 was sensitized by cyclic AMP, while FR 95 was not. Cyclic AMP also restored the utilization of L-α-glycerophosphate and glycerol in FR 90, but not in FR 95. This effect is though to be due to the induction of the *glpT* gene. The authors stated that FR 90 resembles a mutant which lacks enzymes of the phosphoenolpyruvate phosphotransferase system, while FR 95 seemed to be *glpT* .

Mutations that diminish the affinity of fosfomycin for its target enzyme also make cells resistant, although there is also a decrease in the affinity of the enzyme for phosphoenolpyruvate, resulting in a lower rate of synthesis of peptidoglycan. Venkateswaran and Wu (21) described the isolation of a fosfomycin resistant mutant of *E. coli* K12 which grows normally in minimal media containing L-*α*-glycerophosphate or glucose-6-phosphate as sole carbon source. The authors picked fosfomycin resistant cells that grew in minimal media supplemented with amino acids and either L-*α*-glycerophosphate or glucose-6-phosphate as the sole carbon source. None of these mutants had an elevated level of enolpyruvyl transferase activity in the crude extract. They picked one mutant, strain E187, which showed increased resistance to this enzyme towards fosfomycin. The minimal concentration of fosfomycin needed to lyse cells of mutant E187 was very high in comparison with that needed for wild-type cells. The minimal amount needed for lysis of mutants could be lowered by growth in media containing L-*α*-glycerophosphate or glucose-6-phosphate. E187 grew on minimal media containing glucose, glycerol, DL-*α*-glycerophosphate, or glucose-6-phosphate as did the wild-type cells. E187, however, grew poorly in rich media at 42°C and became elongated and less rigid before gradually undergoing lysis. Both the rate of growth (increase in turbidity) and the rate of cell wall synthesis (incorporation of ^{3}H-diaminopimelic acid) were unaffected by a concentration of fosfomycin (0.3 mM) that rapidly lysed wild-type cells. When a crude extract of the wild type strain was preincubated with 0.05 mM fosfomycin at 37°C, the activity of enolpyruvyl transferase was irreversibly inactivated. On the other hand, the activity of this enzyme in the crude extract of E187 cells was more resistant to this inactivation by fosfomycin. When increasing amounts of fosfomycin were added to the crude extracts of wild type and mutant cells in the presence of varying amounts of phosphoenol pyruvate, the mutant enzyme appeared to have fourfold lower affinity toward fosfomycin than that of the wild type. This might account for the resistance of this mutant to fosfomycin. There was also a three to fourfold increase in the K_m for phosphoenol pyruvate of the mutant enzyme as compared to that of the wild type, which results in a lower rate of synthesis of peptidoglycan and indicates that the enzyme also has less affinity for its natural substrate.

The third type of mutation is plasmid-mediated and involves the inactivation of fosfomycin by the formation of an adduct between fosfomycin and glutathione. This is accomplished by an intracellular glutathione S-transferase that catalyzes the formation of a covalent bond between the sulfhydryl residue of the cysteine in glutathione and the C-1 of fosfomycin.

Mendoza et al (22) first described the isolation of plasmids conferring resistance to fosfomycin from clinical isolates of *Serratia marcescens*. They tested 31 strains for transfer of resistance to *E. coli*. They discovered at least two different plasmids of 97 and 57 megadaltons coding for high levels of resistance to fosfomycin. The plasmids are different in size, show a distinct antibiotic resistant pattern, and give rise to a different minimal inhibitory concentration for fosfomycin. The 97 megadalton plasmids, pOU500 and pOU700 although from different parenteral *Serratia* strains are indistinguishable on agarose gel electrophoresis and seem to specify identical minimal inhibitory concentrations of various antibiotics. The plasmid derived from strain SM5 was designated pOU500, and that derived from SM7 was called pOU700. These two plasmids are probably the same. They both carry resistance to carbenicillin, sulfonamide, kanamycin, gentamicin, tetracycline, and chloramphenicol in addition to fosfomycin. Transconjugants obtained from strain SM9 carried a single plasmid (pOU900) of 57 megadaltons. This plasmid carried resistance to carbenicillin, streptomycin and fosfomycin.

Suarez and Mendoza (23) found that conjugative plasmid-encoded fosfomycin resistance has extended to *Serratia liquefaciens* and *K. oxytoca* (pUO900) and *K. pneumoniae, K. oxytoca,* and *E. coli* (pUO500). No transmissibility was found among *E. cloacae, Proteus* and *Morganella* spp., *P. stuartii,* and *Pseudomonas* spp. Besides gram-negative species, plasmid-mediated fosfomycin resistance has also been seen in *S. epidermidis* (24). Unlike transport mutants, these isolates were quite capable of incorporating the drug, and they have a fully sensitive enolpyruvyl transferase.

Using *E. coli,* Arca et al (25) showed that plasmid-resistance to fosfomycin is due to the formation of an adduct between fosfomycin and glutathione (γ-Glu-Cys-Gly). The responsible enzyme is glutathione S-transferase, which catalyzes the formation of a covalent bond between the sulfhydryl residue of the cysteine in glutathione and the C-1 of fosfomycin. This bonding was determined by chemical shifts in the NMR analysis of the product with pH. This result was confirmed by obtaining an extract of fosfomycin resistant cells, which was dialyzed to eliminate any possible intracytoplasmic glutathione. The undialyzed extract was capable of modifying fosfomycin, but this activity was lost upon dialysis and was recovered by addition of exogenous glutathione. The degree of modification was a function of the amount of glutathione added.

Arca et al (26) purified and characterized the glutathione S-transferase responsible for the modification of fosfomycin. They found that it was a homodimer of two 16,000 dalton polypeptides, which showed an antiparallel structure.

Many papers reported on the frequency of development of resistance. Courtieu et al (27) used 109 fosfomycin susceptible isolates, an inoculum of a 10^{-1} and 10^{-2} dilution of a 24 hour broth culture and Mueller Hinton agar plates containing 250 µg/mL of fosfomycin. Resistant colonies were seen in 24 hours of incubation. Of 109 isolates, stable mutants were detected in 88 and unstable mutants in 13. By species, the number of isolates producing resistant mutants/the number of isolates tested were as follows: *S. aureus* 41/46, *E. coli* 2/2, *Serratia* 11/11, *Proteus* 32/33, and *P. aeruginosa* 15/17. The mutation frequencies were as follows: 8 strains, no mutants detected; 39 strains at $1:10^8$; 46 at $1:10^7$; and 16 at $1:10^6$. The frequency of mutations appears to be slightly higher than usually seen for many antibiotics (usually around 10^{-9} to 10^{-7}) but the rate seen in this experiment is to 250 µg/mL of drug, which is well below the level available in the urine for an extended period of time after the 3 gram dose being evaluated in this submission.

Ferrara et al (16) determined the frequency of emergence of resistant variants to fosfomycin (in the presence of different selecting concentrations) in nutrient broth and in urine at different pH (6, 7.4, 8.5) values. The lowest incidence of resistant variants was observed at acid pH 6 (the normal pH of human urine) . When the concentration was 2000 µg/mL, *Klebsiella pneumoniae* was the only tested species that demonstrated resistant variants (at pH 8.5 only). These mutations occurred at a frequency of 10^{-9}. In the presence of 1000 µg/mL, *K. pneumoniae* and a strain of indole positive *Proteus* showed some incidence of resistant variants at pH 6 (at 10^{-9} frequency) while at pH 7.4 and 8.5 these species and *Pseudomonas* showed resistant variants (at a frequency of 10^{-9} to 10^{-7}). The same trend was observed in the presence of 500 µg/mL, but only at 250 µg/mL did some resistant variants of *S. aureus, K. pneumoniae,* indole-positive *Proteus* and *P. aeruginosa* appear at higher frequencies of 10^{-4} to 10^{-6}. *E. coli* and *P. mirabilis* (usually associated with urinary tract infections) were the species less prone to resistant variants.

Rossi et al (28) used an inoculum of 10^7 bacteria/mL and plated them on Brain-Heart agar containing 150, 1000, and 2000 μg/mL of fosfomycin. After 18 hours of incubation the number of colonies formed on these plates were counted. Only at 150 μg/mL were resistant mutants selected at a rate higher than 1×10^{-7}. *Enterococcus faecalis, P. aeruginosa* and *Proteus* showed the greatest mutation rate. Once again, *E. coli* the most common urinary tract pathogen showed the least tendency toward mutation. These mutants were found to be susceptible to 1000 and 2000 μg/mL of fosfomycin. At the two higher concentrations the frequency of resistant rate was $> 10^{-9}$.

EPIDEMIOLOGICAL STUDIES

Fosfomycin has been used in Europe, especially in Spain, for a number of years so there are studies that have been performed to assess the resistance profile after several years of clinical use.

Naber and Thyroff-Freiesinger (10) in Germany determined the activity of fosfomycin against 249 pathogens causing uncomplicated urinary tract infections in females. They used an MIC of ≤128 μg/mL as susceptible. The overall MIC_{50} value was 4 μg/mL and the MIC_{90} value was 64 μg/mL. They found that 97% of the isolates were susceptible. The susceptibility rates for designated species were: *E. coli,* 100%; *P. mirabilis*, 80%; other gram-negative rods, 91%; *Staphylococcus* spp., 84%, and *Enterococcus* spp., 100%.

Schito et al (29) performed a study to assess the resistance profile for fosfomycin after several years of clinical use in Italy. They explored the susceptibility of 6,021 urinary isolates from three teaching hospitals in 1990 to fosfomycin and eight other drugs using NCCLS agar-diffusion methods. They found that gram-negative strains, notably *E. coli* (41.6% of all strains) predominated, representing 82.2% of strains from out-patients, 70.2% from in-patients, and 74.1% overall. The frequency of isolation of resistant strains is shown for fosfomycin, norfloxacin, and netilmicin in Table 42 below. Fosfomycin showed the lowest rate of resistance. This was followed by norfloxacin and netilmicin. Amoxicillin was the least active compound with resistance in 41.4% of the isolates (data not shown in Table). The results shown in the Table are ranges from three different hospitals and show that their are differences in resistance even within the same country at different sites. The results also indicate that fosfomycin is still active in Italy.

Table 43
Antibiotics Most Active *in vitro* Against Common Urinary Pathogens in Italy

Pathogen (number)	% of Isolates Resistant to *		
	Fosfomycin	Norfloxacin	Netilmicin
E. coli (2508)	0.3 to 2.7	0.3 to 1.8	0.7 to 3.4
Enterococcus spp. (917)	1.2 to 2.1	22.6 to 57.0	35.7 to 59.6
Staphylococcus spp. (623)	6.3 to 6.7	20 to 33.8	1.6 to 16.4
Proteus spp. (467)	9.9 to 15.3	0.0 to 6.8	6.6 to 16.9
Klebsiella spp. (421)	0.9 to 4.6	1.1 to 7.5	2.3 to 4.4
Enterobacter spp. (269)	3.8 to 6.5	6.5 to 25.8	15.2 to 27.4
Other (226)	0.0 to 15.8	9.1 to 30.7	13.6 to 29.8
Total (5431)	2.8 to 3.9	9.8 to 13.1	10.0 to 16.3

* Range of results from three study centers
Pseudomonas species were not tested

Greenwood et al (30) determined the activity of fosfomycin against 500 urinary pathogens obtained from patients in Great Britain in 1992. Tests were performed using Isosensitest agar fortified with glucose-6-phosphate. Using a susceptibility breakpoint of 64 μg/mL, the authors found 83% of isolates to be susceptible to fosfomycin (89% of the out-patient strains and 77% of the in-patients strains). The degree of susceptibility was similar to that of cephalexin, nalidixic acid, and trimethoprim (84%, 83%, and 82%, respectively). Less susceptibility was seen with ampicillin (60%), nitrofurantoin (74%), and sulfamethoxazole (70%). The relative fosfomycin susceptibility is shown in Table 44. Results show that some *Klebsiella* and streptococci are resistant at ≥64 μg/mL. Only three of the *Klebsiella* strains (7%) and two (6%) of the streptococci were resistant to ≥256 μg/mL of fosfomycin (a concentration that is well below urinary levels). These results offer an estimate of the baseline level of resistance in the population since fosfomycin has not been marketed in the United Kingdom and has been used only on a very limited experimental basis.

Table 44
Fosfomycin Susceptibility of Urinary Isolates in Great Britain

Organism	Number of Isolates	% Susceptible
E. coli	324	95
Klebsiella spp.	42	52
Proteus spp.	46	85
Other *Enterobacteriaceae*	10	90
Pseudomonas spp.	17	12
Staphylococcus spp.	25	76
Streptococcus spp.	36	47

In Spain where the drug has been used extensively for a number of years in various infections, it appears that the level of resistance has leveled off. Data from annual surveys (23) in one hospital (reveal that fosfomycin resistance frequency in *Serratia marcescens* has reached an equilibrium since 1982 (paper published in 1991) at about 50% susceptibility. Screenings of blood and urine samples consistently show more that 90% susceptibility of *E. coli* and *S. aureus,* from 80 to 45% susceptibility of *S. epidermidis*, from 50 to 35% susceptibility of *P. aeruginosa*, and from 50 to 66% susceptibility of *S. marcescens*. In a si ar study in in Valencia, Spain comparisons of the f: uencies of susceptibility to fosfomycin from 1973 to 1984 have revealed consistent 90% susceptibility of *S. aureus, Salmonella* spp., *Shigella* spp., and *E. coli;* 80 to 90% susceptibility of *E. faecalis, Klebsiella* spp., *Serratia* spp. and *P. mirabilis;* and over 70% susceptibility of *Enterobacter* spp. and *P. aeruginosa*. The overall susceptibility frequency in Valencia is 82%.

These data reveal that the frequency of resistance to fosfomycin, in countries where it has been used, has not reached epidemic proportions. High and prolonged urine levels should greatly diminish the likelihood of resistance development.

PRECLINICAL EFFICACY *(IN VIVO)*

PHARMACOKINETICS/BIOAVAILABILITY

The information in this section is taken from the studies submitted in the NDA and have not been evaluated by a Biopharmaceutical Reviewer at the present time.

The tromethamine salt of fosfomycin is highly soluble in water and well-absorbed after oral administration. Most investigators report urine concentrations of fosfomycin of μg/mL following a single oral dose of fosfomycin tromethamine containing three grams of fosfomycin base. Segel et al (31) reported mean concentrations of 977, 2895, 1741, 724, 479, 171, and 67 μg/mL at the following intervals after oral dosing: 0-2, 2-4, 4-6, 6-12, 12-24, 24-36, and 26-48 hours.

The sponsor conducted a study to determine the pharmacokinetics in fed and fasted subjects who received a single oral dose of fosfomycin tromethamine containing three grams of fosfomycin base. This study was a single dose, single-center randomized two-way crossover (oral) study followed by a single-dose period (IV). Twelve healthy male and twelve female subjects were used. The study lasted three weeks. For the first two weeks, subjects received on the first day of each week a 3 gram dose of fosfomycin with 180 mL of water either after a 10 hour overnight fast or immediately following a standard high-fat breakfast. During the final visit (third week) subjects received 3 grams of fosfomycin (as the disodium salt) intravenously.

The study showed that food did not significantly affect urinary concentrations (sponsor's data). Fosfomycin does appear to be more rapidly absorbed under fasting conditions. Subjects that received a high fat diet had concentrations of fosfomycin in the urine greater than 64 μg/mL for 16-24 hours, and the concentration was above 128 μg/mL for at least 10-12 hours.

Following single oral doses of fosfomycin tromethamine, mean peak serum concentrations of fosfomycin were 26.28 μg/mL two hours post dosing in fasted patients and 18.07 μg/mL at four hours post dosing in fed patients. The serum half-life is about 5.7 hours. About 20% of the dose was found in fecal samples.

The absolute bioavailability of oral dosing with fosfomycin tromethamine was 37% and 30% following fasted and fed conditions, respectively. Food decreased both the rate and extent of absorption. Over 90% of fosfomycin following IV treatment is recovered in urine. Practically no fosfomycin was excreted in the feces following IV administration.

ANIMAL PROPHYLACTIC AND THERAPEUTIC STUDIES

Two studies were submitted in the NDA which evaluated the efficacy of fosfomycin in experimental mouse and rat models of infection produced by a variety of bacterial pathogens.

Albini (32) compared the efficacy of the calcium and tromethamine salts of fosfomycin against experimental infections in mice with a range of microorganisms. The mice were challenged by the intraperitoneal route with the test organism suspended in 0.5 mL of 5% hog gastric mucin. The bacterial challenge dose used was at least 50 times the median lethal dose (LD_{50}), and all untreated animals died within 48 hours post challenge. Fosfomycin tromethamine and calcium salt were administered orally in different doses one hour after challenge. Ten animals were used for each dose level. The number of animals surviving on day five was used to calculate the 50% protective dose (PD_{50}). Table 45 shows the results of this mouse protection study. Against all infections, fosfomycin tromethamine and calcium fosfomycin show a high degree of efficacy, and the two salts appear to be equivalent. A 3 gram dose is equivalent to about 43 mg/kg in a 70 kg person. The PD_{50} doses in this experiment are all well below the normal human dose on a mg/kg basis.

Table 45
Efficacy of Fosfomycin in Experimental Infections in Mice

Organism	Challenge Dose Cells/Mouse	PD_{50} of Fosfomycin Salt in mg/kg (95% Confidence Limits)	
		Calcium	Tromethamine
E. coli 21301	4.6×10^7	1.98 (1.15-3.41)	1.93 (1.08-3.46)
P. mirabilis Vi	4.5×10^5	0.188 (0.121-0.291	0.158 (0.109-0.231)
Pasteurella multocida NCTC 10722	1.0×10^3	16.1 (10.9-23.7)	14.8 (11.2-19.4)

The effectiveness of a single oral dose of fosfomycin against experimentally induced bacterial cystitis in rats was evaluated and compared to the effectiveness of single doses of norfloxacin, trimethoprim/ sulfamethoxazole, and pipemidic acid by Dubini and Riviera (54). Infections were produced with clinical isolates of *Klebsiella pneumoniae, Proteus mirabilis,* and *Escherichia coli.* The susceptibility of these three strains was evaluated *in vitro* by broth dilution in Mueller Hinton broth. Forty-five rats in each group were infected with a culture of about 2 x 10^8 CFU/mL of one of the three bacteria. Two hours after infection into the bladder, a single oral dose of the different antibiotics was administered. Five rats in each of the above three groups were given either a 60 mg/kg dose or a 200 mg/kg dose of one of the four antibiotics. A total of 120 rats were treated and 14 were kept as untreated controls. Twenty-four hours after treatment the animals were killed and their bladders removed and homogenized. The suspensions were diluted and plated on selective agar for each of the three organisms tested. The CFUs were counted after 24 hours incubation. Tables 46-48 show the results obtained *in vivo* for the four drugs against each of the three infections in comparison with the corresponding MICs.

Table 46
Activity of Fosfomycin and Comparison Agents Against Experimental Cystitis in Rats Produced with *K. pneumoniae*

Antibacterial Agent	MIC (μg/mL)	CFU/Bladder (Mean of 5 Rats) After Single Oral Dose of	
		60 mg/kg	200 mg/kg
None-Control	--	3.1×10^7	
Fosfomycin	100	9.3×10^6	3.9×10^5
Norfloxacin	0.19	9.7×10^3	1.0×10^3
Pipemidic Acid	12.5	4.6×10^5	1.8×10^5
Trimethoprim/ Sulfamethoxazole	0.78	2.8×10^4	1.7×10^3

Table 47
Activity of Fosfomycin and Comparison Agents Against Experimental Cystitis in Rats Produced with *E. coli*

Antibacterial Agent	MIC (μg/mL)	CFU/Bladder (Mean of 5 Rats) After Single Oral Dose of	
		60 mg/kg	200 mg/kg
None-Control	--	2.5×10^8	
Fosfomycin	6.25	8.8×10^3	4.0×10^3
Norfloxacin	0.04	1.2×10^3	3.0×10^2
Pipemidic Acid	0.78	4.6×10^3	1.2×10^4
Trimethoprim/ Sulfamethoxazole	0.19	1.8×10^5	4.5×10^3

Table 48
Activity of Fosfomycin and Comparison Agents Against Experimental Cystitis in Rats Produced with *P. mirabilis*

Antibacterial Agent	MIC (μg/mL)	CFU/Bladder (Mean of 5 Rats) After Single Oral Dose of	
		60 mg/kg	200 mg/kg
None-Control	--	3.4×10^8	
Fosfomycin	12.5	1.8×10^5	9.3×10^3
Norfloxacin	0.09	2.3×10^3	$<1.0 \times 10^3$
Pipemidic Acid	1.56	1.1×10^5	7.8×10^3
Trimethoprim/ Sulfamethoxazole	0.19	1.8×10^4	1.0×10^4

It appears that a single oral dose of 60 mg/kg body weight was sufficient to decrease the CFU by 2-4 logs/bladder when the infection is caused by *K. pneumoniae*, except for fosfomycin which showed less than one log reduction at this dose. Administration of a larger dose further decreased the CFU/bladder. Norfloxacin and pipemidic were the most effective drugs against this infection, which corresponds to the *in vitro* MICs for these agents against *K. pneumoniae*.

Against *E. coli* infection a single dose of 60 mg/kg decreased the CFU by logs. The effectiveness of fosfomycin was about the same as that of pipemidic acid, better than that of trimethoprim/sulfamethoxazole and slightly less than that of norfloxacin (even though fosfomycin's MIC was about 100 times that of norfloxacin for this organism). The higher dose was more effective for fosfomycin, norfloxacin and trimethoprim/sulfamethoxazole although only the later showed very much of an increase in effectiveness.

Against *P. mirabilis* infection a single dose of 60 mg/kg of fosfomycin or pipemidic acid had about the same effectiveness, which was slightly less than that of trimethoprim/sulfamethoxazole and slightly less again than that of norfloxacin. The 200 mg/kg dose gave better results for all drugs.

These result show that a dose of 200 mg/kg body weight of fosfomycin effective for urinary infections caused by *E. coli* and *P. mirabilis*. At this dose fosfomycin had the same effect against *E. coli* infection as norfloxacin, even though it's *in vitro* MIC is about 100 times that of norfloxacin. The data for *P. mirabilis* show that fosfomycin had activity equal to that of pipemidic acid and trimethoprim/sulfamethoxazole although the *in vitro* sensitivity of the strain to fosfomycin is much less than to the other two drugs. This lack of correlation between *in vitro* and *in vivo* activity may be due to the effective absorption of fosfomycin from rat intestine, which leads to peak urinary concentrations of 1500-2500 μg/mL after a single oral dose of 200 mg/kg. This would indicate that a 200 mg/kg dose in the rat may be equivalent to a 3 gram oral human dose, proposed for marketing in this application. Fosfomycin did not give very good results in this study against infection caused by *K. pneumoniae*. The strain in this experiment had a high MIC value. From this experiment it appears that fosfomycin at a 3 gram single dose may be effective for uncomplicated urinary tract infections, but may not be effective against urinary *K. pneumoniae* infections.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

ISOLATES/RELEVANCE TO APPROVED INDICATIONS

The sponsor presented the following studies for the indication of single dose, oral treatment of uncomplicated urinary tract infections in women.

MON-US-01--Multicenter, randomized, double-blind, double-dummy comparison of fosfomycin as a single 3 gram dose vs ciprofloxacin 250 mg tablet twice a day for seven days.

MON-US-02--Multicenter, randomized, double-blind, double-dummy comparison of fosfomycin as a single 3 gram dose vs trimethoprim/sulfamethoxazole 160mg/800mg tablet twice a day for ten days.

A total of 1731 women were enrolled--858 received fosfomycin, 445 received ciprofloxacin, and 428 received trimethoprim/sulfamethoxazole. Of the 858 who received fosfomycin 574 were evaluated for efficacy in the intent to treat analyses; in these patients a urine culture was taken prior to therapy and that culture yielded one or more uropathogens with a count of $\geq 10^5$ CFU/mL. Bacteriological and clinical effectiveness were evaluated 5-11 days following completion of active treatment [Visit #2 for fosfomycin; Visit #3 for comparators]. A satisfactory bacteriological response indicates that the uropathogen detected at baseline was eradicated at Visit #2 for fosfomycin. The same organism or another species may be present at a later timepoint and the sponsor has still classified this as a bacteriological success.

Pathogens found in the above studies:
Escherichia coli--412 of 466 (88%) satisfactory bacteriological response.
Klebsiella pneumoniae--23 of 31 (74%) satisfactory bacteriological response.
Proteus mirabilis--19/23 (85%) satisfactory bacteriological response.
Staphylococcus saprophyticus--8/13 (62%) satisfactory bacteriological response.
Enterococcus faecalis--20/23 (87%) satisfactory bacteriological response.
Enterobacter spp.--9/11 (82%) satisfactory bacteriological response.
Enterobacter aerogenes--5/7 (71%) satisfactory bacteriological response.
Enterobacter cloacae--3/3 (100%) satisfactory bacteriological response.

These pathogens are the ones the sponsor has listed in their microbiology subsection of the proposed label as having both *in vitro* and clinical efficacy. The final determination of the organisms to include in the indications for this drug will be provided by the medical reviewer.

DISK CONTENT STUDIES

Pinasi et al (12) did a study comparing 5[illegible]g and 200-μg fosfomycin disks with and without 50 μg of glucose-6-ph[illegible]ate (G-6-P) added to the disks. They compared the MICs obtained usi[illegible] agar dilution method using Mueller-Hinton agar supplemented with 10 μg/mL G-6-P and zone diameters obtained with these different disks for 245 bacterial strains isolated from urinary infections. The regression lines and the correlation coefficients for each of the four disks types is given below:

50-μg disk no G-6-P:	-2.37x + 28.02	r = -0.822
50-μg disk + 50 μg G-6-P:	-1.77x + 24.9	r = -0.832
200-μg disk no G-6-P:	-2.67x + 34.7	r = -0.866
200-μg disk + 50 μg G-6-P:	-1.65x + 38.8	r = -0.755

These data show that the relation between MIC and zone size was dependent on the presence of G-6-P. The slope values of the regression lines obtained with both the 50-μg and 200-μg disk in the absence of G-6-P were significantly higher ($p < 0.01$) than the corresponding slope values without G-6-P. Without G-6-P the slope value with the 200-μg disk was significantly higher ($p < 0.05$) than that obtained with the 50-μg disk, but with G-6-P the two slope values were about the same. Since a single oral 3 gram dose gives about 2000 μg/mL in the urine, the authors decreased this value 10 times and used a susceptible breakpoint of 200 μg/mL. Using this breakpoint the authors then plotted the data and determined the number of false susceptible and false resistant isolates. They discovered that there were more false resistant strains with both disks when no G-6-P was present. The percentage of false resistant strains was 8.2% in the case of the 50-μg disk and 3.3% in the case of the 200-μg disk. When G-6-P was added the false resistant percent was 0.4% for the 200-μg disk and 3.3% with the 50-μg disk. The authors recommend the 200-μg disk with 50-μg of G-6-P added to it since this gives the lowest percentage of major errors.

Pfaller et al (34) determined the interpretive errors observed when they prepared and tested 200-μg disks containing 0, 25, 50, or 100 μg of glucose-6-phosphate (G-6-P) against 350 common urinary tract pathogens. The disk test results were compared with broth microdilution MICs obtained using fosfomycin plus 25 μg/mL G-6-P. These authors used a susceptible breakpoint of ≤128 μg/mL and resistant ≥256 μg/mL and performed tests according to the procedures outlined by NCCLS. They determined that the corresponding breakpoints were essentially the same for all the supplemented disks. With these breakpoints they determined the error rates for each of the four disks. The results of this study are presented in Table 49.

Table 49
Evaluation of Fosfomycin Disks with Varying Amounts of G-6-P

Disk (μg)		Criteria (mm)			Error Rate (%)		
Fosfomycin	G-6-P	Susceptible	Intermediate	Resistant	Very Major	Major	Minor
200	0	≥16	13-15	≤12	0	21.9	6.6
200	25	≥16	13-15	≤12	0	3.7	10.8
200	50	≥16	13-15	≤12	0	2.8	6.3
200	100	≥16	13-15	≤12	0	2.8	5.4

These data show that fosfomycin disks without added glucose-6-phosphate gave false-resistant results in many cases (21.9%). The addition of G-6-P decreased the major errors to 3.7% with 25 μg and to 2.8% with either 50 or 100 μg added. The authors recommend a disk with either 50 or 100 μg of G-6-P added.

Both studies recommended a 200-μg fosfomycin disk. Pinasi recommends this disk also contain 50 μg of G-6-P and the Pfaller study agrees that the disk contain either 50 or 100 μg of G-6-P. A 200-μg disk with 50-μg of G-6-P was used in the clincial trails and is recommended in the labeling for this drug.

MIC BROTH/AGAR DILUTION COMPARISONS

Barry et al (5) performed agar dilution and broth microdilution susceptibility tests according to NCCLS procedures with the media fortified with 25 μg/mL of G-6-P. The data are presented in Table 50 and show that susceptibility results were virtually identical when tests were performed in G-6-P augmented cation-adjusted Mueller Hinton broth (CAMHB) or Mueller Hinton agar (MHA).

Table 50
Comparison of Broth and Agar-Dilution Tests for Determining the Antibacterial Activity of Fosfomycin *in vitro*

Organism (No. Tested)	MIC (μg/mL)					
	Broth Microdilution			Agar Dilution		
	50%	90%	Range	50%	90%	Range
Escherichia coli (31)	2.0	8.0		1.0	4.0	
Citrobacter spp. (30)	≤1.0	2.0		2.0	4.0	
Klebsiella spp. (30)	32	64		16	32	
Enterobacter spp. (45)	32	128		16	32	
Serratia marcescens (20)	16	32		8.0	16	
Proteus spp. (25)	2.0	128		ND*	ND	
Morganella morganii (10)	256	512		128	>256	
Providencia spp. (25)	16	128		16	128	
Pseudomonas spp. (35)	64	256		128	256	
Acinetobacter calcoaceticus subsp *anitratus* (10)	128	128		128	128	
Enterococcus spp. (41)	32	64		32	64	
Staphylococcus saprophyticus (30)	64	512		128	512	

* ND = No data, *Proteus* species were not tested in agar

Iwantscheff examined the activity of fosfomycin against a variety of *Staphylococcus* species (35). He used both broth microdilution and agar dilution methods. The results are given in Table 51.

Table 51
***In vitro* Activity of Fosfomycin against *Staphylococcus* Species**

Organism	No. Tested	No. of Strains Susceptible to ≤ 16 µg/mL		No. of Strains Susceptible to ≤ 64 µg/mL	
		Broth	Agar	Broth	Agar
S. aureus	20	12	7	20	19
S. epidermidis	23	18	16	20	19
S. hominis	22	15	1	20	13
S. haemolyticus	20	15	7	20	14
S. warneri	20	13	2	18	10
S. capitis	20	0	0	0	0
S. simulans	8	6	8	8	8
S. saprophyticus	5	4	0	5	1
S. cohnii	2	1	1	2	2
S. xylosis	2	2	2	2	2
S. auricularis	1	0	0	0	0

Unlike the studies that Barry performed, this study indicates that there is a difference in the two methods. Lower MICs were obtained in most cases when broth microdilution methods were used. This study only studied staphylococci, however, and there is no indication if this is true for other genera. The author also used DST (Diagnostic Test) agar for the agar dilution test and Mueller Hinton broth for the broth microdilution test and used 20 µg of G-6-P instead of the 50 µg that Barry used. It appears that if NCCLS methods are used the difference between agar dilution and broth microdilution methods is not great and that either method may be used.

MIC/DISK DIFFUSION CORRELATION STUDIES

Barry et al (36) performed a study using 149 microorganisms selected from common uropathogens that would normally be tested by the disk procedure and which included a wide range of on-scale MICs. Disk containing 200-μg of fosfomycin and 50 μg of glucose-6-phosphate were prepared by Difco Laboratories. Agar dilution test were carried out according to NCCLS metnods using two-fold dilutions of fosfomycin ranging from 2.0 to 512 μg/mL. All test were performed in Mueller Hinton agar supplemented with 25 μg/mL of G-6-P. Disk diffusion tests were also performed according to NCCLS procedures. All strains were tested in triplicate and the modal MIC was plotted against the average zone diameters. Control strains were also tested along with the test organisms. The regression line correlating MICs to zones of inhibition gave the regression formula $y = -1.9x + 44.8$ with a correlation coefficient $r = 0.70$. This study compares fairly well with Pinasi's (12) study in which the regression formula was $y = -1.65x + 38.8$ with a correlation coefficient of $r = 0.755$ when MICs obtained using an agar dilution test and Mueller-Hinton agar with 10 μg/mL of G-6-P were compared with zone diameters using a 200-μg fosfomycin disk with 50-μg of G-6-P.

Barry's study showed that zone-diameter breakpoints of ≥16 mm and ≤12 mm correlated with MICs of ≤64 μg/mL and ≥256 μg/mL, respectively. The investigators proposed a three category system to avoid interpretive errors. Zone diameter of 13-15 mm correlated with a intermediate category of MIC = 128 μg/mL. With this three category system, they obtained no false-susceptible (very major errors) and only three (2%) false-resistant (major errors) isolates. Of the 149 selected strains, 36 had intermediate MICs of 128 μg/mL, including 9 of 10 *Acinetobacter* spp., 1 of 10 *Pseudomonas aeruginosa*, 7 of 8 *Pseudomonas fluorescens*, 3 of 4 *Pseudomonas stutzeri*, 5 of 5 *Xanthomonas maltophilia*, 9 of 15 *Staphylococcus saprophyticus*, 1 of 10 *Klebsiella pneumoniae* and 1 of 5 *Providencia stuartii*. Only the *Staphylococcus saprophyticus* and the one *Klebsiella pneumoniae* would normally be tested for this drug. Of these 36 strains with intermediate MICs, 25 were resistant according to the disk test criteria. Five of the nine *Staphylococcus saprophyticus* strains with intermediate MICs were susceptible in the disk test and four were intermediate. Only 11 strains gave intermediate zones of 13-15 mm and five of these 11 strains were susceptible in agar dilution tests.

Pfaller et al (34) compared MICs and zone-diameters from 350 bacterial isolates using a susceptible breakpoint of ≤128 μg/mL. Broth microdilution was used to determine MICs in Mueller Hinton broth supplemented with 25 μg/mL of G-6-P. Disk diffusion testes were performed using disk with 200 μg of fosfomycin and 0, 25, 50, or 100 μg of G-6-P. Regression analyses were performed by the method of least squares and error rates for diffusion tests with each of the four different disks were calculated. Using breakpoints of ≤128 μg/mL for susceptible and ≥256 μg/mL for resistant the corresponding zone diameters breakpoints for the 200 μg disks with 50 μg of G-6-P were ≥16 mm and ≤12 mm, respectively. A 3-mm intermediate category was arbitrarily assigned, although there was no intermediate MIC category. With these breakpoints (See Table 49) there were no false-resistant (very major errors) results and only 2.8 % major errors. Most of these major errors would be eliminated (only one isolate would be in this category) with the inclusion of an intermediate MIC category of 128 μg/mL.

QUALITY CONTROL STUDIES (MIC AND DISK DIFFUSION)

Five laboratories collaborated in a study designed to develop MIC limits for quality control strains (36). Each participant prepared broth microdilution trays using a different lot of Mueller Hinton broth, and a control lot of trays was distributed to all participants. The participants tested three quality control stains. Each performed 20 separate tests with the lot of trays that they prepared and five additional tests with the common lot of trays. MIC limits were defined as the mode plus/minus one doubling dilution interval. If the true mode appeared to fall between the even $\log_2$ dilution intervals that were tested a four dilution range was used. The distribution of MIC values obtained is shown in Table 52.

Table 52
Distribution of MIC Values for Quality Control Strains with Fosfomycin

Control Strain	Number of Times Each MIC (µg/mL) Recorded								
	0.25	0.5	1.0	2.0	4.0	8.0	16	32	64
E. coli ATCC 25922	1	[10	52	42	18]*	2			
P. aeruginosa ATCC 27853			6	[46	37	32]	4		
S. aureus ATCC 29213	15	27	12	57	14				
E. faecalis ATCC 29212							[15	90	20]

* MICs that are within the proposed control limits are enclosed within brackets

Test with *Enterococcus faecalis* and *Pseudomonas aeruginosa* control strains were fairly reproducible and control limits (mode ± one doubling dilution) included three-dilution interval ranges. A four-dilution interval range was needed for *Escherichia coli* because the mode appeared to fall between 1.0 and 2.0 µg/mL. The results with *Staphylococcus aureus* were too variable to be useful and the use of this strain as a quality control strain is not recommended. The recommended quality control ranges in dilution susceptibility tests are as follows:

Enterococcus faecalis ATCC 29212	16 to 64 µg/mL
Escherichia coli ATCC 25922	0.5 to 4.0 µg/mL
Pseudomonas aeruginosa ATCC 27853	2.0 to 8.0 µg/mL

As part of additional ongoing studies with clinical isolates, quality control agar-dilution tests were performed with reference strains. These tests were done in Mueller Hinton agar containing 25 µg/mL G-6-P. In 64 of 65 (98.5%) tests, the MIC for *E. coli* ATCC 25922 was ≤ 2 µg/mL; only one test was outside of the QC maximum with an MIC of 64 µg/mL. All of the 59 results with *E. faecalis* ATCC 29212 were within the 16 to 64 µg/mL QC range. Since *Pseudomonas aeruginosa* is not indicated for this drug, it was not tested in the clinical trials.

Although only one collaborative study was submitted to the NDA (performed in 1991), two other studies were recently submitted to the NCCLS (performed in 1994 and 1995). The 1994 study did not confirm the results of the 1991 study so a new 1995 study was performed. Since we do not have all the data, the QC ranges established by the FDA may be different from those finally approved by the NCCLS. The NCCLS did not vote on the selection of QC ranges for the sponsor's submission at its meeting since the 1994 data was not included in the final analysis.

Barry et al (36) also collaborated in a six laboratory effort to develop quality control limits for disk diffusion tests. Investigators performed replicate procedures with three different quality control strains of bacteria. Two different manufacturers, prepared the disks containing 200 μg of fosfomycin and 50 μg of G-6-P. The study participants used different lots of Mueller Hinton agar and a lot common to all laboratories. Each participant performed 30 separate tests (20 on the lot of agar assigned to them and 10 on the common lot control medium), thus generating 300 zone diameter determinations. In one laboratory, the zone diameters produced with *S. aureus* were markedly different from the other five sites. The overall range of values for the latter were 23 to 35 mm for common and unique lots of media. The outlying facility provided a zone diameter range of 36 to 44 mm. If the zones from this laboratory were included, Gavin statistics would produce a range of mm for all the data, but 20.8% of the zones would be excluded. If the results from this laboratory were eliminated from further consideration a range of mm would result and only 8.3% of the zones would be excluded. Since this laboratory had large zones even on the common lot of media, it appears that an unknown problem existed in this laboratory during the performance of this testing. Zone diameter limits for each control strain were tentatively defined using the median's statistics of Gavan. Table 53 shows the distribution of zone sizes for the five laboratories with data that was not excluded.

Table 53
Distribution of Zone Diameters in 300 Replicate Tests in Five Laboratories Using 200 μg Fosfomycin Disks

Zone Diameter (mm)	Number of Times Each Zone Diameter Recorded		
	E. coli ATCC 25922	*S. aureus* ATCC 25923	*P. aeruginosa* ATCC 27853
20	2*		
21	2*		
22	8		2
23	36	3*	1
24	62	3*	2
25	62	8	13
26	58	20	25
27	41	40	27
28	28	44	20
29	1	60	20
30	0*	61	25
31		32	21
32		18	18
33		[illegible]	8
34		[illegible]	19
35		1*	28
36			29
37			21
38			17
39			4
40			

* Asterisks designate zones outside of proposed control limits: useful limits could not be defined for disk diffusion tests with *P. aeruginosa* ATCC 27853.

The medians statistic of Gavan defined 7 mm ranges of acceptable zone sizes for *E. coli* ATCC 25922 (23-29 mm) and *S. aureus* ATCC 25923 (26-32 mm when laboratory is excluded). However, these ranges would include less than 95% of the reported values (94.2% for *E. coli* and 91.7% for *S. aureus).* To be consistent with NCCLS practice, these ranges need to be extended one mm at each end (only at the lower end for *E. coli* since there are no 30 mm zones). The adjusted ranges are mm for *E. coli* ATCC 25922 (98.8% of data) and mm for *S. aureus* ATCC 25923 (97.3% of data). The sponsor has incorrectly listed the range for *E. coli* in the proposed label as mm. Gavan statistics give a range of mm for *Pseudomonas aeruginosa* ATCC 27853. This range, however, excludes 39.2% of the data. A 14-mm range mm) would be needed for tests with *P. aeruginosa* ATCC 27853 to include 95% of the data. The extensive intralaboratory variability in zone diameters makes this strains useless for Quality Control Testing. Disk zone diameter QC tests performed with reference strains during the clinical trails showed that among 62 zones diameters observed with *S. aureus* ATCC 25923, 96.8% (60 values) were within the mm limits; the other two zones diameters were 24 mm. With *E. coli* ATCC 25922, 65 zone diameters ranged from mm. Only one, at 18 mm, was below the mm range.

Once again, only the 1991 study was submitted to the NDA. Another study was performed in 1994 and submitted to the NCCLS. Since we do not have all the data to review, our QC ranges may be different than those finally approved by the NCCLS.

CROSS RESISTANCE/CROSS SUSCEPTIBILITY STUDIES

Fosfomycin exerts its effect on bacterial cells by blocking the first step in cell wall synthesis. It is, therefore, in a class by itself and there are no other similar drugs to compare it too. The only studies that have shown cross resistance between fosfomycin and other drugs are those in which resistance to fosfomycin is conferred by plasmids. These mutants were also resistant to carbenicillin, streptomycin, kanamycin, gentamicin, tetracycline, chloramphenicol, and sufonamides. None of these drug's mode of action is similar to that of fosfomycin and resistance comes from the fact that the plasmid carries many resistant factors on it.

During the clinical trials, 129 patients showed the same species of pathogen pre and post treatment. The microbes were tested to see if they shifted from an initial interpretation of susceptible to post therapy resistance. Of the 129 isolates (28 of them *Klebsiella pneumoniae* isolates) four *Klebsiella pneumoniae* isolates went from an MIC of μg/mL to an MIC of μg/mL and thus developed resistance to fosfomycin.

ANAEROBIC STUDIES

Fosfomycin is not indicated for anaerobic bacteria and no studies were, therefore, performed on anaerobes.

HAEMOPHILUS AND *NEISSERIA* STUDIES

Fosfomycin is not indicated for these two organisms and no studies were, therefore, performed.

BACTERIOLOGICAL EFFICACY

CORRELATION OF TEST RESULTS WITH OUTCOME

Correlation of Outcome with and without G-6-P

Data relating the bacteriological success obtained with fosfomycin therapy to the MICs obtained against baseline pathogens, are summarized in Table 54. Results with and without the addition of G-6-P (glucose-6-phosphate) are compared for the species in which G-6-P enhanced activity.

Table 54
Relationship Between MICs with and without G-6-P and Bacteriological Success

Species	Presence of G-6-P in MHB	No. of Isolates in MIC Range			No. of Bacterio Cures	% Cures
		≤64 µg/mL	128 µg/mL	≥256 µg/mL		
C. diversus	-	1	0	0	1	100
	+	1	0	0		
E. aerogenes	-	0	1	4	3	60
	+	5	0	0		
E. cloacae	-	1	1	0	2	100
	+	2	0	0		
E. coli	-	381	10	3	350	89
	+	394	0	0		
K. pneumoniae	-	1	4	24	21	72
	+	25	4	0		
All Species	-	384	16	31	377	87
	+	427	4	0		

As seen in the above table the need for the addition of G-6-P is especially relevant in tests involving *K. pneumoniae*. In 21 of 29 cases (72%) bacteriological cure was obtained with fosfomycin in this species. Tests not using G-6-P would have falsely predicted that 24 of the isolates were not susceptible (MIC ≥ 256 μg/mL), and that four were in the intermediate range. Only one isolate would be considered susceptible. On the other hand, with the addition of G-6-P, 25 of the isolates were found to be susceptible and four were in the intermediate category. These data clearly support the contention that the use of G-6-P in the medium provides fosfomycin clinical isolate susceptibility values that provide a better correlation with bacteriological outcome. This latter classification is much more appropriate than the first one without G-6-P. Table 55 gives a more detailed summary of the results with *K. pneumoniae* broken down by MIC values.

Table 55
Influence of G-6-P in Susceptibility Tests on the Predictability of Fosfomycin Therapy Against *K. pneumoniae*

MIC (μg/mL)	Tested without G-6-P		Tested with G-6-P	
	No. of isolates	No. of Cures	No. of Isolates	No. of Cures
4	0		3	3
8	0		11	7
16	0		8	4
32	0		3	3
64	1	1	0	
128	4	3	4	4
256	12	9		
512	12	8		
≤ 64	1	1	25	17
128	4	3	4	4
≥ 256	24	17	0	

In the case of *Escherichia coli*, where there was an 89% bacteriological cure rate among 394 isolates, the deletion of G-6-P from the test medium would predict that 12 successful cures were in the intermediate or resistant category (Table 56). Once again the need for G-6-P is shown.

Table 56
Influence of G-6-P in Susceptibility Tests on the Predictability of Fosfomycin Therapy Against *Escherichia coli*

MIC (µg/mL)	Tested without G-6-P		Tested with G-6-P	
	No. of isolates	No. of Cures	No. of Isolates	No. of Cures
2	0		378	336
4	0		8	8
8	1	1	3	2
16	12	9	2	1
32	153	137	0	
64	215	191	3	3
128	10	10	0	
256	2	1	0	
512	1	1	0	
≤ 64	381	338	394	350
[illegible]	10	10	0	
≥ 256	3	2	0	

Correlation of MICs with Outcome

MICs obtained from baseline pathogens were related to the bacteriological outcomes obtained during clinical trials against uncomplicated urinary tract infections in women. Results are given in Table 57.

Table 57
Relationship Between MICs and Bacteriological Success

Species	MIC (µg/mL)	No. Isolates	No. Cured
Citrobacter diversus	2	1	1
Enterobacter aerogenes	8	2	2
	16	3	1
Enterobacter cloacae	4	2	2
Enterococcus faecalis	16	2	2
	32	17	14
	64	4	4
Escherichia coli	2	378	336
	4	8	8
	8	3	2
	16	2	1
	64	3	3

Table 57 (cont)
Relationship Between MICs and Bacteriological Success

Species	MIC (µg/mL)	No. Isolates	No. Cured
Klebsiella pneumoniae	4	3	3
	8	11	7
	16	8	4
	32	3	3
	128	4	4
Proteus mirabilis	2	14	12
	4	3	2
	8	1	1
	32	1	0
	128	1	1
	256	1	1
Providencia rettgeri	2	1	1
Staphylococcus saprophyticus	2	1	1
	64	6	4
	512	3	1

From the above table it can be seen that MICs and bacteriological outcome are related as follows:

MIC	Cure/No. Isolates	% Cure
2	351/395	88.9
4	15/16	93.8
8	12/17	70.6
16	8/15	53.3
32	17/21	81.0
64	11/13	84.6
128	5/5	100
256	1/1	100
512	1/3	33.0

This data indicates that some failures have an MIC of 2 μg/mL. There is also a lower cure rate at 8 and 16 μg/mL, but if the susceptibility breakpoint is set at 8 or 16 μg/mL then the isolates at 32 an 64 μg/mL would be considered resistant (or at least intermediate) and the cure rate for these isolates is almost as high as for those at 2 μg/mL. It appears that isolates at 128 and 256 μg/ mL are also cured, but there are very few of them, especially at 256 μg/mL. It appears that isolates at 512 μg/mL are not cured very well, but once again there are only a few of them to base this judgement on. The best situation is probably to set a breakpoint for susceptible at 64 or 128 μg/mL and consider isolates above them resistant. The only common urinary pathogen that would normally fall in this area is *Staphylococcus saprophyticus* and breakpoints would probably be useful to predict susceptibility for this species. Unfortunately, there are only 10 of these isolates and only three of them have MICs > 64 μg/mL. If we use a breakpoint of 64 μg/mL for susceptible and 128 μg/mL for intermediate, since this eliminates many major errors when comparing MICs and zone diameters, we should be able to predict at least that certain isolates (those with MICs of ≥ 256 μg/mL) will usually lead to failure. Predicting a success is much harder since many isolates with low MICs (8 to 16 μg/mL and even at 2 μg/mL) sometimes lead to failures.

The relationship between zone diameters obtained from baseline pathogens and bacteriological outcome was also investigated. Most zones were between mm. Table 58 shows this relationship for individual species.

Table 58
Relationship Between Zone Diameter and Bacteriological Outcome

Species	Zone Diameter (mm)	No. Isolates	No. Cured
Citrobacter diversus	23	1	1
Enterobacter aerogenes	19	3	2
	21	2	1
Enterobacter cloacae	21	1	1
	22	1	1
Enterococcus faecalis	14	1	1
	15	1	0
	18	4	4
	19	2	2
	20	4	4
	21	4	4
	22	1	1
	23	2	2
	24	3	2
	25	1	0
Klebsiella pneumoniae	6	1	1
	11	1	1
	12	1	1
	15	1	1
	16	5	4
	17	2	0
	18	6	3
	19	5	5
	20	6	5
	21	1	0

Table 58 (continued)
Relationship Between Zone Diameter and Bacteriological Outcome

Species	Zone Diameter (mm)	No. Isolates	No. Cured
Escherichia coli	12	1	1
	14	1	1
	17	2	2
	19	1	1
	20	3	3
	21	5	4
	22	21	18
	23	45	42
	24	65	55
	25	108	97
	26	79	65
	27	44	39
	28	16	14
	29	3	3
Proteus mirabilis	11	1	1
	17	1	1
	19	1	0
	25	2	2
	26	1	0
	29	3	3
	30	2	2
	31	1	1
	32	4	3
	33	1	1
	34	4	3
Providencia rettgeri	26	1	1

Table 58 (continued)
Relationship Between Zone Diameter and Bacteriological Outcome

Species	Zone Diameter (mm)	No. Isolates	No. Cured
Staphylococcus saprophyticus	6	3	1
	13	2	2
	15	3	2
	16	1	0
	35	1	1

From the above table it can be seen that zone diameter and bacteriological cure rate is related as follows:

Zone Diameter (mm)	No. Cured/No. Isolates	% Cured
6	2/4	50
11	2/2	100
12	2/2	100
13	2/2	100
14	2/2	100
15	3/5	60
16	4/6	66.6
17	3/5	60
18	7/10	70
19	10/12	83.3
20	12/13	92.3
21	9/12	75
22	20/23	87
23	45/48	93.8
24	57/68	83.8
25	99/111	89.2
26	66/81	81.5
27	39/44	88.6
28	14/16	87.5
29	6/6	100
30	2/2	100
31	1/1	100
32	3/4	75
33	1/1	100
34	3/4	75
35	1/1	100

As can be seen there are very few zones smaller than 18 or greater than 28 millimeters on which to base a breakpoint. The percentage cures does not really tell us much about these zone diameter since one or two failures can cause the percentage cures to decrease greatly since the number of isolates is small. Most of the cure rates for zone diameters that had a sufficient number of isolates varied from the low 80's to 90's percent. There does not seem to be a logical breakpoint for susceptibility. There may be some evidence of a difference between zone diameters of 18 and 19 (cure rates of 70% or lower for zones of 15-18 mm and 83.3% or greater (except for 21mm at 75% and 26 mm at 81.5%) for larger zones, respectively), but this may be due to the low number of isolates present at the smaller zone diameters.

The regression line calculated from the data from the clinical trials in which both an MIC and a zone diameter were given for the baseline pathogen gave the line $y = -0.038x + 24.4$ with a correlation coefficient of only -0.509. This indicates that there is basically no correlation between zone diameters and MICs. This is probably due to the fact that most of the MICs had a value of 2 μg/mL and almost all zone diameters were mm. There were almost no large or small zone diameters or high MICs. This regression line gives a zone diameter of 22 mm for an MIC of 64 μg/mL, 20 mm for an MIC of 128 μg/mL, and 15 mm for an MIC of 256 μg/mL. If 15 mm is used as resistant and 22 mm as susceptible, we have a very large intermediate zone range of mm. This is unacceptable. If 22 is used as susceptible and the normal three millimeters for intermediate, this gives us 21, 20 and 19 mm as intermediate and 18 mm as resistant. This gives us 19/505 zone diameters that would be classified as major errors. This is 3.8% which is above the acceptable 1% range. This regression line does not represent what Barry et al (36) or Pfaller et al (34) found. Barry's study found that a susceptible breakpoint of ≥16 mm correlated with an MIC of ≤ 64 μg/mL and a zone of ≤12 mm correlated with an MIC of ≥ 256 μg/mL. Pfaller's study found a suceptible breakpoint of ≥16 mm correlated with an MIC of 128 μg/mL. In Pfaller's study these breakpoints led to 2.8% major errors, which were eliminated if breakpoints of ≥16mm and ≤64 μg/mL were used for susceptible. Both of these studies used a variety of organisms that had a wide dispersion of MIC values and zone diameters and thus had more isolates at either end of the susceptibility spectrum. It appears that the data obtained from the clinical trials leads to a skewed regression line since almost all MICs are 2 μg/mL and most zones are 22 to 28 mm. The data obtained from Barry's and Pfaller's studies appear to more closely represent what the zone diameter breakpoints should be for fosfomycin.

The major question for this drug product is the need for susceptibility testing. This product will be used for UTI and will be given as a single dose product. In most cases susceptibility testing probably will not be performed. The patient will visit and an uninary tract infection will be verified. The drug will be given and if the patient is cured, she will not come back for another visit. If the patient is not cured, she will come in again and another drug will be administered.

If the need for susceptibility testing is confirmed, the following zone diameters and MIC breakpoints should be considered for fosfomycin:

MIC (µg/mL)	Interpretation
≤64	S = Susceptible
128	I = Intermediate
≥256	R = Resistant

Zone Diameter (mm)	Interpretation
≥ 16	S = Susceptible
13-15	I = Intermediate
≤ 12	R = Resistant

The following Quality Control criteria should be used:

Organism	MIC Limit (µg/mL)	Zone Diameter (mm)
E. coli ATCC 25922		22-29
E. faecalis ATCC 29212		------
P. aeruginosa ATCC 27853		------
S. aureus ATCC 25923		25-33

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INTERPRETATIVE CRITERIA ESTABLISHED

The final interpretative criteria will be established after the clinically relevant organisms are determined for this product. The proposed criteria below, however, will probably be the final criteria no matter what organisms are given. *Staphylococcus saprophyticus* is the organism that usually falls close to the borderline of the criteria given below. If this organism is not given as a causative pathogen, the use of susceptibility criteria becomes less useful, since most other organisms have only a few isolates near these breakpoints. These breakpoints may, however, be useful in explaining why an infection is not cured. Most organisms that had MICs of 64 µg/mL or less gave a satisfactory bacteriological response when treated with fosfomycin. There were almost no isolates above this MIC (except for a few isolates of *S. saprophyticus).*

The following criteria should be used:

MIC (µg/mL)	ZONE DIAMETER (MM)	INTERPRETATION
≤ 64	≥ 16	SUSCEPTIBLE (S)
128	13-15	INTERMEDIATE (I)
≥ 256	≤ 12	RESISTANT (R)

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The following issues should be discussed (perhaps at an advisory committee meeting.

1) Since this product is going to be given as a single dose to women with uncomplicated UTI infections is there a need for susceptiblity breakpoints?

2) Should the sponsor be required to submit all data and studies that have been completed to the NDA. Two studies on ranges for Quality Control organisms were submitted to the NCCLS, but never submitted to the NDA for review. A third clinical trial was also performed and never submitted.

The following information should be relayed to the sponsor:

1) The following organisms that are listed in the proposed labeling should be deleted:

The MICROBIOLOGY section of the package insert should be revised to read as follows:

2 Pages (99-100)
Deleted

REFERENCES

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically--Third Edition; Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25 NCCLS, Villanova, PA, December, 1993.

2. National Committee for Clinical Laboratory Standards, Performance Standard for Antimicrobial Disk Susceptibility Tests--Fifth Edition; Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24 NCCLS, Villanova, PA, December, 1993.

Peter A. Dionne
Peter A. Dionne
Review Microbiologist

cc: Orig. NDA 50-711
HFD-520/Division File
HFD-520/MO/Soreth
HFD-520/Pharm/Joshi
HFD-520/Chem/Timper
HFD-520/CSO/Dillon-Parker
HFD-520/Micro/Dionne

Concurrence Only:
HFD-520/ActingDir/LGavrilovich
HFD-520/SMicro/ATSheldon

OCT 1 8 1996

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Clinical Microbiological Review

NDA #: 50-717 **REVIEW #:** #2 **REVIEW DATE:** 8/21/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
(I) NDA Amendment	28-JUN-96	28-JUN-96	07-JUL-96
(II) NDA Amendment	17-MAY-96	17-May-96	07-JUL-96
(III) NDA Amendment	30-JUL-96	01-AUG-96	09-AUG-96

PROVIDING FOR

(I) 28-JUN-96: Answers to September 20, 1995 Non-Approval Letter
(II) 17-MAY-96: New Clinical Study MON-US-03
(III) 30-JUL-96: Revised Package Insert

NAME & ADDRESS OF APPLICANT:

ZAMBON CORPORATION
DIVISION OF ZAMBON GROUP, SpA
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DRUG PRODUCT NAME

Proprietary:	MONURAL™
Nonproprietary/USAN:	Fosfomycin Tromethamine
Code Names/#'s:	Z1282
Chemical Type/ Therapeutic Class:	1 S

ANDA Suitability Petition/DESI/Patent Status:

Patent 4,863,908 expires 2/23/2005--method of UTI treatment with fosfomycin tromethamine; Patent 5,162,309 expires 11/10/2009--relates to solid fosfomycin tromethamine physico-chemical characteristics; Patent 5,191,094 expires 3/2/2010--relates to process of preparation of fosfomycin tromethamine. All patents held by Zambon Group, Vincenza, Italy.

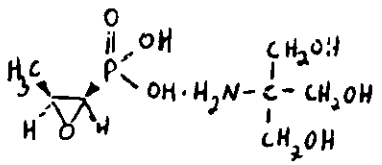
PHARMACOLOGICAL CATEGORY/INDICATION: Antibiotic/single dose treatment of uncomplicated UTI

DOSAGE FORM:	Powder (Sachets)
STRENGTHS:	3 grams
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	_X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name: Mono-(2-ammonium-2-hydroxymethyl-1,3-propanediol)-(2R-cis)-(3-methyloxiranyl)phosphonate-(2R-cis)-(3-methyloxiranyl)phosphonic acid, compd. with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Chemical Structure:



Molecular Formula: $C_7H_{18}NO_7P$
Molecular Weight: 259.2

SUPPORTING DOCUMENTS: DMF

DMF

DMF

DMF

DMF

DMF

RELATED DOCUMENTS: IND

CONSULTS: None

REMARKS/COMMENTS:

(I) AMENDMENT--28-JUN-96

The amendment dated June 28, 1996 is a response to the Non-Approval Letter dated September 20, 1995. Each of the Comments is listed below along with the Sponsor's response and Reviewer Comments.

1. *Based on our review of the microbiology data submitted, we have determined that the following organisms are resistant to fosfomycin--they have MIC_{90} values which exceed the susceptibility breakpoint.*

Enterobacter species--we now normally require each species to be studied and listed in the labeling. The MIC_{90} values for species other than Enterobacter aerogenes were > 64 μg/mL.

Response:

"Due to limited data for *Enterobacter* species isolates in the clinical trials, at present, species other than *Enterobacter aerogenes* should not be considered susceptible to FT."

Reviewer Comments: Response is satisfactory

Providencia rettgeri--MIC_{90} values were >64μg/mL.

Response:

"Due to limited data for *Providencia rettgeri* isolates in the clinical trials, at present, this organism should not be considered susceptible to FT."

Reviewer Comments: Response is satisfactory

Providencia stuartii--MIC_{90} values were > 64μg/mL.
Response:
"Due to limited data for *Providencia stuartii* isolates in the clinical trials, at present, this organism should not be considered susceptible to FT."
Reviewer Comments: Response is satisfactory

Pseudomonas aeruginosa--Not usually an urinary tract pathogen. MIC_{90} values were > 64μg/mL.
Response:
"Due to limited data for *Pseudomonas aeruginosa* isolates in the clinical trials, at present, this organism should not be considered susceptible to FT."
Reviewer Comments: Response is satisfactory

Xanthomonas maltophilia--Not usually an urinary tract pathogen. MIC_{90} values > 64 μg/mL.
Response:
"Due to limited data for *Xanthomonas maltophilia* isolates in the clinical trials, at present, this organism should not be considered susceptible to FT."
Reviewer Comments: Response is satisfactory
This name of the organism has been changed by the nomenclature committee and is now

Staphylococcus saprophyticus--MIC_{90} values were > 64 μg/mL.
Response:
"The antibacterial spectrum of FT has been investigated in a study of 3,176 isolates representing 21 species associated with urinary tract infection. This study was included in NDA (now 50-717) for Monurol as Reference 61 in Volume 50, Pages 7/00888-00901. There were 128 isolates of *Staphylococcus saprophyticus* in this sample, 52% of which were susceptible to ≤ 64 μg/mL, with an additional 12% susceptible to 128 μg/mL."
"In the modified ITT populations of Studies, MON-US-01, MON-US-02 and MON-US-03, there were 26 patients with uncomplicated UTIs in which *Staphylococcus saprophyticus* was the uropathogen identified on baseline culture. Table 1 shows the agar dilution MICs and disk diffusion zones of inhibition of these 26 *S. saprophyticus* isolates and the bacteriological outcomes of patients infected with these organisms. The agar dilution and disk diffusion testing was done by the central reference laboratory in the trials,
on 21 of the isolates. The other five isolates were not received by the central laboratory so that only disk

diffusion results, which were obtained at the local laboratories are available. At the primary efficacy assessment 5-11 days after single-dose FT, 17/26 (65%) patients were cured of their infection. Fourteen of the 17 patients who experienced a cure at the initial visit remained free of infection at the final visit 25-57 days after FT treatment."

TABLE 1

In Vitro Susceptibility Test Results and Bacteriological Outcomes
Patients with Uncomplicated UTI due to *Staphylococcus saprophyticus*

Pt ID Study/Center/Patient	MIC (CMI)	Disk Zone (CMI)	Disk Zone (Local Lab)	Bact Outcome (Primary Visit)	Bact Outcome (Final Visit)
	--	--	0	Fail	--
	--	--	21	Cure	Cure
	512	6	--	Fail	--
	--	--	No zone	Cure	Cure
	2	35	--	Cure	Cure
	64	16	--	Fail	--
	64	15	--	Cure	Cure
	512	6	--	Cure	Cure
	64	15	--	Cure	Cure
	64	13	--	Cure	Cure
	512	6	--	Fail	--
	--	--	40	Cure	Cure
	512	6	--	Fail	--
	128	8	--	Cure	Cure
	64	17	--	Cure	Fail
	2	36	--	Cure	Cure
	64	16	--	Fail	--
	32	19	--	Cure	Cure
	64	13	--	Cure	Cure
	256	6	--	Cure	Fail
	--	--	16	Fail	--

TABLE 1 (continued)
In Vitro Susceptibility Test Results and Bacteriological Outcomes
Patients with Uncomplicated UTI due to *Staphylococcus saprophyticus*

Pt ID Study/Center/Patient	MIC (CMI)	Disk Zone (CMI)	Disk Zone (Local Lab)	Bact Outcome (Primary Visit)	Bact Outcome (Final Visit)
	64	17	--	Cure	Cure
	256	6	--	Cure	Cure
	64	15	--	Fail	--
	256	9	--	Cure	Cure
	512	6	--	Fail	--

Abbreviations

Bact Outcome	Bacteriological outcome
CMI	Clinical Microbiology Institute, Inc., the reference laboratory
Disk Zone	Zone of inhibition by the disk diffusion method
Local Lab	Investigator's local laboratory
MIC	Minimum inhibitory concentration by the agar dilution method
Pt ID No.	Patient's identification number

"The data show that *in vitro* susceptibility testing of *S. saprophyticus* isolates in the clinical trails was only a fair predictor of a patient's response to therapy."

- "Agar dilution MIC results were available for 21 patients (Table 2). Ten of 13 patients (77%) whose isolates of *S. saprophyticus* had MICs of ≤128 μg/mL, which defines organisms as susceptible or intermediate, were cured at the primary assessment visit. Although an MIC of ≥256 μg/mL defines organisms as resistant to FT, 3/3 (100%) of patients with MIC values of 256 μg/mL were bacteriological cures. Even at an MIC of 512 μg/mL, which was the value for 5 isolates, one patient (20%) was a cure."

TABLE 2
Relationship between MIC and Bacteriological Response
(Primary Assessment Window)
Uncomplicated UTI due to *Staphylococcus saprophyticus*

MIC (μg/mL)	Interpretive Criteria	No. Isolates	No. Cure (%)	No. Fail (%)
2	Susceptible	2	2 (100%)	0 (0%)
32	Susceptible	1	1 (100%)	0 (0%)
64	Susceptible	9	6 (67%)	3 (33%)
128	Intermediate	1	1 (100%)	0 (0%)
256	Resistant	3	3 (100%)	0 (0%)
512	Resistant	5	1 (20%)	4 (80%)

Abbreviations

MIC Minimal Inhibitory Concentration by agar dilution method using Mueller-Hinton agar media supplemented with 25 μg/mL of glucose-6-phosphate

No. Cure Number of patients with bacteriological cure at primary assessment

No. Fail Number of patients with bacteriological failure at primary assessment

No. Isolates Number of isolates of *S. saprophyticus*

- "Disk diffusion results were available for 26 patients (Table 3). Eleven of 15 patients (73%) whose isolates had zone diameters of ≥13 mm, which defines organisms as intermediate to FT, were cured. Six of 11 patients (55%) whose isolates of *S. saprophyticus* had zone sizes of ≤12 mm, which defines organisms as resistant to FT, were also cured."

TABLE 3
Relationship between Zone Diameter and Bacteriological Response
(Primary Assessment Window)
Uncomplicated UTI due to *Staphylococcus saprophyticus*

Disk Zone (mm)	Interpretive Criteria	No. Isolates	No. Cure (%)	No. Fail (%)
≤ 12	Resistant	11	6 (55%)	5 (45%)
13	Intermediate	2	2 (100%)	0 (0%)
14	Intermediate	0	0	0
15	Intermediate	3	2 (67%)	1 (33%)
≥ 16	Susceptible	10	7 (70%)	3 (30%)

Abbreviations

Disk Zone (mm)	Zone of inhibition in millimeters by disk diffusion using disks containing 200 μg of fosfomycin and 50 μg of glucose-6-phosphate
No. Cure	Number of patients with bacteriological cure at primary assessment
No. Fail	Number of patients with bacteriological failure at primary assessment
No. Isolates	Number of isolates of *S. saprophyticus*

"In Study MON-US-03, which compared fosfomycin (FT) to nitrofurantoin (NF), a drug approved for the treatment of uncomplicated UTI due to *S. saprophyticus*, 13 patients treated with FT and 12 patients treated with NF had *S. saprophyticus* as the baseline pathogen. Of the three studies submitted to the NDA, MON-US-03 had the largest number of FT treated patients with this uropathogen. The bacteriological cure rate for FT in the primary assessment window was 9/13 (69%) for FT and 10/12 (83%) for NF, which are similar for this sized sample."

"In view of the similarity of cure rates for FT and NF and the inability of *in vitro* susceptibility testing to consistently predict response to FT for this species, it is proposed that *S. saprophyticus* be included in the Indications and Usage section as a uropathogen for which FT treatment is an acceptable choice and be included in the Microbiology section of FT's labeling as an organism against which FT has been shown to be active."

Reviewer Comments: The reference referred to by the applicant was one of many studies included in the original NDA submission that tested isolates of *Staphylococcus saprophyticus* (see TABLE 4). In all of these studies except the Pinasi study in which all species of *Staphylococcus* were included, The MIC_{90} values were >128 μg/mL. The MIC_{50} value in these studies was 64 μg/mL or higher. Since in order to be included in the *in vitro* activity listing in the labeling the organisms must have an MIC_{90} value less than or equal to the susceptibility breakpoint (64 μg/mL for fosfomycin) the reference study and most of the other studies in which this organism was tested indicate that

The fact that many isolates that are resistant, using *in vitro* testing, are bacteriological cures is not unusual. Many of the isolates that are indicated as being susceptible may also be bacteriological failures in clinical trials. *In vitro* testing is only a rough estimate of what might happen in clinical trials. Table 2 shows that most of the isolates with MIC values of 512 μg/mL are failures as would be expected. Although all three isolates with MIC values of 256 μg/mL were cured, there were only three isolates and it is difficult to base conclusions on such a small number of isolates. Table 3 shows that isolates with zone sizes that indicate they should be resistant have only a 55% bacteriological cure rate while isolates with intermediate or susceptible zone diameters have a higher cure rate.

In study MON-US-03, the cure rate for fosfomycin was only 69% compared to a cure rate for nitrofurantoin of 83% for infections caused by *Staphylococcus saprophyticus*. Table 5 shows that nitrofurantoin has better *in vitro* activity against *Staphylococcus saprophyticus* than fosfomycin.

TABLE 4

In vitro activity of fosfomycin against *Staphylococcus saprophyticus*

Investigator	Country	# Tested	Method	Range	MIC_{50}	MIC_{90}
Barry	USA	30**			128	512
					64	512
					128	>256
					64	256
					64	512
					64	256
					64	256
Wise	UK	42			64	>128
Pinasi	Italy	19 species			4	64
Barry	USA	128			64	>512

** The same 30 isolates were tested under each of the conditions stated.

TABLE 5
Susceptibility of Baseline Pathogens to Individual Study Drugs
Modified ITT Population (STUDY MON-US-03)

	FT Susceptible?				NT Susceptible?			
	Yes	Int	No	N/D	Yes	Int	No	N/D
Citrobacter diversus	2	0	0	0	1	0	0	1
Enterobacter	0	0	1	0	0	1	0	0
Enterobacter aerogenes	4	3	1	0	3	2	3	0
Enterobacter cloacae	2	0	0	0	2	0	0	0
Enterococcus faecalis	3	0	0	0	3	0	0	0
Enterococcus group D	1	0	0	0	1	0	0	0
Escherichia coli	397	3	1	5	357	16	19	14
Klebsiella	1	0	0	0	0	0	1	0
Klebsiella ozaenae	1	0	0	0	1	0	0	0
Klebsiella pneumoniae	18	3	3	0	12	9	2	1
Proteus mirabilis	22	0	2	0	1	5	18	0
Pseudomonas aeruginosa	1	0	0	0	0	0	1	0
Staphylococcus saprophyticus	13	2	9	1	23	1	0	1
Streptococcus Group D	1	1	0	0	1	1	0	0
Sub-Total	466	12	17	6	405	35	44	17
Total Number of Pathogens Tested		495				484		

N/D = Not Tested
Int = Intermediate Susceptibility
Note: For FT, intermediate susceptibility size = 13-15 mm. For NF, intermediate susceptibility size zone = 15-16 mm.

If it is determined that fosfomycin is indicated for uncomplicated UTI caused by *Staphylococcus saprophyticus* then this organism will be allowed in the microbiology subsection in the listing of organisms for which both *in vitro* and clinical efficacy have been shown but the following statement should follow its listing: **"(although many strains are resistant *in vitro*, clinical efficacy has been demonstrated)".**

2. *Based on our analyses of the study submitted, the QC limits for Escherichia coli ATCC 25922 should be mm instead of mm. It appears that an error was made when the data from Barry's study were interpreted. Gavan statistics indicated limits of mm, but this included only 94.2% of the data. It was suggested that the range be extended mm on each end, but since no zones of mm were found in the collaborative study, a range of mm is indicated.*

Response:
"Due to an error, the adjusted QC range for *E. coli* was stated to be mm, rather than mm in subsection 7.9.4 Quality Control Guidelines for Disk Diffusion Susceptibility Tests of the Microbiology Section of the NDA (Volume 48, Page 7/00093). This erroneous value also appeared in subsection 7.13(J) Conclusions (Volume 48, Page 7/00120)."

"In this submission, reports of studies which have generated data designed to determined and evaluate the QC parameters for fosfomycin susceptibility tests are included, together with a synopsis of the studies and conclusions drawn from them. With regard to QC limits for *E. coli* ATCC 25922 by the disk diffusion method, the synopsis provides justification for a range of mm (Exhibit 4, Page 3). If a narrower range of mm is still preferred by the Agency, Forest would like the opportunity to discuss this issue further."
Reviewer Comments: The applicant's response is satisfactory. The study included in the original submission was performed in 1991 and Gavan statistics gave a range of mm. This range included only 94% of the total number of zones reported by all six laboratories. To attain the ≥95% requirement of NCCLS Document M-23, one millimeter was added to each end of the range and this included 98.9% of all test results. A reviewer error was made in copying the data and there were nine zone diameters of mm in the 1991 study. In a subsequent ten-laboratory study performed in 1994, 96% of the results fell within this mm range and only 93% were within a range of mm. A range mm for . ATCC 25922 is acceptable

FDA knows that there is some controversy regarding QC ranges for this drug, especially for MIC QC limits. Although only one collaborative study was submitted to the NDA (performed in 1991), two other MIC studies were submitted to the scientific community (performed in 1994 and 1995). The 1994 study did not confirm the results of the 1991 study so a new 1995 study was performed. Only the 1991 study for zone diameters has been submitted. Another 1994 study was performed. FDA must have all data to determine QC ranges.

Response:
"Additional studies bearing on the determination of MIC QC ranges for fosfomycin by the microbroth and agar dilution methods are presented in Exhibit 4. A synopsis of the results and conclusions are also included. With regard to the broth microdilution method, the experimental data demonstrated that useful QC limits for the standard test organisms were difficult to define, primarily because of failure to precisely control inoculum size. Therefore, agar dilution is recommended as the standardized dilution susceptibility testing method for the quantitative measurement of the in vitro activity of fosfomycin against bacterial isolates. Exhibit 4 provides confirmation that acceptable MIC QC ranges for the four standard QC organisms are achievable by the agar dilution technique."
Reviewer Comments: Information is submitted on quality control studies of susceptibility tests with fosfomycin performed by:

Disk Diffusion Test

In 1991 a six laboratory study following the approach outlined in Document M-23 of the NCCLS was conducted to determine the appropriate QC zone diameter ranges for *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853 when testing fosfomycin with disks containing 200 μg fosfomycin and 50 μg glucose-6-phosphate. Each laboratory generated 60 zone diameters for each organism. This was the study presented in the original NDA.

In 1994 another ten-laboratory reproducibility study was conducted to confirm the QC ranges found in the 1991 study. Each of the ten laboratories generated 10 zone diameters for each control strain.

The results of disk tests in the two studies are summarized in TABLE 6.

TABLE 6
Fosfomycin Disk Test QC Studies
Six laboratory Study generating 300 zones per strain (1991)
Ten laboratory reproducibility Study generating 100 zones per strain (1994)

Zone Diameter (mm)	Number of Times each Zone Diameter Reported *E. coli* ATCC 25922		*S. aureus* ATCC 25923		*P. aeruginosa* ATCC 27853	
	1991	1994	1991[a]	1994	1991	1994
18		1				1
19						
20	2					
21	2	2				2
22	8	3			2	1
23	36	7	3		1	
24	62	14	3	2	2	2
25	65	18	8	6	13	2
26	60	26	20	4	25	10
27	54	18	40	9	27	10
28	46	7	44	15	20	3
29	16	3	60	25	23	7
30	9		61	19	35	21
31			32	13	32	19
32			18	5	32	14
33			9		25	8
34			1		23	
35			1		29	
36					29	
37					21	
38					17	
39					4	

[a] Excludes data from 1 of 6 laboratories because zone were ≥36 mm in diameter
[b] Horizontal lines identify the upper and lower limits that included ≥95% of all data points. Realistic limits could not be defined for tests of *P. aeruginosa* ATCC 27853.

Using the media n statistic of Gavan, the calculated QC range for *E. coli* ATCC 25922 would be mm. This range includes only 94% of the total number of zones reported by all six laboratories in the 1991 study. To obtain the ≥95% requirement of M-23, one millimeter was added to each end of this range, the resulting mm (9 mm) range included 98.9% of all test results. In the subsequent ten laboratory study 96% of the results fell within this mm range, and only 93% were within a nm range.

Using the median statistic of Gavan, the calculated QC range for *S. aureus* ATCC 25923 would be mm. One of the six laboratories was excluded from the calculations and TABLE 6 because all of its zone diameters were >35 mm on the agar medium used only by this laboratory, but were satisfactory on the common lot. It appears that they had a bad lot of agar. This recommended range included 97.4% of the results of the original study and 98% of the results in the ten laboratory confirmation study.

For *P. aeruginosa* ATCC 27583, the range of zone diameters reported in both studies was too broad to be useful for QC purposes. This organism is not recommended for disk tests.

The following QC ranges will be placed in the label:

Broth Microdilution Tests

In the past six years four studies have been performed attempting to determine and evaluate QC parameters for fosfomycin broth microdilution tests. In 1991 a five laboratory study was performed following the method of Document M-23 of the NCCLS. Fosfomycin was serially diluted in broth containing 25 μg/mL of glucose-6-phosphate. QC organisms included *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, and *Enterococcus faecalis* ATCC 29212. Each laboratory generated 25 MICs for each organism. This was the study submitted in the original NDA.

In 1994, a reproducibility study was conducted and that generated 10 MICs from each of the ten laboratories for each organism (one laboratory reported on 8 MICs for each organism). This study was intended to assess the appropriateness of the QC ranges derived from the first study.

In 1995, another study involving 8 laboratories was performed following the M-23 guidelines. In this study specific instructions on reading endpoints for trailing phenomena and skipped wells were provided to each participant. The endpoints were to be defined as an 80% inhibition of growth or a sharp decrease in growth as compared to that seen in the growth control well. Small buttons, trailing light growth and skipped wells were to be ignored.

In 1996 a three laboratory study designed to identify the more important variables that affect fosfomycin MIC endpoints was performed. This study produced 54 MIC results (18 from each laboratory) for each organism.

The MIC distribution for each organism in each of the four studies is given in TABLE 7. The modal MIC value in the four studies varied by over a three-dilution range for three organisms and over a two dilution range for *Escherichia coli* ATCC 25922. The MIC range encompassing 95% of the results for three organisms differed from study to study. *Escherichia coli* ATCC 25922 control ranges required four to six two-fold concentrations to include 95% of the results. No useful QC limits could be defined for fosfomycin testing by broth microdilution

The 1996 study was designed to test the variables in the test system that could cause the variation in the above studies. It was found that the major variable affecting MIC results was the inoculum size. With *E. coli* ATCC 25922, for example, a half log change in inoculum concentration resulted in a one to two dilution change in MICs. The authors state that unless the inoculum concentration is more precisely controlled than is currently practical, fosfomycin MICs by broth microdilution are not likely to be reproducible. It is recommended that broth microdilution susceptibility testing of fosfomycin not be considered for clinical laboratory use and that disk diffusion tests be used.

TABLE 7

Fosfomycin broth microdilution QC studies: Frequency distribution of MICs obtained with four QC organisms in four multi-laboratory studies performed in 1991, 1994, 1995, and 1996

Number of times each MIC was recorded for each organism in each study

MIC	*E. coli* ATCC 25922				*S. aureus* ATCC 29213				*P. aerug.* ATCC 27853				*E. faecalis* ATCC 29212			
(µg/mL)	1991	1994	1995	1996	1991	1994	1995	1996	1991	1994	1995	1996	1991	1994	1995	1996
0.125							1									
0.25	1	1			15		7									
0.5	10		8	6	27	1	43	3								
1	52*	21	66	5	12	22	72*	19	6		1			2		
2	42	28*	98*	23*	57*	21	64	23*	46*		31	7		1		
4	18	23	35	13	14	32*	48	7	37	25	99*	32*				
8	2	16	24	6		18	5		32	30*	72	13		2	1	
16		2	7	1		4		1	4	17	26	2	15		26	
32		3	2					1		10	6		90*	2	52	4
64		3								5	5		20	54*	43	40*
128										7				32	105*	10
256														5	13	
512										3						
>512										1						

* Mode of each series

___ Horizontal lines enclose MIC values that include ≥ 95% of the data in each study year.

Agar Dilution Test

In 1996 a seven laboratory study was conducted to determine the fosfomycin QC ranges for the four standard QC organisms when tested by agar dilution. Each laboratory tested each QC strain 32 times--16 on a Mueller-Hinton agar lot unique to their laboratory and 16 on a lot common to all participant laboratories. Colony counts were performed on each inoculum preparation. The inoculum concentrations varied somewhat among the seven participants with average colony counts ranging from 8.4×10^3 CFU/spot to 6.8×10^4 CFU/spot. No correlation between inoculum concentrations and fosfomycin MICs was observed within this range of colony counts. TABLE 8 shows the results of this study.

TABLE 8
Fosfomycin agar dilution QC study. Frequency distribution of MICs obtained in a seven-laboratory study--1996

MICs (µg/mL)	*E. coli* ATCC 25922	*S. aureus* ATCC 29213	*P.aeruginosa* ATCC 27953	*E. faecalis* ATCC 29212
≤0.125	16			
0.25				
0.5	25	17		
1	134	92		
2	48	97	33	
4	1	16	181	
8			8	
16				
32				94
64				128
128				
256				

All (100%) of the fosfomycin MICs fell within the proposed ranges for *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27953, and *E. faecalis* ATCC 29212. With *E. coli* ATCC 25922, 16 MIC results were ≤ 0.125 µg/mL, which is two $\log_2$ concentrations below the low end of the proposed range. These 16 results all occurred with the unique lot of Mueller-Hinton agar from one laboratory. The common lot MICs for this laboratory were within the proposed range. The unique lot of this laboratory appears to be a problem lot and should be excluded from the results. Excluding this laboratory, 99.5% of the remaining testes were within the proposed range. Differences in the inoculum concentration do not seem to affect agar dilution MICs as they do microdilution

MICs, all results are included within a four dilution range and seem to be consistent between laboratories. The following fosfomycin agar dilution QC ranges should be in the label along with a statement that broth microdilution should not be used to determine fosfomycin MICs:

3. *The statement*

should be deleted. The same statement is made later but in a more appropriate manner;

Response:
"The statement will be deleted."
Reviewer response: The response is satisfactory and the statement will be deleted.

4. *The statement*

should be deleted since the evidence for this is presented in only one brief study and this does not seem to be the primary mode of action of this drug.

Response:
The statement will be deleted."
Reviewer response: The response is satisfactory and the statement will be deleted.

(II) AMENDMENT--17-MAY-96

CLINICAL MICROBIOLOGY (STUDY MON-US-3)

ISOLATES/RELEVANCE TO APPROVED INDICATIONS)

The sponsor has amended this application on May 17, 1996 to include an additional clinical study, MON-US-03-"Single Dose Fosfomycin Tromethamine versus Multiple Dose Nitrofurantoin Monohydrate/Macrocrystals for the Treatment of Uncomplicated Urinary Tract Infections in Female Patients.

MON-US-03--Multicenter, randomized, double-blind, double-dummy comparison of fosfomycin as a single 3 gram dose vs nitrofurantoin 100 mg capsule every 12 hours for seven days.

A total of 749 patients were enrolled--375 received fosfomycin and 374 received nitrofurantoin. Of the 375 who received fosfomycin, 103 patients had no baseline pathogen at levels $\geq 10^5$ CFU/mL and were not evaluated in the Intent to Treat (ITT) or the Modified ITT analyses. Twelve patients were excluded from the ITT population for reasons other than treatment failure or treatment failure-related reasons and were not included in the Modified ITT analyses, there were, therefore, 260 patients in the Modified ITT group that were evaluated. Bacteriological and clinical effectiveness were evaluated 5-11 days following completion of active treatment [Visit #2 (days 5 to 11)for fosfomycin; Visit #3 (days 11 to 17) for nitrofurantoin]. Evaluation was also performed at Visit #4 (after study day 17) for recurrence of new infection. A patient who had a urine culture taken at or 96 hours prior to Day 0 that yielded one or more uropathogens with a count of $\geq 10^5$ CFU/mL was defined as having a bacteriological cure in the Day 5 to 11, Day 11 to 17, or after Day 17 window if all uropathogens found at baseline at levels $\geq 10^5$ CFU/mL were reduced to levels $\leq 10^4$ CFU/mL. If more than one sample was taken the worst case was used. If a concomitant antibiotic for UTI was taken, this was a bacteriological failure. Patients who had a documented bacteriological cure in the Primary Evaluation Window were considered to have recurrence if one or more of the cultures evaluated after documentation of a cure showed that the original pathogen was again present at levels of $\geq 10^5$ CFU/mL or a concomitant antibiotic for UTI was started after documentation of a cure. If a new species of pathogen was detected after a cure this was indicated as a new infection.

In this study there were 220 isolates of *Escherichia coli*. One isolate was not tested for susceptibility. The susceptibility testing of *E. coli* isolates produced zone diameters of 18 to 30 mm. Most isolates had zones from 22 to 28 mm. All isolates were, therefore, susceptible (≥ 16 mm). Almost all MICs for these isolates were 2 μg/mL. There was no correlation between bacteriological failures and zone diameters.

Proteus mirabilis. Total 10 isolates (All susceptible by proposed breakpoints)(4/20 Failures)

Zone Diameter (mm)	MIC (μg/mL)	Bacteriological Outcome (5-11 days)
19	16	Failure
27	2	Failure
28	4	Success
30	2	Success
30	2	Failure
31	2	Success
32	2	Failure
33	2	Success
33	2	Success
35	2	Success

Although the isolates with the smallest zone diameters were failures one large zone diameter isolates also failed.

Klebsiella pneumoniae: 11 total isolates (2 resistant, 2 Intermediate, 7 susceptible). No MICs performed.

Zone Diameter (mm)		Bacteriological Outcome (5-11 days)
0 (may be 6 mm)	Resistant	Failure
10		Failure
15	Intermediate	Failure
15		Success
17	Susceptible	Success
17		Success
17		Success
18		Success
18		Success
19		Success
25		Success

These isolates fit into the proposed breakpoint scheme for zone diameters very well. The two resistant isolates were failures, the two intermediate isolates were split and all the susceptible isolates were successes.

Staphylococcus saprophyticus: 13 isolates (6 resistant, 1 intermediate, 1 not done, 5 susceptible). No MIC testing performed.

Zone Diameter (mm)		Bacteriological Outcome (5-11 days)
Not Done		Failure
0 (may be 6 mm)		Success
6	Resistant	Success
6		Failure
7		Success
10		Success
14		Success
15	Intermediate	Success
16		Failure
16		Success
18		Success
18		Failure
33		Success

There appears to be little correlation between zone diameter and outcome for this organism.

Other pathogens.

Organism	Zone diameter (mm)		Outcome (5-11 days)
Citrobacter diversus	27	(MIC=2)	Success
Enterobacter aerogenes	15		Failure
Enterobacter aerogenes	14		Success
Enterobacter	0		Failure
Enterococcus faecalis	26		Success
Enterococcus group D	25		Success
Klebsiella ozaenae	21		Success
Streptococcus group D	14		Success
Streptococcus group D	30		Failure

Only the *Enterobacter* isolate was resistant and it failed. There were three intermediate isolates and 2 of the 3 were successes. Only one of the five susceptible isolates failed.

It appears that the proposed breakpoints of ≥ 16 mm, Susceptible; 13-15 mm, Intermediate; and ≤ 12 mm, Resistant work well except for *Staphylococcus saprophyticus* which tends to have a successful outcome even though the breakpoints predict a resistant isolate. All *E. coli* isolates which were the vast majority of the pathogens detected were susceptible. There were some failures, but the failures were not clustered at any zone diameter range.

Bacteriological Cure Rates in the Primary Assessment Window by Pathogen is given in the following TABLE.

TABLE 9 (STUDY MON-US-3)
Bacteriological Cure Rate in the Primary Assessment Window by Pathogen

Pathogen	FT No. Cures/Total (%)	NF No. Cures/Total (%)
Citrobacter diversus	1/1 (100)	1/1 (100)
Enterobacter	0/1 (0)	0/0 (-)
Enterobacter aerogenes	1/2 (50)	3/6 (50)
Enterobacter cloacae	0/0 (-)	2/2 (100)
Enterococcus faecalis	1/1 (100)	1/2 (50)
Enterococcus group D	1/1 (100)	0/0 (-)
Escherichia coli	188/220 (86)	145/186 (78)
Klebsiella	0/0 (-)	1/1 (100)
Klebsiella ozaenae	1/1 (100)	0/0 (-)
Klebsiella pneumoniae	8/11 (73)	10/13 (77)
Proteus mirabilis	6/10 (60)	6/14 (43)
Pseudomonas aeruginosa	0/0 (-)	0/1 (0)
Staphylococcus saprophyticus	9/13 (69)	10/12 (83)
Streptococcus group D	1/2 (50)	0/0 (-)
	Total 217/263(83)	179/238 (75)

Note: More than one pathogen may have been isolated from one patient. Therefore, the number of pathogens may exceed the number of patients.

Bacteriological cure rates at each evaluation window are shown in TABLE 10.

TABLE 10
Bacteriological Evaluations --Study MON-US-03

	FT No. (%) (N=260)	NF No. (%) (N=237)
Days 5-11 (Primary Assessment Window for FT)		
Cure	215 (83)	209 (88)[b]
Failure	45 (17)	28 (12)
Days 11-17 (Primary Assessment Window for NF)		
Cure	200 (77)	175 (76)
Failure	60 (23)	58 (24)
After Day 17*		
Cure	181 (70)	155 (65)
Failure	79 (30)	82 (35)

* Eradication with respect to the original pathogen only
Two FT treated patients that were considered cures had exactly 10^4 CFU/mL of the original pathogen present [one at the after Day 17 visit--patient and one at the Day 5-11 visit--patient One NF treated patient had exactly 10^4 CFU/mL of the original pathogen present at Day 5-11 visit--patient
[b] Patients may still be receiving NF at this visit. The Day 11-17 visit is the primary efficacy visit for NF treated patients.

Recurrence and new infections were also assessed. Recurrence was assessed after documentation of a bacteriological cure. New infection could occur any time post therapy. Recurrence was not possible in 45 of the fosfomycin patients and in 58 of the nitrofurantoin patients due to their bacteriological failure at the primary evaluation visit. Of the remaining patients (84%) of FT patients and 153/179 of the NF patients had no recurrence. As for new infections 239/260 (92%) of the FT patients and 218/231 (94%) of NF patients had no new infections. TABLE 11 shows these results.

TABLE 11
Bacteriological Evaluations of Recurrence and New Infection (Study MON-US-03)

	FT No. (%) (N=260)	NF No. (%) (N=237)
Recurrence		
No	180 (84)	153 (86)
Yes	35 (16)	26 (15)
Not Evaluable	45	58
New Infection		
No	239 (92)	218 (94)
Yes	21 (8)	13 (6)
Not Evaluable	0	6

The outcome at the final visit was also examined. A patient was a failure is they were not cured or developed a new infection or had a recurrence of the original pathogen. Patients who required additional antibiotic therapy for UTI were also failures. These results are shown in TABLE 12.

TABLE 12
Bacteriological Evaluations of Cure and Failure--At last Visit (Study MON-US-03)

Outcome At Final Visit	FT No. (%)	NF No. (%)
	(N=260)	(N=237)
CURE	170 (65)	147 (62)
FAILURE	90 (35)	90 (38)

These data show that as far as bacteriological cure the two antibiotics are about equal against uncomplicated UTI in female patients.

TABLE 13 compares the fosfomycin bacteriological cure rates for each pathogen in the three studies.

MON-US-01--Multicenter, randomized, double-blind, double-dummy comparison of fosfomycin as a single 3 gram dose vs ciprofloxacin 250 mg tablet twice a day for seven days.

MON-US-02--Multicenter, randomized, double-blind, double-dummy comparison of fosfomycin as a single 3 gram dose vs trimethoprim/sulfamethoxazole 160mg/800 mg tablet twice a day for ten days.

TABLE 13
Bacteriological Cure Rate in the Primary Assessment Window by Pathogen

Pathogen	Study MON-US-01 No. Cures/Total (%)	Study MON-US-02 No. Cures/Total (%)	Study MON-US-03 No. Cures/Total (%)
Citrobacter diversus	2/2 (100)	1/1 (100)	1/1 (100)
Citrobacter freundii	1/1 (100)	2/2 (100)	---
Enterobacter	--	1/1 (100)	0/1 (0)
Enterobacter aerogenes	2/3 (67)	2/3 (67)	1/2 (50)
Enterobacter cloacae	1/1 (100)	2/2 (100)	---
Enterococcus faecalis	5/5 (100)	3/4 (75)	1/1 (100)
Enterococcus group D	3/4 (75)	5/6 (83)	1/1 (100)
Escherichia coli	194/227 (85)	200/229 (87)	188/220 (85)
Klebsiella	2/3 (67)	1/3 (33)	---
Klebsiella ozaenae	---	----	1/1 (100)
Klebsiella pneumoniae	9/13 (69)	6/9 (67)	8/11 (73)
Proteus	1/2 (50)	---	---
Proteus mirabilis	6/8 (75)	11/11 (100)	6/10 (60)
Staphylococcus saprophyticus	5/8 (63)	3/5 (60)	9/13 (69)
Streptococcus group D	1/1 (100)	2/2 (100)	1/1 (100)
Total	232/279 (83)	239/278 (86)	217/263 (83)

The eradication rates are about equal in each of the three studies.

In the three studies the eradication rates for the most frequent pathogens were as follow:

Escherichia coli	582/656 (89%)
Klebsiella pneumoniae	23/33 (70%)
Proteus mirabilis	23/29 (79%)
Staphylococcus saprophyticus	17/26 (65%)
All pathogens	688/819 (84%)

(III) AMENDMENT-30-JUL-96

The MICROBIOLOGY section of the package insert should read as follows:

Fosfomycin (the active component of fosfomycin tromethamine) has *in vitro* activity against a broad range of gram-positive and gram-negative aerobic bacteria which are associated with uncomplicated urinary tract infections. Fosfomycin is bactericidal in urine at therapeutic doses. The bactericidal action of fosfomycin is due to its inactivation of the enzyme enolpyruvyl transferase, thereby irreversibly blocking the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate, one of the first steps in bacterial cell wall synthesis. It also reduces adherence of bacteria to ureopithelial cells.

There is generally no cross-resistance between fosfomycin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Fosfomycin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

2 Pages (28-29)
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REFERENCES

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically--Third Edition; Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25 NCCLS, Villanova, PA, December, 1993.

2. National Committee for Clinical Laboratory Standards, Performance Standard for Antimicrobial Disk Susceptibility Tests--Fifth Edition; Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24 NCCLS, Villanova, PA, December, 1993.

This revision of the microbiology section varies from that submitted by the sponsor in their amendment dated July 30, 1996 in the following places:

In the first paragraph the sponsor states,

This has been altered to read,

Although this mode of action may be unique at the present time, other drugs with a similar mode of action could be approved and this statement would then be false and would require a change.

The statement

has been changed to read.

The headings for the two lists of organisms have been altered to wording that was standardized in the January 26, 1993 letter to ALL NDA HOLDERS.

The statement

has been added after

The positions of the dilution and diffusion techniques subsection of the susceptibility tests section have been changed so that the dilution techniques subsection is first under the susceptibility tests which is now our Division's standardized format. The wording of these sections has also been altered to our now standardized format. The wording

have been added to the dilution techniques subsection to indicate that this method should not be used due to the problems encountered when quality control limits were being tested.

The definition of ' has been altered to indicate what this truly means for this drug which is that this category is a buffer zone and that the result should be considered equivocal. The sponsor has added the statement

Since this drug is only for urinary tract infections and the indication was granted because the drug concentrates in the urine, the intermediate category does not imply clinical applicability in body sites where the drug is concentrated. In this case this category is only a buffer zone which tends to indicate that the drug may or may not work, it does not mean that if higher doses are used or the drug is more concentrated in some fluid than it is normally in blood that it might work.

Conclusions and Recommendations

From the microbiological viewpoint the drug should be approved with a microbiology section of the package insert written as stated above.

Peter A. Dionne
Review Microbiologist

cc: Orig. NDA 50-717
HFD-520/Division File
HFD-520/MO/Soreth
HFD-520/Pharm/Joshi
HFD-520/Chem/Timper
HFD-520/CSO/Debellas
HFD-520/MICRO/Dionne

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/GLMicro/ATSheldon

Clin. Pharm
& Bio

DIVISION FILE
DEC 18 1996

NDA 50-717

Submission Date: June 28, 1996
July 30, 1996

Fosfomycin tromethamine Sachet, 3 gm
MONUROL™

Sponsor: Zambon Corporation
East Rutherford, NJ 07073

Reviewer: F. Pelsor

Submission Type: Amendment
Revised Final Product Label

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

BACKGROUND:

The purpose of this submission is to respond to the Agency letter to the sponsor dated September 20, 1995. The letter informed the sponsor that the application was not approvable.

The letter contained 10 comments regarding the Biopharmaceutics Section of the NDA. In addition, the letter requested one Phase IV study to document the effect of calcium salts on the bioavailability of fosfomycin.

> Two comments requested the sponsor to fully document the disposition of fosfomycin following oral administration of fosfomycin tromethamine by a combination of in vivo and in vitro methods. Four comments requested the sponsor to provide further clarification for the pharmacokinetics data analyses. Two comments criticized analytical methodology reports. One comment requested further evaluation of dose adjustment for patients with renal insufficiency and one comment suggested an association between the amount of excipient (sucrose) and the frequency of the adverse reaction, diarrhea.

The submission included a revised proposal for final product labeling.

COMMENTS:

1. The sponsor conducted two in vitro studies to evaluate the stability of fosfomycin at pH 1.2, 4.5, 6.5 and 7.5. The results showed that fosfomycin trometamol drug substance is not stable at pH 1.2. At this pH, the glycol derivative was the major degradation product, accompanied by less than % of 1-hydroxy-2-trometamoyloxy-n-propyl fosfonic acid (Z1282DA) (See Attachments, Figures 2). Fosfomycin is stable at pH 4.5, 6.5 and 7.5 where glycol formation is negligible (See Attachments, Figures 3-5).

Since fosfomycin degrades at pH 1.2, the sponsor expects that in the human stomach some degradation of fosfomycin takes place. The sponsor noted that about % of the oral dose of

fosfomycin tromethamine was recovered as fosfomycin during human bioavailability studies. In contrast, the pH of rat stomach is about . at which pH, fosfomycin is stable and about % of the oral dose was recovered as fosfomycin.

In any event, the sponsor stated that they are synthesizing ^{14}C-fosfomycin. They will use the radiolabeled material to do additional ADME studies in rats and mice, as well as humans.

2. The sponsor provided a lengthy analysis to compare fosfomycin pharmacokinetic parameters estimated by compartmental methods and non-compartmental methods

3. The sponsor noted corrections to the analytical methodology reports.

4. Since MONUROL therapy is a single dose, there is no concern about the accumulation of plasma concentrations in patients with renal insufficiency. Rather, the concern is whether the 3 gm dose is adequate to treat urinary tract infections in patients with renal insufficiency.

The sponsor reported that although urinary excretion of fosfomycin decreased as the degree of renal failure increased, urinary concentrations of fosfomycin remained greater than 100 µg/mL for sufficient time to be effective.

5. The sponsor noted that they did not find a dose-response relationship between oral fosfomycin tromethamine and diarrhea. The sponsor further noted that the incidence of diarrhea following iv administration (iv formulation did not contain sucrose) was comparable, therefore, it is unlikely that there is any substantial correlation between sucrose and diarrhea

6. The sponsor stated that they are willing to commit to conduct a pharmacokinetics drug-drug interaction study of calcium containing antacids and fosfomycin in Phase IV.

7. The proposed final product label should be revised to include the following information.

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The label comments were faxed to the sponsor on December 10 , 1996 and discussed briefly during a meeting between FDA and the sponsor on December 12, 1996. During the meeting, the sponsor indicated that they will arrange for a telecon to discuss our proposed revision in more detail.

RECOMMENDATIONS:

The information submitted by the sponsor (letter dated: June 28, 1996) is acceptable. The Office of Clinical Pharmacology and Biopharmaceutics looks forward to reviewing the results of the ^{14}C-fosfomycin mass balance study in humans and the pharmacokinetics drug-drug interaction study of calcium containing antacids and fosfomycin, when they are submitted to the Agency. The proposed MONUROL label should include our comments

Francis R. Pelsor 12/18/96
Francis R. Pelsor, Pharm. D.
Division of Pharmaceutical Evaluation III

JA Lazzaro, PharmD
For
FT Initialed by NFleischer, Ph.D. 12/18/96

CC:
ND 50-717 orig.
HFD-520 (Soreth, Duvall-Miller)
~~HFD-870 (Clarence Bott, PKLN 13B-31)~~
HFD-880 (DPEIII, Pelsor)
HFD-340 (Viswanathan)

Bio

NDA 50-717
PRODUCT: Fosfomycin Tromethamine
BRAND NAME: Monurol™
SPONSOR: Forest Laboratories, Inc.
150 East 58th Street
New York, NY 10155-0181

SUBMISSION DATE: 9/28/94

REVIEWER: Dan Wang, Ph.D.

TYPE OF SUBMISSION: Original

BIOPHARMACEUTICS REVIEW
NDA 50-717

SYNOPSIS

Fosfomycin Tromethamine is a synthetic broad spectrum antibacterial agent, administered orally, intended for single dose therapy in the treatment of uncomplicated urinary tract infection for women. The recommended dosage for adults and children over 12 years is one sachet containing 5.631 grams of fosfomycin tromethamine (equivalent to 3 grams of fosfomycin). The contents of a single-dose sachet should be dissolved in 3 to 4 ounces of tap water and be taken orally.

This submission consists of eighteen human pharmacokinetic studies of which three are pivotal studies. Others are supportive studies. These studies evaluated the bioavailability of fosfomycin, food effect, gender effect, age effect, PK of patients with impairment of renal function, PK of pregnant women, drug interaction (co-administrated with cimetidine or metoclopramide) and tissue concentrations. The summary of these PK studies is shown in table I.

RECOMMENDATION:

1. The Pharmacokinetics and Biopharmaceutics Section of the submission is acceptable to the Division of Biopharmaceutics provided the comments (1) to (6) on pages 10-11 to the firm is adequately addressed.

2. More information is needed to determine the dose adjustment for renal impaired patients (see comment (2) on page 11).

BIOPHARMACEUTICS REVIEW
NDA 50-717

TABLE OF CONSENTS: Page No.

7 Pages (3-9)
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COMMENTS (need not to be sent to the sponsor):

(1) In Study Report #15, pharmacokinetics of Monurol was study in healthy subjects, elderly subjects and subjects with impaired renal function. According to their creatinine clearances (mean values of 54, 16 and 7 ml/min, the subjects with renal function impairment were divided to groups I, II and III. The mean Cmax values (26.02, 35.66 and 27.44 μg/mL) after 25 mg/kg oral administration of FT to patients in group I, II and III are comparable to that of healthy volunteers after 50 mg/kg oral dose of FT (26.8 μg/mL, study report #4) and that after 3 g oral dose (26.1 μg/mL, study report #1). The AUC values (388.5, 1266.8 and 2108.6 μg.h/mL) for group I, II and III are 2, 7 and 11 times of that of heathy volunteers after 50 mg/kg oral administration of FT (181.5 μg.h/mL, study #4) and that after 3 g dose (184 μg.h/mL, study #1). No safety data were reported in this study for these Cmax and AUC values. Furthermore, the mean dose used in this study for each group ranged from 1.667 to 2.032 g which is lower than the recommended dose (3 g) for the treatment. If the same dose (3 g) is given to patients with normal renal function and with renal impairment, both Cmax and AUC values could be much higher than the Cmax and AUC ranges studied. Then, the safety at this dosing level may become an issue. On the other hand, in order to have an effective therapy, urinary concentration of the drug has to be higher than the MIC. In this study, the author only mentioned that urinary concentrations of FT remained effective during 48 hours for the subjects with mean creatinine clearance of 7 ml/min (> 100 μg). The urinary concentrations were not reported for any group studied. If urinary concentration can not be maintained above MIC, dosage of FT should be adjusted when safety permits.

COMMENTS (need to be sent to the sponsor):

(1) In study report #1, the total recovery (urine and feces) after a single 3 g dose was % following intravenous dose and % and % respectively following oral administration under fasting and fed conditions. There was no discussion of where the rest of the drug went, especially for those following oral administration which accounted for % of the dose.

This question was raised in the 45 day meeting. The sponsor's response on December 15, 1994 is not satisfactory. The evidence of lack of metabolites they provided is that "an examination of the chromatograms generated from the urine and fecal samples after oral and I.V. administration of fosfomycin from study R/3700/0002 (Study Report #1) revealed no peaks other than fosfomycin indicating that fosfomycin is probably not metabolized". This observation can only support that only fosfomycin has absorption under this condition, but can not rule out the existence of other metabolites.

The sponsor also proposed that since fosfomycin was a strong acid, ionization of fosfomycin was likely in the milieu of the intestinal tract. They believe in the ionized state fosfomycin is likely to be reactive leading to its degradation. This statement needs to be supported by experimental data.

Ideally, clearest information for the % loss of the drug can be obtained by conducting an *in vivo* mass balance study. In any event, considering the unstable characteristics of the compound and potential penetration problem caused by the compound breaking down to smaller molecules, the following *in vitro* experiments are suggested to more fully characterize the profile of fosfomycin in gastrointestinal milieu.

1. Provide a pH stability profile with kinetic rate constants for degradation of fosfomycin dissolved at 37°C in buffer solutions pH 1.2, 4.5, 6.5, 7.5. Also for these solutions provide the rate constants and assay values for the 4 degradation products: glycolic derivative; 1-hydroxy-2-trometamoyloxy-n-propyl fosfonic acid; tromethamine fosfate ester; and trometamoyloxy fosfomycin dimer. Perform the study in each buffer solution up to 12 hours.

2. Simulate gastric passage by adjustment of a solution of the drug substance to be pH 1.2 for 2 hours, then subsequently at pH 4.5 for 2 hours, pH 6.5 for 2 hours, and pH 7.5 for 2 hours. Assay and evaluate, as above, the degradation of the drug substance at each test station in the experiment.

(2) In the proposed labeling, the sponsor indicates that dosage adjustment is not necessary for renal impaired patients. This is not well supported by the study submitted (Study Report #15). The sponsor should provide more data to determine if dosage adjustment is necessary in patients with renal impairment, including the safety data and urinary concentration data at 3 g dose to uremic patients.

(3) Since fosfomycin calcium salt has a low bioavailability, the co-administration of antacid, especially those containning calcium salts, may reduce the bioavailability of the Monurol. Therefore, the sponsor is requested to conduct a PK drug-drug interaction study of antacids and fosfomycin in phase IV.

(4) The amount of sucrose is fairly large in the dosage form. There might be a corelation between the amount of sucrose used and one of the adverse reaction, diarrhea.

(5) Some PK parameters obtained from non-compartmental analysis in study report #1 did not match those obtained from compartmental analysis. The sponsor should explain the difference.

(6) Mean total recovery (A_∞) result of fosfomycin in urine (0-infinity) summarized in Table A6-8 (Study report #1) for treatment A (1433 mg) is different from that listed in Table 19 (1128). The result of 1433 will give a urine recovery of % rather than % which is the reported recovery value for the study. The mean A_∞ for treatment B is 1082 mg in both tables mentioned above. However, if averaging the individual recovery in table A6-8, the A_∞ value should be 1580 mg (53%). Among the individual results in Table A6-8, subject 8 has a A_∞ value of 6210.9 mg which is more than doubled amount of drug given (3000 mg). If subject 8 is considered an outlier, the mean A_∞ of fosfomycin is 1360 mg. The sponsor should explain these calculations.

The sponsor did not mention the value of λ_z used to calculate A_∞. Since λ_z value obtained from non-compartmental analysis is different from the one obtained from compartmental analysis, the use of wrong λ_z will produce a wrong A_∞. Therefore, it may be more proper to use urine recovery from 0 to 84 hours rather than A_∞. Eighty four hours cover more than 14 half-lives. The urine recovery values from 0 - 84 hours are 37.6 for fast condition and 36.1 for fed condition.

(7) The model used in Study Report #2 for oral data fitting is one compartmental model with first order absorption. The fitting is poor. According to study #1 and I.V. data in this study, the disposition of fosfomycin is described by two compartmental model. Therefore, the one compartmental model used in this study is not proper. The λ_z value obtained from the one compartmental fitting may not reflect the terminal elimination rate. Thus, the absolute bioavailability values calculated based on λ_z values might not be accurate. Urine recovery data may be a better measurement of the bioavailability than the AUC values calculated from wrong λ_z values. The sponsor should be aware of the misuse of the PK model.

(8) Some of the assay validation data and assay results for study #2 were documented under study #3 which caused confusion in the review process.

7/12/95

Dan Wang, Ph.D.
Pharmacokinetics Evaluation Branch II

Biopharm Day July 6, 1995, Attendees: T. Ludden, H. Malinowski, N. Fleischer, ML. Chen, P. Hepp, A. Hussain, F. Pelsor, D. Wang, J. Timper (HFD-520)

FT initialed by F. Pelsor, Pharm.D

cc: NDA 50-717 original, HFD-520(Clinical, Dillon-Parker), HFD-427(ML. Chen, Pelsor), Chron, Drug, Reviewer, HFD-19(FOI), HFD-340(Viswanathan)

Table I: Human Pharmacokinetics and Bioavailability Study Summary

6.3 (A) SUMMARY OF STUDIES

Study No	Investigator/ Location	Study Title	Study Design	No. of Subjects	Analytical Method/Matrix	Results and Conclusions
A. Pharmacokinetic and Bioavailability Studies in Healthy Volunteers						
1		A study to characterize the Pharmacokinetics/Bioavailability of Fosfomycin Following a Single 3 Gram Dose Administered Orally as Fosfomycin Tromethamine (Monurol™) to Fasted and Fed Volunteers or Intravenously as the Disodium Salt to Fasted Volunteers	single-dose crossover for oral fasted and fed phases followed by i.v. phase healthy volunteers	24 12F, 12M	GC/npd and microbiological serum, urine and feces	Absolute bioavailability of FT was 37% following oral administration under fasting conditions and 30% following oral administration with food. Food decreased both rate and extent of absorption. Following I.V. administration of 3 g of FNa, over 90% of fosfomycin is excreted renally and less than 0.1% excreted in the feces. Upon oral administration, the urinary recovery of fosfomycin was 38% and 37% respectively following fasted and fed conditions. Fecal excretion of fosfomycin following oral administration was 18% and 19% respectively following fasted and fed conditions. Following I.V. administration, there was a statistically significant but not clinically relevant difference between female and male subjects for the half-life of elimination and volume of distribution at steady state. All other pharmacokinetic parameters were similar in both genders Comparison of serum concentration data, urinary excretion and fecal excretion data and pharmacokinetic parameters (AUC_t and C_{max}) from GC/npd assay and microbiological assay indicated that results from both assays were similar.

Table 1: Human Pharmacokinetics and Bioavailability Study Summary (continued)

Study No.	Investigator/ Location	Study Title	Study Design	No. of Subjects	Analytical Method/Matrix	Results and Conclusions
2		*Fosfomycin Pharmacokinetics and Bioavailability of Fosfomycin Trometamol after Oral Administration*	single-dose crossover healthy volunteers	12 6F, 6M	microbiological/ serum, urine and feces	The absolute bioavailability of FT was 32% Fosfomycin kinetics were linear over the dose range tested. The mean urinary recovery after the intravenous administration of 3g of FNa was 92%. The mean urinary recovery after the oral administration of 3g FT was 39%.
3		Urinary Recovery of Fosfomycin after Taking Fosfomycin Trometamol (Monurol) by Mouth in Elderly Subjects	single-dose crossover healthy elderly volunteers	12 6F, 6M	microbiological urine	Following oral doses of 2 g and 3 g in the elderly subjects aged 75 years and over, there is a difference in the amount of fosfomycin recovered in urine during the first and last fractions and the total percent recovered There is *no correlation between creatinine clearance*, age and total percent recovery
4		Comparative Pharmacokinetics of Fosfomycin Trometamol, Sodium Fosfomycin and Calcium Fosfomycin in Humans	single-dose crossover healthy volunteers	13 3F, 10M	microbiological/ serum and urine	Absolute bioavailability of FT was 37%. Fosfomycin kinetics were linear over the dose range tested. Double the FT dose doubled the AUC. Improved rate and *extent of oral absorption compared to calcium* fosfomycin (FCa). Half the dose of FT produced double the serum concentration of FCa.
5		Trometamol-Fosfomycin (Monuril) Bioavailability and Food-Drug Interaction	single-dose crossover healthy volunteers	10 6F, 4M	microbiological/ serum and urine	With food Cmax was reduced by 36% AUC was reduced by 28% and Tmax was prolonged, however, urinary concentrations were only reduced for the first two hours and comparable fasting and fed after 2 hours indicating that FT can be administered without regard to meals
6		Relative Bioavailability of Fosfomycin and of Trometamol After Administration of Single Dose by Oral Route of Fosfomycin Trometamol in Fasting Conditions and After a Meal	single-dose crossover healthy volunteers	6 5F, 1M	GC/MS serum and urine	No statistically significant difference in any FT pharmacokinetic parameters, except Cmax which was statistically lower under fed condition. Urinary concentrations of FT were less then 10% lower fed than fasting at all intervals indicating that FT can be administered fasting or fed.

Table I: Human Pharmacokinetics and Bioavailability Study Summary (continued)

Study No.	Investigator/ Location	Study Title	Study Design	No. of Subjects	Analytical Method/Matrix	Results and Conclusions
7		Pharmacokinetics of Fosfomycin and Influence of Cimetidine and Metoclopramide on the Bioavailability of Fosfomycin Trometamol	single-dose crossover healthy volunteers	9 9M	microbiological/ serum and urine	Cimetidine had no significant effect on pharmacokinetics of FT when given concomitantly FT had lower AUC and increased half-life when metoclopramide was given concomitantly
8		Fosfomycin Absorption Following Oral Treatment with FZ 588 by Zambon Farmaceutici S p A , Observations in Healthy Volunteers	single-dose single treatment healthy volunteers	5 4F, 1M	microbiological/ serum and urine	Average FT Cmax was 33 μg/mL, AUC_{12} was 172 μg hr/mL and urinary recovery over 48 hrs was 47%
9		Z 1282 (FZ 588) A New Fosfomycin Derivative with Much Improved Bioavailability by Oral Route	single-dose crossover healthy volunteers	6 3F, 3M	microbiological/ serum and urine	Rate and extent of absorption and urinary recovery of fosfomycin from FT were 3-4 times that of FCa Serum levels of FT increased in proportion to increasing doses Urinary recovery was independent of dose
10		Pharmacokinetic Profile of Fosfomycin Trometamol (Monurol)	single-dose crossover healthy volunteers single-dose crossover healthy volunteers	5 5M 4 4M	GC/MS and microbiological/ serum and urine	The absolute bioavailability of FT was 44% Serum levels of FT appear to increase less than in proportion to increasing dose Urinary recovery decreases as dose increases Data is inconsistent with other studies

Table I: Human Pharmacokinetics and Bioavailability Study Summary (continued)

Study No.	Investigator/ Location	Study Title	Study Design	No. of Subjects	Analytical Method/Matrix	Results and Conclusions
B. Supportive studies in Population at Increased Risk						
11		Urinary Tract Infections in Pregnancy Monural Single-Dose Treatment versus Traditional Therapy	single-dose crossover pregnant women	4 4F	microbiological/ plasma and urine	Plasma and urinary concentrations of FT following a single 3g dose were comparable during and after pregnancy
12		Trometamol Salt of Fosfomycin (Monural) Preliminary Pharmacokinetic and Clinical Experience in the Treatment of Urinary Tract Infections in Children	single-dose parallel children	23 7F, 16M	microbiological/ serum and urine	FT half-life (approx. 2 hr) was comparable to that in adults. Cmax and AUC were dose proportional in the dose range tested (0.5 to 2g). Two g of FT provided serum and urinary levels comparable to 3 g of FT in adults
13		Pharmacokinetics in Children of a New Fosfomycin Derivative with Improved Bioavailability	single-dose crossover	6	GC/MS plasma and urine	FT was more bioavailable than FCa (AUC was 2-fold greater and Cmax was 2.5 times higher). Urinary concentration was higher with FT
14		Oral Bioavailability of Z 1282 in Elderly Patients	single-dose single treatment elderly	6 5F, 1M	GC/MS plasma and urine	Mean Cmax and AUC of FT were slightly higher than values observed in other studies in healthy volunteers
15		Comparative Pharmacokinetics of Fosfomycin Trometamol versus Calcium Fosfomycin in Elderly Subjects and Uraemic Patients [redacted]	single-dose crossover in healthy volunteers parallel in elderly and chronic renal impaired patients	5 healthy volunteers 5M, 8 healthy elderly 4F,4M 23 chronic renal impairment patients 5F, 18M	microbiological/ serum and urine [redacted]	Bioavailability of FT in healthy volunteers was greater than FCa. FT was less well absorbed based upon urinary recovery and renal clearances were lower in elderly subjects compared to young volunteers for both drugs. In uremic patients, Cmax was higher with longer Tmax, half-life was longer and urinary elimination decreased in relation to degree of renal impairment

Table I: Human Pharmacokinetics and Bioavailability Study Summary (continued)

Study No.	Investigator/ Location	Study Title	Study Design	No. of Subjects	Analytical Method/Matrix	Results and Conclusions
16		Renal, Plasmatic and Urinary Concentrations of Fosfomycin After an Oral Single Dose of Trometamol or Calcic Fosfomycin	single-dose parallel patients	45 15F, 7M 11F, 12M	microbiological and GC/MS plasma, urine and tissue	FT produced higher plasma and urine concentrations as well as higher concentration in kidney tissue than FCa Urinary concentrations following FT were 3 times greater than those produced by FCa
17		Study of Fosfomycin Trometamol Kinetics for the Purpose of Evaluating the Concentrations of this Antibacterial Agent in Various Human Tissue	single-dose single treatment patients	11 2F, 9M	microbiological/ serum, urine and tissue	The fosfomycin concentration after FT was 21 7 μg/ml. in the serum, 11 6 μg/ml. in the prostate, 9 8 μg/ml. in the pericystium and 8 8 μg/ml. in seminal vesicle
18		Fosfomycin Serum and Prostatic Tissue Concentrations Following the Administration of Fosfomycin Trometamol, a New Fosfomycin Derivative with High Bioavailability by the Oral Route	single-dose parallel patients	24 24M	microbiological/ serum, urine and tissue	The fosfomycin concentrations in the serum and prostatic tissue after FT were 7 times higher at 3 hrs and more than 3 times higher at 12 hrs than FCa

Table A6-8
TR/3700/0002
Individual and Mean Pharmacokinetic Results
Total Recovery of Fosfomycin in Urine (0 to infinity) (mg)

Subject	Treatment A (fasted)	Treatment B (postprandial)	Treatment C (intravenous)
Mean	1433	1082	2705
SD	501	195	414
%CV	35	69	15

* Subject withdrew from the study.
N No sample for one or more collection intervals prevented calculation of total amount excreted.

6- 02486

Table 19 (continued)
Summary of Fosfomycin Pharmacokinetics Parameters[a] Obtained Using Non-Compartmental Analysis

Parameter	Treatment		
	Fasted	Postprandial	I.V.
V_{ss} (L)	136 (44.1)[b] (32.4)	201 (54.6)[b] (27.2)	16.5 (4.73) (28.7)
$Ae_{(0\text{-}84),u}$ (mg)	1128 (240) (21.3)	1082(195) (18.0)	2687 (404) (15.0)
$Ae_{(0\text{-}\infty),u}$ (mg)	1140 (238) (20.9)	1118 (201) (18.0)	2688 (404) (15.0)
$Ae_{(0\text{-}84),f}$ (mg)	530.6 (317.1) (59.8)	565.6 (389.1) (68.8)	1.34 (3.69) (275)
λ_z (u) (hr^{-1})	0.090 (0.125) (139)	0.080 (0.107) (134)	0.336 (0.253) (75)
$t_{1/2\lambda z}$ (u) (hr)	16.6 (10.8) (65)	23.2 (41.9) (181)	3.1 (1.5) (48)
CL (L/hr)	16.9 (3.46)[c] (20.5)	20.4 (4.35)[c] (21.3)	6.1 (1.0) (16.4)
CL_R (L/hr)	6.3 (1.7) (27.0)	7.6 (2.2) (28.9)	5.5 (1.2) (21.8)

[a]Data are presented as mean (± SD) values and the %CV is in parentheses below these values.
[b]V_{ss} calculated as V_{ss}/F
[c]Total Clearance calculated as CL/F

APPENDIX 1

Study Report #1 - A Study to Characterize the Pharmacokinetics/Bioavailability of Fosfomycin Following a Single 3 Gram Dose Administered Orally as Fosfomycin Tromethamine (Monurol™) to Fasted and Fed Volunteers or Intravenously as the Disodium Salt to Fasted Volunteers.

STUDY NO: R/3700/0002 VOLUME:1.29-1.39

INVESTIGATOR:

OBJECTIVES:

1. Evaluate effect of food on the rate and extent of absorption of fosfomycin after oral administration of a single dose of fosfomycin tromethamine (Monurol).
2. Compare results obtained using a microbiologic assay to results obtained using assay.
3. Characterize pharmacokinetics of fosfomycin following I.V. administration in both male and female subjects.
4. Determine absolute bioavailability of fosfomycin following oral administration of fosfomycin tromethamine.

FORMULATION: (1) MONUROL™ Sachets. Supplier: Zambon Group. Manufacture Site: Zambon Vicenza plant. Manufacture Date: 6/20/91. Lot Number: 11608 (2) FOSFOCIN Injectable (fosfomycin disodium salt powder). Supplier:
Manufacture Date: 11/92. Lot Number: 78.

STUDY DESIGN: This was a single dose, single-center randomized two-way crossover (oral) study followed by a single-dose period (IV) in 24 healthy (12 male and 12 female) subjects aged 21 to 40 years. The study lasted for 3 weeks. For the first two weeks, subjects received on the same day of each week one sachet of Monurol 5.631 g (equivalent to 3 g of fosfomycin) with 180 mL of water either after a 10 hour overnight fast or immediately following a standardized high-fat breakfast. During the final visit (third week) all subjects received 3 g of fosfomycin (as the disodium salt) intravenously.

Blood samples following the oral treatment were drawn at 0, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0, 30.0 and 36.0 hours post-dose. Blood samples following intravenous dose were drawn at 0.0 (predose), 0.17, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 20.0 hours post-dose. Urine samples were drawn at -2-0, 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-16, 16-24, 24-36, 36-48, 48-60, 60-72 and 72-84 hour intervals post-dose following the oral treatments and at -2-0, 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-16, 16-24, 24-36 and 36-48

hour intervals post-dose following the intravenous administration. In addition fecal samples were collected at -36-0, 0-24, 24-48, 48-72 and 72-84 hour intervals following the oral treatments and at -24-0, 0-24 and 24-48 hour intervals post-dose following the intravenous administration.

Fosfomycin in serum, urine and feces were quantitated by (a) a microbiological assay using *Proteus mirabilis* ATCC 21100 as the test organism and (b) also by a assay.

ASSAY:

Serum, urine and feces concentrations obtained using assay were regressed on the serum, urine and feces concentrations obtained using a microbiological assay and ANOVA was performed on these regressions. PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}) obtained from assay and the microbiological assay were compared to each other.

PK parameters derived from the serum, urine and feces concentrations from the assay were compared using proc GLM in SAS to evaluate the effect of food on the absorption of fosfomycin and to assess the absolute and relative bioavailability of fosfomycin.

RESULTS:

Serum, urine and feces fosfomycin concentrations for each subject are tabulated for treatments 1, 2 and 3 in Tables 1 to 9. Mean serum, urine and feces fosfomycin concentrations for each treatment are listed in Tables 10 to 12. Plots of mean fosfomycin concentrations in serum, urine and feces as a function of time following each treatment are presented in Figures 1 to 4. Table 13 and summarizes fosfomycin pharmacokinetics parameters obtained using non-compartmental analysis and compartmental analysis respectively. Comparisons of pharmacokinetic parameter for fasted and postprandial treatment are shown in Table 15. Mean fosfomycin serum and urine concentrations following a single 3 g I.V. bolus dose are listed for male and female subjects in Tables 16 and 17. Plots of mean serum and urine fosfomycin concentrations as a function of time are male and female subjects are shown in Figure 5 and Figure 6 respectively. Comparison of pharmacokinetic parameters following I.V. for male and female subjects are summarized in Table 18.

Comparison of concentration data and pharmacokinetic parameters (AUC and Cmax) from assay and microbiological assay indicated that the results from both the assays were similar.

The absolute bioavailability of fosfomycin following oral administration was 37% and 30% respectively under fasted and fed conditions. The relative bioavailability of fosfomycin after oral administration with food as compared to oral administration under fasting conditions was 81%. Based on non-compartmental analysis, the mean half-life for elimination of fosfomycin was 2.7 hours following I.V. administration and 5.7 and 5.8 hours following oral-fasted and oral-fed treatments, respectively suggesting that continuing absorption may have contributed to the larger half-life following oral administration. The AUC_{0-} following oral treatments was 184 µg.hr/mL and 154 µg.hr/mL respectively after fasted an fed regimens. The Cmax was 26.1 µg/mL and 15.4 µg/mL respectively after fasted an fed regimens. The corresponding Tmax following fasted and fed regimens was 2.1 hours and 4.0 hours respectively, suggesting that food decreased both the rate and extent of absorption.

Over % of fosfomycin is recovered in urine after I.V. administration. Following I.V. administration, fecal excretion of fosfomycin was insignificant. However, upon oral administration, the urinary recovery of fosfomycin from time 0 to infinity was % and % respectively following fasted and fed conditions and the percent recovery from time 0 to 84 hours was % % respectively following fasted and fed regimens. Compared to I.V. administration, fecal excretion of fosfomycin following oral administration was significant, % and % respectively, following fasted and fed conditions. The total recovery (urine and feces) after a single 3 g dose was % following intravenous dose and % and % respectively

following oral administration under fasting and fed conditions.

There was a significant difference between female subjects and male subjects for the half-life of elimination (3.08 hours and 2.31 hours respectively) and volume of distribution at steady state (19.5 L and 12.9 L respectively). The sponsor claimed that these differences are not clinically significant. Other pharmacokinetic parameters (AUC, Ae, CL and CL_R) were similar.

Following fasting or after food, the concentrations of fosfomycin in urine were maintained above the minimum inhibitory concentrations (MIC, 128 µg/ml) for at least 24 hours, indicating that fosfomycin can be given with or without food for the treatment of lower urinary tract infections. Concentrations above the MIC are maintained for at least 84 hours for *E. coli* following oral administration regardless of food.

CONCLUSIONS:

1. assay is a precise and sensitive assay and can be used to reliably quantitate fosfomycin in biological matrices.

2. The total recovery urine and feces) after a single 3 mg dose was % following intravenous dose and % and % respectively following oral administration under fasting and fed conditions.

3. Food reduced the rate of absorption. This can be indicated by delayed Tmax (2.1 vs. 4.0 hours) and the difference between MRT for fasted treatment (8.2 hours) and postprandial treatment (9.9 hours). Based on serum data, the extent of absorption with food was also reduced compared to that without food (% vs. %). However, the difference in absorption extent is minimal from the urine recovery data (% vs. %).

4. Following fasting or after food, the concentrations of fosfomycin in urine after 48 hours were above the minimum inhibitory concentrations (MIC), indicating that fosfomycin can be given with or without food for the treatment of lower urinary tract infections. Concentrations above the MIC are maintained for at least 84 hours for *E. coli* following oral administration regardless of food.

5. There was a significant difference between female subjects and male subjects for the half-life of elimination (3.08 hours and 2.31 hours respectively) and volume of distribution at steady state (19.5 L and 12.9 L respectively). The sponsor claimed that these differences are not clinically significant. Other pharmacokinetic parameters (AUC, Ae, CL and CL_R) were similar. All these results are based on I.V. study.

Study Report #2 - Fosfomycin Pharmacokinetics and Bioavailability Study of Oral Fosfomycin Trometamol with Intravenous Sodium Fosfomycin in Healthy Volunteers

STUDY NO: MON-N-01 VOLUME: 1.40-1.41

INVESTIGATOR:

OBJECTIVES: To compare the oral bioavailability of fosfomycin tromethamine at doses of 2, 3 and 4 g with the disodium salt of fosfomycin given intravenously at a 3 g dose

FORMULATION: Fosfomycin trometamol (lot 148A/F223) in sachets each of 3.754 g corresponding to 2 g of fosfomycin acid. Fosfomycin trometamol (lot 148B/F223) in sachets each of 5.631g corresponding to 3g of fosfomycin acid. Fosfomycin trometamol (lot 148C/F223) in sachets each of 7.508 g corresponding to 4 g of fosfomycin acid. Fosfomycin disodium salt powder (lot 916/F20) in vials each containing 1 g of acid fosfomycin and 14.5 mEq of Na.

STUDY DESIGN: This was a four-way cross-over study in twelve (12) healthy volunteers (6 females and 6 males) with a mean age of 26.5 years. The subjects have been randomly allocated into the sequences, according to the randomization list below:

Balanced (Latin-Square) Cross-Over

Subjects	Drugs			
	A	B	C	D
	B	A	D	C
	C	D	B	A
	D	C	A	B
	A	B	C	D
	B	C	D	A
	C	D	A	B
	D	A	B	C
	A	B	C	D
	B	D	A	C
	C	A	D	B
	D	C	B	A

A = Fosfomycin Trometamol, 2 g as fosfomycin acid
B = Fosfomycin Trometamol, 3 g as fosfomycin acid
C = Fosfomycin Trometamol, 4 g as fosfomycin acid
D = Fosfomycin Disodium, 3 g as fosfomycin acid (3 g as vials of 1 g)

A wash-out period of 1 to 3 weeks was allowed between the treatment periods.

Fosfomycin disodium salt (100 mg/mL in distilled water) was given intravenously over 5 minutes; fosfomycin tromethamine at the doses of 2, 3 and 4 g was dissolved in 100-125 mL of water and given orally. The same quantity of water was ingested after the intravenous dose.

Following the intravenous administration of fosfomycin sodium, blood samples were drawn prior to the dose, 1 min after completion of the injection and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours after the dose. Following oral administration, blood samples were drawn at 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose. Urine samples were collected at 0-2, 2-4, 4-6, 6-12, 12-24, 24-36, 36-48, 48-60 and 60-72 hour intervals following oral and I.V. administrations. Feces was collected from 6 male volunteers 1 day before treatment and on days 1, 2, 3 and 4 of the study. Feces have been collected only from the male volunteers 1 day before treatment and on day 1, 2, 3 and 4 of the study.

The subjects were on a balanced food intake and only a limited amount of alcohol was allowed (i.e. 1/2 beer/day). they have not been allowed to take solid foods overnight before each dose administration and for at least two hours after the drug administration and they have avoided strenuous physical activity during each test day.

ASSAY:

RESULTS:

The individual serum concentration values of fosfomycin for each treatment are shown in Tables 1 to 4. Mean values for the 4 treatments are shown in Table 5. The experimental and modelled concentrations versus time curves are graphically shown in fig. 1-5. The individual and mean PK parameters calculated for the 4 treatments are shown in Tables 6 to 10. The mean PK

parameters for each treatment are shown in Table 11. The mean PK parameters divided by sex are shown in Table 12. The individual and mean calculated bioavailability factors are shown in Table 13. Individual and mean cumulative urinary recovery are shown in Tables 14 to 18. Individual and mean fecal excretion and recovery data for 6 male volunteers are shown in Tables 19 to 22.

CONCLUSION:

(1) Following intravenous administration, the mean peak fosfomycin plasma concentration was 370.6 µg/mL. The mean half-life was 2.1 hours. A mean of 92.7% of the dose was recovered unchanged in the urine with less than 0. 1 % of the dose recovered in the feces.

(2) Following oral administration of 3 g FT, mean urinary concentrations of fosfomycin were 334.3 µg/ml over 12-24 hours, 131.7 µg/ml over 24-36 hours, and 90.9 µg/mL over 36-48 hours. The mean urinary recovery was independent of dose and was 38%, 39% and 40% following oral administration of 2, 3 and 4 g of fosfomycin tromethamine, respectively. The mean fecal recovery following 3 g oral dose of FT was 28.0%. The total recovery (urine and feces) after a single 3 g oral dose was 71%.

(3) The absolute bioavailability values were 35.6%, 32.8% and 30.9% after 2, 3 and 4 g of FT oral dose. There is a significant difference of bioavailability between dose. However, these calculated bioavailability values may not be correct since the kel value used in AUC_{0-} calculation may not be adequately determined. (See comment (5))

(4) Fosfomycin pharmacokinetics were linear over the dose range tested based on Cmax.

(5) Concentrations above the MIC are maintained for at least 72 hours for *E coli* following oral administration.

(6) There is no evidence of differences related to the subjects'sex. However, for AUC and Clearance the interaction between sex and linear regression on oral doses is significant ($p<0.05$).

Study Report #3 - Urinary Recovery of Fosfomycin after Taking Fosfomycin Trometamol (Monurol) by Mouth in Elderly Subjects

STUDY NO: MON-UK-11 VOLUME: 41-1.

INVESTIGATOR:

OBJECTIVES: To determine the urinary recovery of fosfomycin following the ingestion of fosfomycin trometamol (Monurol) by elderly subjects.

FORMULATION: Monurol (lot 171/F223) in sachets containing the equivalent of 2 g or 3 g of fosfomycin trometamol

STUDY DESIGN: This was a randomized, double-blind, cross-over study in twelve (12) volunteers (7 male and 5 female) aged 75 years and over (mean age 78.6 years). The study lasted for 3 weeks. For the first two weeks, subjects received on the same day of each week either 2 g or 3 g of Monurol with 100 mL of water. On each occasion they had fasted overnight apart from drinking water. The final visit (third week) was for a safety check. Urine samples were collected at predose, 0-4, 4-9, 8-12, 12-24 and 24-48 hour intervals post-dose.

ASSAY:

RESULTS: Following oral administration of Monurol, the urinary recovery data for 2 g dose and 3 g dose are shown in Tables 1 and 2, respectively. Mean urinary concentration and total recovery % in elderly subjects after oral administration of Monurol (2 and 3 g) in each urine collection interval, standard error and ANOVA results are shown in Table 3.

The mean amount of fosfomycin recovered in urine over a 48 hour period following 2 g of Monurol was 833.7 ± 177.0 mg (41.7 + 8.9%, n = 12). Following oral administration of 3 g of Monurol, the mean amount of fosfomycin recovered in urine over a 48 hour period was 1109.6 ± 175.7 mg (37.0 ± 5.9 %, n = 11).

In the elderly subjects, there is a statistically significant difference between 2 g and 3 g doses for the recovery of fosfomycin during the first and last urine fractions and the total percent recovered up to 48 hours. There was no correlation between creatinine clearance, age and total percent recovery. No changes in laboratory data were noted after dosing.

Study Report #4: "Comparative Pharmacokinetics of Fosfomycin Trometamol, Sodium Fosfomycin and Calcium Fosfomycin in Humans".

This was a supportive study. The objectives of the study were to determine bioavailability of fosfomycin tromethamine (FT) at 25 and 50 mg/kg p.o. compared to 50 mg/kg sodium fosfomycin (FNa) given intravenously or 50 mg/kg calcium fosfomycin (FCa) given orally. The PK parameters (Cmax, AUC and bioavailability) obtained from this study is comparable with study #1. Almost 50% of fosfomycin was recovered from urine after oral administration of FT for both dose. Fosfomycin kinetics after FT were linear over the dose range tested. Following FT, mean Cmax was 14.9 µg/ml (25mg/kg) and 26.8 µg/ml (50 mg/kg) at 3 and 2 hours, respectively. The mean AUC values were 112.0 µg.hr/ml and 181.5 µg.hr/ml for 25 mg/kg and 50 mg/kg dose, respectively. Following FCa, the mean Cmax was 6.6 µg/ml at 3 hours. The mean AUC values was 59.5 ug.hr/ml and 16% of dose was recovered in the urine. FT produced higher serum and urinary concentrations than FCa. This study demonstrated that there was an improved oral absorption of fosfomycin from FT as compared to FCa.

Study Report #5: "Trometamol Fosfomycin (Monurol). Bioavailability and Food-Drug Interaction."

The objectives of the study were to evaluate the pharmacokinetics of fosfomycin tromethamine in serum and in urine after oral administration of a single dose of 50 mg/kg (fosfomycin acid) and to evaluate the possible influence of food on the pharmacokinetics and bioavailability of fosfomycin.

The result of this study is consistent with study #1.

Study Report #6: "Relative Bioavailability of Fosfomycin and of Trometamol After Administration of Single Dose by Oral Route of Fosfomycin Trometamol in Fasting Conditions and After a Meal."

The objectives of the study were to assess the pharmacokinetics of fosfomycin after a single oral dose of 1 g of fosfomycin tromethamine (1.867 g FT) in fasting subjects and after a meal. The result of this study is consistent with study #1. Urinary recovery of fosfomycin was 58% without meal and 52% after meal. Based upon urinary concentrations data, fosfomycin tromethamine can be administered without regard to meals. This study also measured the trometamol concentration in serum and urine. The results showed that there is no significant effect of food on both serum and urine trometamol levels.

Study Report #7: **"Pharmacokinetics of Fosfomycin and Influence of Cimetidine and Metoclopramide on the Bioavailability of Fosfomycin Trometamol". Neu. Williams (eds.), New Trends in Urinary Tract Infections. Int. Symp., Rome 1987. pp. 157-166, T. Bergan[a], G. Mastropaolo[b], F.D. Mario[b] and R. Naccarato[b], [a]Dept. of Microbiology, Inst. of Pharmacy, Univ. of Oslo, Norway, [b]Cattedra di Malattie dell Apparato Digerente, Istituto di Medicina Interna, Univ. of Padua, Italy**

The objectives of this study were to determine if the pharmacokinetics of fosfomycin is changed when it is given together with a drug which reduces gastric acid secretion (cimetidine) or a compound which increases gastrointestinal motility (metoclopramide).

This was an open three-way, cross-over study conducted in nine (9) healthy male volunteers with a mean age of 22.5 yrs. The three treatments were as follows: (1) During Week 1, 50 mg/kg of fosfomycin moiety was given alone; (ii) during week 2, 20 mg of metoclopramide was given 30 minutes prior to administration of 50 mg/kg of fosfomycin moiety; (iii) during week 3, 400 mg of cimetidine was given the night before and another dose 30 minutes before administration of 50 m /kg of fosfomycin moiety. The subjects fasted overnight prior to all treatments and up to 3 hours after the morning dose of fosfomycin.

Blood samples were taken at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0. 12.0, 16.0, 20.0. 24.0 and 36.0 hours after fosfomycin. Urine samples were collected at 0-2, 2-4, 4-6, 6-8, 9-12, 12-16, 16-24, 24-36 and 36-48 hr intervals. Serum and urine samples were assayed for fosfomycin by a microbiological agar diffusion method using *Proteus mirabilis* OMB133 as the test organism.

Mean serum concentrations of fosfomycin given as fosfomycin trometamol, either alone or with cimetidine or with metoclopramide to 9 healthy volunteers are shown in Figure 1. Urine results are shown in Table 1. The results showed that metoclopramide altered the absorption of orally administered FT to produce lower peak serum concentrations (30 *versus* 17 µg/ml) and urinary recovery (36 *versus* 28%). The serum half-life of fosfomycin was also increased (5.1 *versus* 7.1 hours). Urinary concentrations of fosfomycin were reduced following metoclopramide over the first 16 hours, but were then higher, suggesting delayed absorption. At all times, fosfomycin urinary concentrations exceeded the minimum inhibitory concentration (MIC) of 128 µg/ml for up to 36 hours.

Cimetidine had no significant effect on fosfomycin pharmacokinetics. When fosfomycin tromethamine was given concomitantly with cimetidine or given alone, the peak serum concentration was 31 and 30 µg/mL, respectively, urinary recovery was 41 and 36%, respectively, and the serum half-life of fosfomycin was 4.8 and 5.1 hours, respectively. Urinary concentrations of fosfomycin given with cimetidine or alone were 4883 and 4415 µg/mL over 2-4 hours, respectively, 1351 and 1006 µg/ml over 8-12 hours, respectively, and 490 and 484 pg/ml over 16-24 hours, respectively.

Study Report #8: "Fosfomycin Absorption Following Oral Treatment with FZ 588. Observations in Healthy Volunteers."

The objectives of this study were to evaluate the pharmacokinetics of FT after oral administration of a 3 g of fosfomycin. Mean AUC, Cmax, Tmax and urinary concentrations were comparable to the values observed in other studies. Urinary recovery of fosfomycin was 46%.

Study Report #9: "Z 1282 (FZ 588) A New Fosfomycin Derivative with Much Improved Bioavailability by Oral Route".

The objectives of this study were to study the human pharmacokinetics of single doses of fosfomycin tromethamine *versus* calcium fosfomycin at three different dose levels (0.5, 1 and 2 g as fosfomycin). Two subjects received repeated doses of fosfomycin tromethamine to determine whether there was any accumulation of the drug. The study concluded that within the dose range studied, the pharmacokinetics of FT were linear. In contrast, the pharmacokinetics of FCa exhibit saturation limited absorption at higher doses. The bioavailability characteristics of FT are superior to those of FCa. About half the dose of fosfomycin after FT was found in the urine with all three doses. Following multiple dose administration of 1 g FT in 2 subjects, no accumulation was observed.

Study Report #10: "Pharmacokinetic Profile of Fosfomycin Trometamol (Monurol)".

The objectives of the study were (i) To study the kinetics of fosfomycin in serum and in urine after I.V. administration of disodium fosfomycin and oral administration of fosfomycin tromethamine at 50 mg/kg. (ii) to study the kinetics of fosfomycin after oral administration of 2, 3, 4 and 5 g (as fosfomycin) of fosfomycin tromethamine.

In part I of the study, following 50 mg/kg orally of FT, the peak concentration was 32.2 µg/mL at 2.2 hours which is comparable with other studies. The average total urinary recovery (0-48 hours) is 50.36%. However, a secondary peak was observed after oral administration for all subjects. The absolute bioavailability of FT was 43%.

In part II of the study, four volunteers received single oral doses of 2, 3, 4 and 5 g of FT. The mean serum concentrations at 3 hours were 15 µg/ml (2 g) , 16 µg/mL (3 g), 23 µg/mL (4 g) and 26 µg/ml (5 g). The urinary recoveries (from 0-48 hours) were 51% (2 g), 32% (3 g), 24% (4 g) and 22% (5 g). The serum concentrations appeared to increase less than in proportion to increasing dose while urinary recovery decreased as dose increased. The result of this study is not consistent with study #2 and #9.

Study Report #11: **"Urinary Tract Infections in Pregnancy: Monurol Single Dose Treatment *versus* Traditional Therapy". Neu. Williams (eds.), New Trends in Urinary Tract Infections. Int. Symp., Rome 1987. pp. 197-206, N. Ragni. C. Pivetta, F. Paccagnella, G. Foglia, Institute of Obstetrics and Gynecololgy, University of Genoa, G. P. Del Bono, P. Fontana, Corporate Medical Department, Zambon Group S.p.A., Bresso/Milan, Italy**

The objectives of this study were to study the bioavailability of fosfomycin tromethamine single dose in pregnant women during and after pregnancy.

This was an open two-way cross-over study in four (4) bacteriuric pregnant women with an age range of 27-35 yrs. A single dose of 50 mg/kg fosfomycin tromethamine was administered on two occasions: on the 27th-32nd week of pregnancy and one month after delivery.

Fosfomycin levels in plasma and urine were quantitated by a microbiological report using *Proteus mirabilis* ATCC 21100 as the test organism.

During pregnancy, the mean peak plasma concentration was 20.5 µg/mL and occurred at 2 hours after dosing. After pregnancy, the mean peak plasma concentration was 23.7 µg/mL and occurred at 3 hours after dosing. Urinary concentrations before and after delivery were 1987 and 1574 µg/ml over 0-2 hours, 1394 and 903 µg/ml over 2-4 hours, 1167 and 1545 µg/mL over 4-6 hours, 801 and 514 µg/mL over 6-8 hours, 688 and 442 µg/ml over 8-12 hours and 358 and 386 µg/mL over 12-24 hours, respectively.

Plasma and urine concentrations following a single 3 g dose of fosfomycin tromethamine were comparable during and after pregnancy indicating that dose adjustment of fosfomycin tromethamine is not necessary in pregnancy.

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Study Report #12: "Trometamol Salt of Fosfomycin (Monurol): Preliminary Pharmacokinetic and Clinical Experience in the Treatment of Urinary Tract Infections in Children". Eur. Urol. 13 suppl. 1, pp 114-118 (1987), P Careddu, M. Borzani, F. Varotto, L. Garlaschi, Pediatric Clinic I. University of Milan, P. Fontana, Corporate Medical Department, Zambon Group S.p.A., Bresso/Milan, Italy

The objectives of this study were to evaluate the pharmacokinetics of fosfomycin tromethamine in children at three different dose levels in order to suggest a dosage schedule adequate for the first clinical use in children.

This was an open parallel study in 23 (7 female and 16 male) hospitalized children (mean age of 9.6 years(5.5-13)) requiring antibacterial treatment. The children were divided into 3 groups, each group received a different single dose of FT.

Group I: 12 children received 0 5 g FT
Group II: 5 children received 1 g FT
Group III: 6 children received 2 g FT

Blood sampling schedules were as follows:

Group I: In the first 6 children blood samples were taken at 0, 1.0, 2.0, 4.0 and 8.0 hours post-dose. In the next 6 children blood samples were taken at 0, 0.5, 1.5, 3.0 and 6.0 hours post-dose.

Groups II and III: Blood samples were collected at 0, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0. 8.0 and 10.0 hours post-dose.

Urine collection schedules were as follows:

Group I and II: 0-2, 2-4, 4-6, 6-8, 8-10, 10-12 and 12-24 hour intervals.

Group III: 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24, 24-36 and 36-48 hour intervals.

Serum and urine samples were assayed for fosfomycin using an agar-plate diffusion microbiological method using *Proteus mirabilis* ATCC 21100 as the test organism.

Individual fosfomycin serum concentrations following oral administration of 0.5, 1 and 2 g FT are shown in tables 1 and 2 and the plot of average serum fosfomycin concentrations versus time are shown in figure 1. Figures 2 and 3 shows the correlations between FT doses (mg/kg) and Cmax (µg) and between FT doses and AUC (µg-h/ml), respectively. Figure 4 shows the FT urine data.

The mean peak serum concentration for Group I was 11.3 µg/mL for Group II was 18.5 µg/mL

and for Group III was 25.3 µg/mL. The AUC values were 54, 84 and 139 µg-hr/mL, respectively. The respective mean urinary recovery of fosfomycin in 24 hours was 43% for Group I, 38% for Group II and 38% for Group III. The mean urinary concentration over 12-24 hours were 50, 163 and 409 µg/mL, respectively. Values for urinary concentration after 24 hours were only available for Group III and were 216 µg/ml for 24-36 hours and 87 µg/mL for 36-48 hours.

A single oral dose of 2 FT provided plasma and urinary concentrations comparable to 3 g of FT in adults.

Study Report #13: "Pharmacokinetics in Children of a New Fosfomycin Derivative with Improved Bioavailability".

The objectives of this study were to study the pharmacokinetics in children of a single oral dose of 50 mg/kg of fosfomycin tromethamine vs calcium fosfomycin. The results of this study is comparable to other studies. The plasma concentrations of fosfomycin were higher after FT than FCa (peak concentration was 146% higher on average). The mean values of AUC were 107 and 56 µg-hr/mL, respectively. Mean urinary concentrations of fosfomycin after FT were always higher than after FCa and were as follows: 2000 versus 530 µg/ml for 0-12 hours, 470 versus 350 µg/mL for 12-24 hours, 350 versus 200 µg/ml for 24-36 hours and 150 versus 130 µg/ml for 36-48 hours.

Study Report #14 : **"Oral Bioavailability of Z 1282 in Elderly Patients". The objectives of this study were to evaluate the bioavailability and kinetics of fosfomycin tromethamine in a single oral dose equivalent to 3 g fosfomycin in elderly subjects.**

This was a single treatment with one single oral dose of FT equivalent to 3 g fosfomycin in six elderly patients (5 female and 1 male) , mean age 75.7 (62-88) years, hospitalized for various kinds of pathologies with no clinical signs of impairment of renal, gastroenteric, hepatic or hemopoietic functions except in one patient

Blood samples were collected at 0.5, 1, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0 and 10.0 hours post-dose. Urine samples were collected at 0-2, 2-4, 4-6, 6-8, 8-10, 10-12 and 12-24 hour intervals after dosing. In one subject the first collection interval was 0-3 hours. Fosfomycin levels in blood and urine were quantitated by a simple selected ion monitoring method.

The result of fosfomycin blood levels at different time are shown in Table 1. Some PK parameters obtained by the sponsor are shown in Table 2. The PK model the sponsor used is one-compartmental model with first-order absorption. The mean creatinine clearance of the subjects was 94 mL/min (patient has a creatinine clearance of 80 ml/min). The mean peak plasma concentration was 33 µg/ml with a Tmax of 3 hours, which was slightly higher and longer than in normal subjects. From the data in Table 1, it is likely that the high mean Cmax value is due to patient which has a relatively low creatinine clearance and Cmax value of 53.1 µg/mL. The mean AUC was 263.7 µg.hr/mL. The mean urinary recovery of 34% at 24 hours was comparable to data in healthy volunteers. Urinary concentration were also similar to healthy volunteers. Fosfomycin urinary concentrations exceeded the MIC of 128 µg/mL in all subjects for the first 24 hours. Mean urinary concentrations of fosfomycin exceeded 1000 µg/mL for the first 12 h.

Although mean Cmax and AUC in the elderly were slightly higher than those in young volunteers from other studies, urinary concentrations were comparable indicating no dosage adjustment necessary in the elderly.

Study Report #15: "Comparative Pharmacokinetics of Fosfomycin Trometamol versus Calcium Fosfomycin in Elderly Subjects and Uremic Patients". Neu. Williams (eds.), New Trends in Urinary Tract Infections. Int. Symp., Rome 1987. pp. 143-156. J. P. Fillastre, S. Josse., Department of Nephrology, A. Leroy, Department of Biochemistry, G. Humbert, F. Borsa, Department of Infectious Diseases, INSERM U 295, University of Rouen, France.

The objectives of this study were to determine the pharmacokinetics of fosfomycin tromethamine and calcium fosfomycin in elderly subjects and uremic patients and to compare the kinetic parameters obtained to those found in a group of 5 healthy young adult volunteers.

This was an open, randomized, two-way cross-over study, comparing the pharmacokinetics of a single doses of fosfomycin tromethamine (25 mg/kg) and calcium fosfomycin (40 mg/kg) in young healthy subjects, elderly healthy subjects and uremic patients.

The characteristics of five young male subjects with a mean age of 29 years, eight healthy elderly subjects with a mean age of 72 years and twenty-three patients with renal impairment of various degrees (mild, moderate, severe and patients on hemodialysis) are listed as follows:

Patients	No. of Patients	Age Range	Renal Function	Creatinine Clearance (ml/min)
Healthy subjects	5		normal (Healthy)	127.0
Elderly Patients	8		reduced (Elderly)	77.9
Uremic Patients-Group I	7		mild impairment	54.2
Uremic Patients-Group II	6		moderate impairment	16.4
Uremic Patients-Group III	5		severe impairment	7.3
Uremic Patients-Group IV	5		hemodialysis	0.0

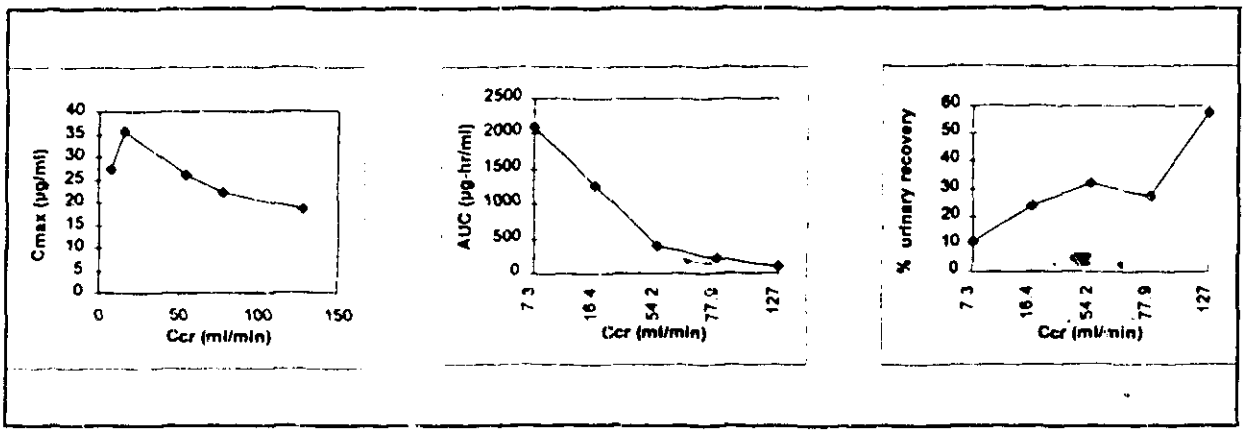
All subjects received a single oral dose of 25 mg/kg fosfomycin tromethamine and a single oral dose of 40 mg/kg calcium fosfomycin. Blood samples were collected at 0.0, 1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, 28.0, 34.0 and 48.0 hours post-dose. Urine samples were collected at 0-4, 4-8, 8-24 and 24-48 hour intervals after dosing. Fosfomycin concentrations in serum and urine were measured by a microbiological assay using *Proteus mirabilis* ATCC 21100 as the test organism.

Following the oral dose of 25 mg/kg of FT or 40 mg/kg of FCa, the mean results are shown in Tables 1 and 2.

The results of this study is consistent with other studies when comparing the bioavailability of FT versus that of FCa and the bioavailability of FT in elderly subjects versus that in young healthy subjects. The increase in Cmax and AUC for elderly subjects may be mainly due to the

reduced renal function of elderly subjects.

In the elderly and the renal impairment subjects, as renal function decreased, Cmax and AUC were increased, Tmax was delayed, elimination half-life was lengthened and urinary recovery was decreased, compared to the healthy subjects. The following figures show the relationship between Cmax, AUC, % of urinary recovery values and creatinine clearance.



The urinary concentrations were not reported for any group studied. The author only mentioned that urinary concentrations of FT remained effective during 48 hours for group III patients (> 100 µg).

The sponsor indicated that dosage adjustment may be necessary in patients with severe renal impairment.

The sponsor also indicated that because only a single dose of FT is administered, no dose adjustment is needed in the treatment of urinary infections in patients with mild to moderate renal impairment (group I and II) or in elderly patients with reduced renal function. However, there are no safety data in this report to support this claim. The mean Cmax values (26.02 and 35.66 µg/mL) after 25 mg/kg oral administration of FT to patients in group I and II are comparable to that of healthy volunteers after 50 mg/kg oral dose of FT (26.8 µg/mL, study report #4) and that after 3 g oral dose (26.1 µg/mL, study report #1). The AUC values (388.5 and 1266.8 µg.h/mL) for group I and II are 2 and 7 times of that of heathy volunteers after 50 mg/kg oral administration of FT (181.5 µg.h/mL, study #4) and that after 3 g dose (184 µg.h/mL, study #1). Furthermore, the mean dose used in this study for each group ranged from 1.667 to 2.032 g which is lower than the recommended dose (3 g) for the treatment. If the same dose (3 g) is given to patients with normal renal function and with mild to moderate renal impairment (group I and II), both Cmax and AUC values could be much higher than the Cmax and AUC ranges studied. Then, the safety at this dosing level for patients with mild to moderate renal impairment may become an issue. On the other hand, in order to have an effective therapy, urinary concentration of the drug has to be higher than the MIC. The sponsor did not provide enough information about urinary concentration of FT. If urinary concentration can not be

maintained above MIC, dosage of FT should be adjusted when safety permits. Therefore, dosage adjustment may also be necessary in patients with mild to moderate renal impairment.

APPEARS THIS WAY
ON ORIGINAL

Study Report #16: "Renal, Plasmatic and Urinary Concentrations of Fosfomycin After an Oral Single Dose of Trometamol or Calcium Fosfomycin".

The objectives of this study were to evaluate the renal, plasma and urinary concentrations of fosfomycin following the oral administration of equivalent doses (50 mg/kg) of fosfomycin tromethamine (FT) and calcium fosfomycin (FCa). This was a randomized parallel study conducted in forty-five (45) patients awaiting renal biopsy for diagnostic purpose. The results from plasma and urine data of this study are consistent with other studies. The mean concentrations in the renal tissue were 213.1 and 196.4 µg/g at 3 hours for FT and FCa, respectively and 78.4 and 37.5 µg/g at 12 hours, respectively. Therefore, FT produced higher plasma and urine concentrations as well as higher concentration in kidney tissue than FCa. Peak urinary concentrations of fosfomycin following FT were 3 times greater than those produced by the FCa.

The concentrations in renal tissue are very high comparing to those in other tissues. The sponsor indicated that the samples must have contaminated renal tubular fluid or urine.

Study Report #17: **"Study of Fosfomycin Trometamol Kinetics to Assess the Concentration of this Antibiotic in Various Human Tissues". F.P. Selvaggi, A. Traficante, M. Battaglia, V. Di Lorenzo, P. Di Tonno, Department of Surgical Nephrology, Policlinic Hospital, University of Bari, Bari, Italy**

The objectives of this study were to determine fosfomycin concentrations in blood, urine and in different tissues.

This was an open study in eleven patients (2 females and 9 males) undergoing urological surgery due to a local carcinoma, without antibacterial treatment during the 48 hours preceding the intervention. The patients received fosfomycin tromethamine orally as a single dose of 50 mg/kg of fosfomycin at different times before the start of the operation. Samples of the bladder, prostate, pericystium and seminal vesicles were taken from the patients undergoing urological surgery. Urine and serum samples were also collected at various times.

The different tissue samples were carefully weighed and homogenized and diluted. The quantitative levels of the drug in the tissues, serum and urine were determined utilizing a microbiological assay using *Salmonella* ATCC 13076 as the test organism.

Table 1 shows the concentration of FT in various tissues, in the urine and serum of patients at different times after administration of the drug. The mean serum concentration at 3 hours was 21.7 pg/ml and at 24 hours was 1.5 µg/mL. The mean urinary concentration was 694 µg/ml at 3 hours and was 192 µg/mL at 24 hours. These values are considerably lower than those observed in other studies. At 3 hours, the mean concentration in prostate, seminal vesicles, bladder and pericystium was 11.6, 8.8, 18.0 and 9.8 µg/g, respectively (the method sensitivity value, 0.4 µg/g, was used in the calculation when levels were below 0.4 µg/g). However, 4 of 7, 3 of 7, 3 of 6 and 2 of 5 concentration levels were under the limit of detection in bladder, pericystium, prostate and seminal vesicles tissues, respectively. At 24 hours, concentrations were undetectable in all tissues except for one patient in bladder tissue and one patient in seminal vesicles.

Study Report #18: "Fosfomycin Concentrations in Serum and Prostatic Tissue with Fosfomycin Trometamol, a New Fosfomycin Derivative with a High Bioavailability by the Oral Route". C.M. Borghi, D. Laveneziana, A. Riva, G. Marca and G. Zannini. Farmaci e Terapia 1986

The objectives of this study were to study the concentrations of fosfomycin in serum and prostatic tissue after fosfomycin tromethamine in comparison to calcium fosfomycin.

This was an open, parallel study in twenty-four males, subjected to prostatectomy for adenoma of the prostate. The subjects were divided into two groups of twelve. The group which received FT had a mean age of 70 years and the group which received FCa had a mean age of 71 years. Six patients in each group received treatment 3 hours before surgery, the other six received the treatment 12 hours before surgery. The patients were administered a single dose of fosfomycin tromethamine or fosfomycin calcium equivalent to 3 g fosfomycin dissolved in 100 mL of water.

Blood specimens were collected immediately before treatment and during removal of the prostate gland. Fosfomycin was determined in serum and homogenized prostatic tissue by a agar-plate-cylinder microbiological method using *Proteus mirabilis* ATCC 21100 as the test organism.

The result of fosfomycin concentrations in serum and prostatic tissue 3 hours and 12 hours after single dose oral administration of FT and FCa are shown in Table 1. Three hours after treatment, the mean concentrations of fosfomycin in serum were 25.6 µg/mL following FT and 3.6 µg/mL after FCa. At the same time the concentrations of the antibiotic in prostatic tissue were 20.8 µg/g after FT and 2.3 µg/g after FCa. The ratio between antibiotic concentrations in the prostatic tissue and those in serum were 0.91 for FT and 0.62 for FCa. Twelve hours after treatment, antibiotic concentrations in serum and in prostatic tissue averaged 6.8 µg/ml and 4.9 µg/g, respectively after FT and 2.0 µg/mL and 1.7 µg/ml respectively after FCa. The ratio between antibiotic concentrations in the prostatic tissue and those in serum were 0.74 for FT and 1.05 for FCa.

Fosfomycin levels in prostatic tissue were about 10-fold higher after FT than FCa.

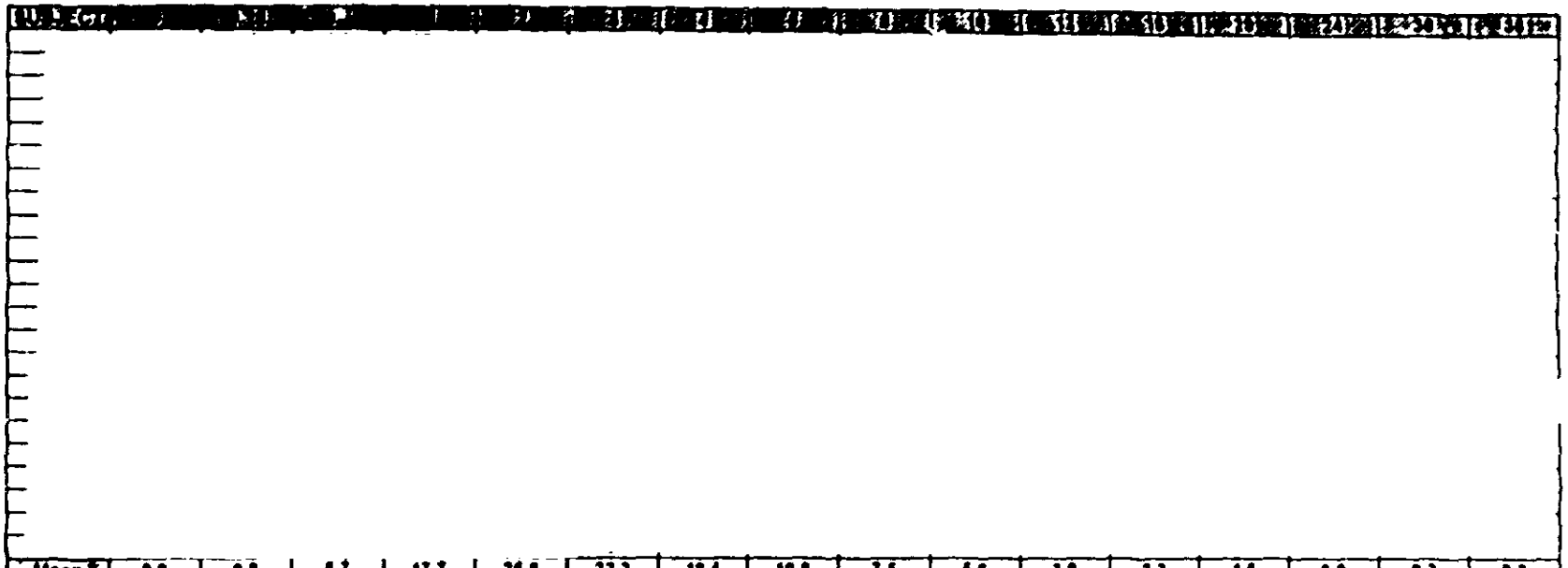
TABLES AND FIGURES

(Study Report #1)

Table
TR/3700/0002

Serum Fosfomycin Concentrations Following a Single Dose Oral Administration of Monurol 3g Under Fasting Conditions (µg/mL)

Time in Hours After Dosing



Mean	0.0	0.8	5.7	17.7	26.8	22.3	18.4	10.9	7.5	5.6	3.9	2.3	1.6	0.9	0.3	0.2
Std. Dev	0.2	0.9	3.3	7.4	7.8	5.3	4.6	2.6	1.7	1.3	1.0	0.9	0.8	0.7	0.4	0.4
CV (%)	488	113	58	42	29	24	26	24	22	24	27	39	52	79	150	208
Min																
Max																

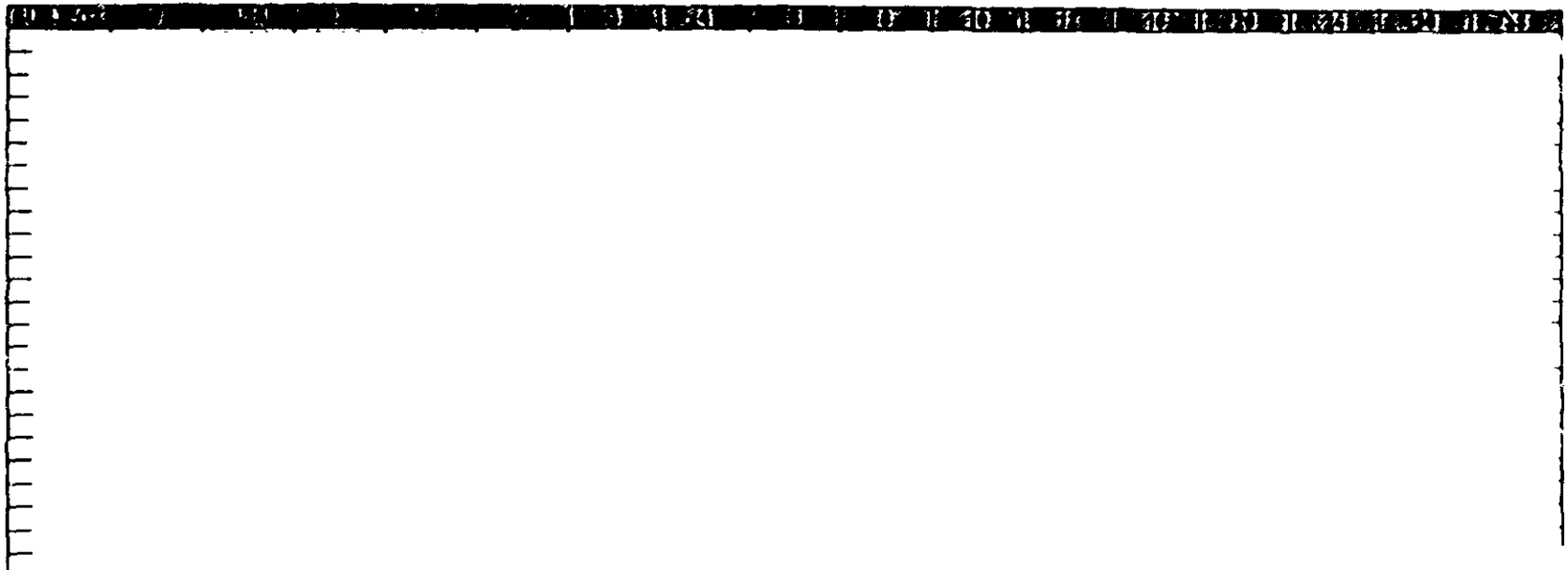
NOTE "BLOQ" STANDS FOR BELOW LIMIT OF QUANTITATION

Table 7

TR/3788/0002

Serum Fosfomycin Concentrations Following a Single Dose Oral Administration of Monurol 3g Under Fed Conditions (µg/mL)

Time in Hours After Dosing



	0.0	0.1	0.5	2.0	3.0	4.0	6.0	8.0	10.0	12.0	16.0	20.0	24.0	28.0	32.0	36.0
Mean	0.0	0.1	0.6	2.8	9.8	16.4	17.3	11.8	8.7	6.2	4.4	2.6	1.6	1.0	0.4	0.2
Std. Dev	0.1	0.2	0.9	2.1	3.4	4.1	4.7	3.4	2.6	1.6	1.3	0.8	0.7	0.8	0.4	0.3
CV (%)	490	344	201	76	36	27	27	29	30	27	29	32	41	80	106	179
N Min																
N Max																

NOTE "BLOQ" STANDS FOR BELOW LIMIT OF QUANTITATION

6-

Table 3
TR/3[illegible]0/0002

Serum Fosfomycin Concentrations Following a Single Dose Intravenous Bolus Administration of Monurol 3g (µg/mL)

Time In Hours After Dosing

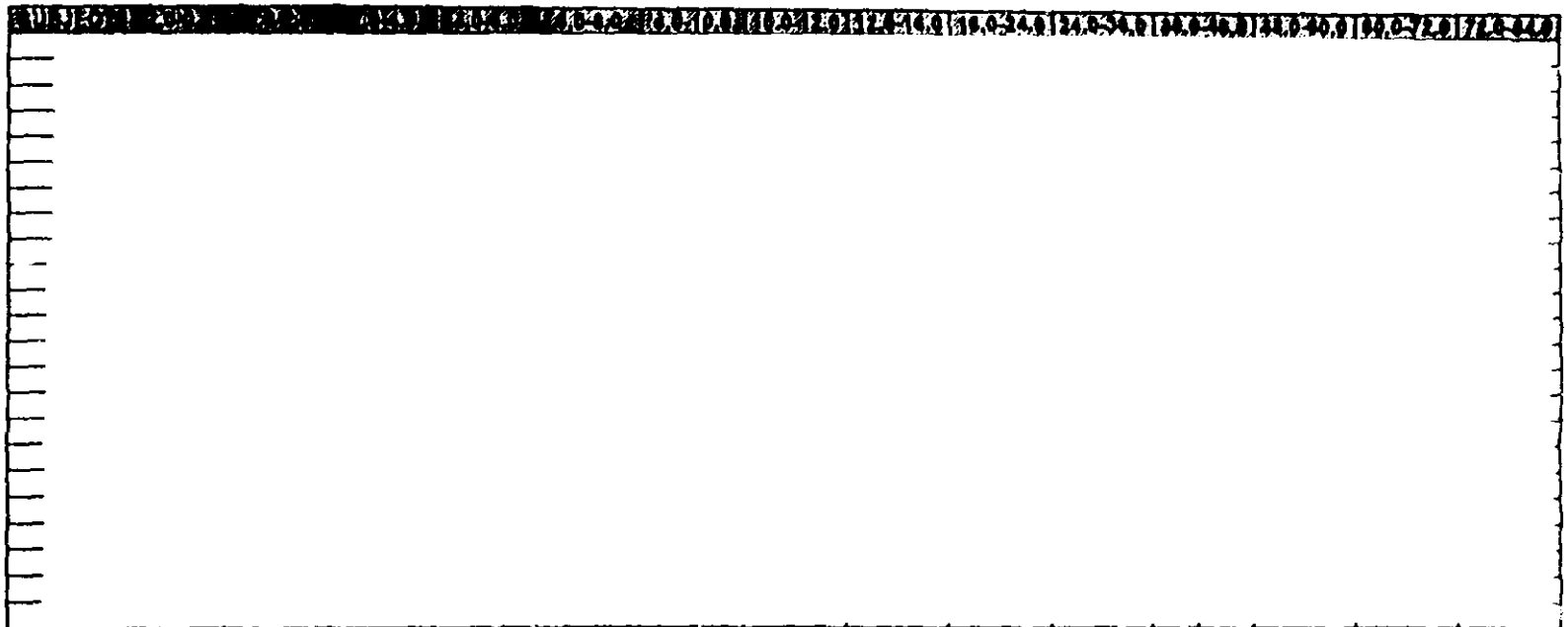
SUBJECT	0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	8	10	12	16	20
Mean	0.0	288.7	229.1	155.7	102.5	63.6	41.4	29.8	15.8	9.1	5.5	3.4	1.2	0.5
Std. Dev.	0.0	89.0	62.9	43.8	29.1	18.2	12.2	9.8	6.3	4.0	2.6	1.8	0.9	0.6
CV (%)	ERR	31	27	28	28	28	30	33	40	44	47	53	76	116
Min														
Max														

6- 42594

Table 4
TR/3700/0002

Fosfomycin Concentrations in Urine Following a Single Dose Oral Administration of Monurol 3g Under Fasting Conditions (µg/mL)

Time in Hours After Dosing



	0.0	649.2	706.6	594.2	649.9	478.5	492.9	265.0	165.0	62.2	84.2	30.5	16.3	10.5
Std. Dev.	1.6	442.1	466.4	28[illegible]6	302.4	176.2	212.2	143.3	106.9	29.8	45.5	24.4	16.7	11.5
CV (%)	200	68	66	48	55	37	43	54	65	48	84	80	91	110
Min														
Max														

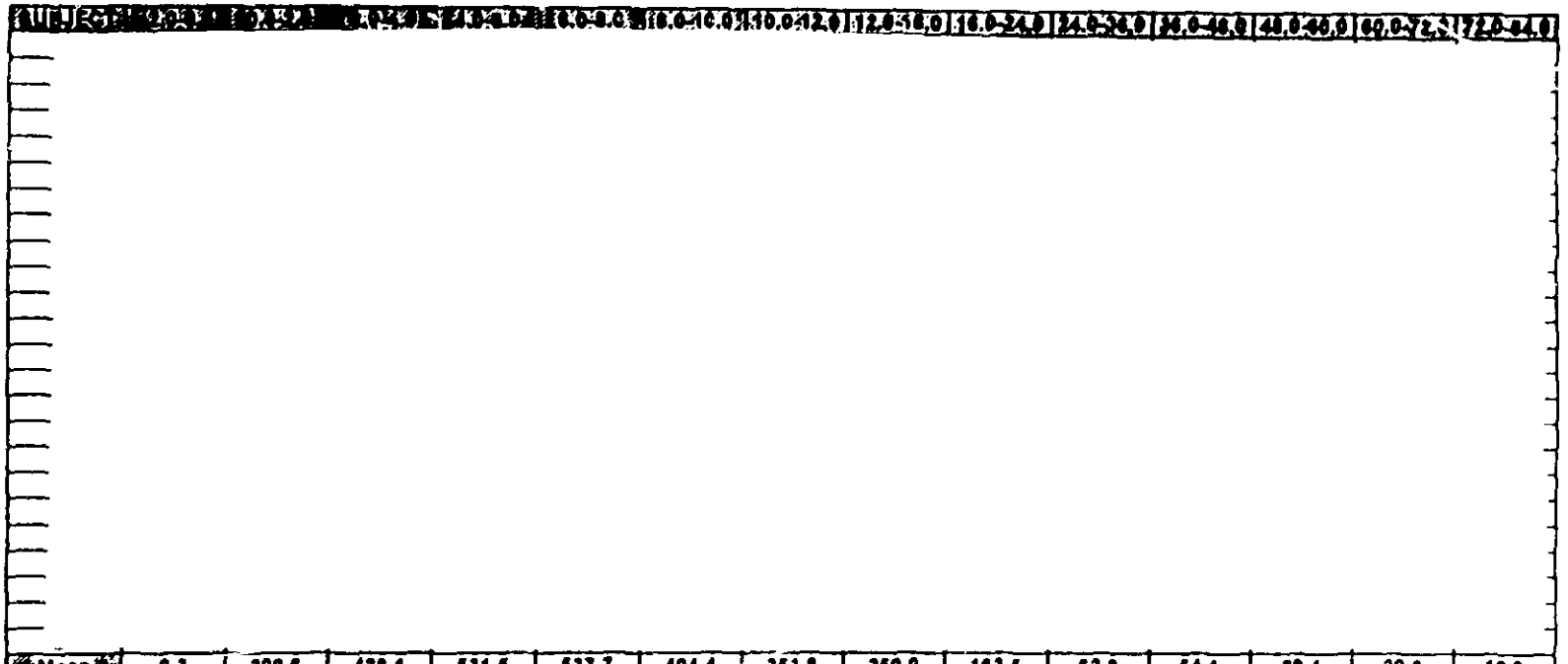
NOTE "BLOQ" STANDS FOR BELOW LIMIT OF QUANTITATION
NOTE "N S " STANDS FOR NO SAMPLE

5 - 02477

Table 5
TR/3700/0002

Fosfomycin Concentrations in Urine Following a Single Dose Oral Administration of Monurol 3g Under Fed Conditions (µg/mL)

Time in Hours After Dosing



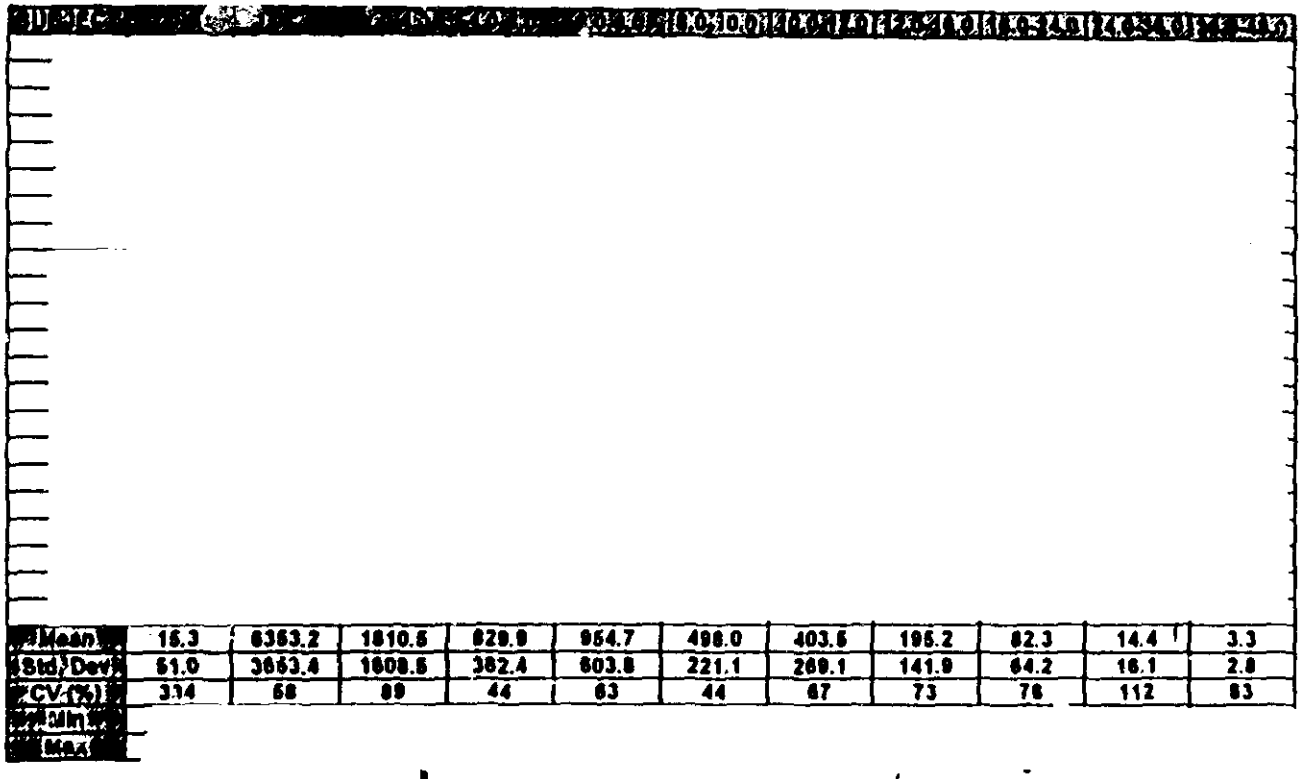
	0.0-0.3	0.3-2	2.0-4.0	4.0-6.0	6.0-8.0	8.0-10.0	10.0-12.0	12.0-16.0	16.0-24.0	24.0-36.0	36.0-48.0	48.0-60.0	60.0-72.0	72.0-84.0
Mean	0.3	209.6	426.1	531.5	537.7	404.4	351.8	250.0	163.5	62.8	54.1	29.4	20.6	10.9
Std. Dev	1.2	127.2	183.5	187.7	251.8	221.3	178.4	123.9	99.3	30.2	30.7	20.1	18.3	10.6
C.V (%)	339	61	38	35	47	55	51	50	61	48	57	68	89	97
Min														
Max														

NOTE 'BLOQ' STANDS FOR BELOW LIMIT OF QUANTITATION
NOTE 'N < ' STANDS FOR NO SAMPLE

Table
TR/3700/0002 6

Fosfomycin Concentrations in Urine Following a Single Dose Intravenous Bolus Administration of Monurol 3g (µg/mL)

Time in Hours After Dosing



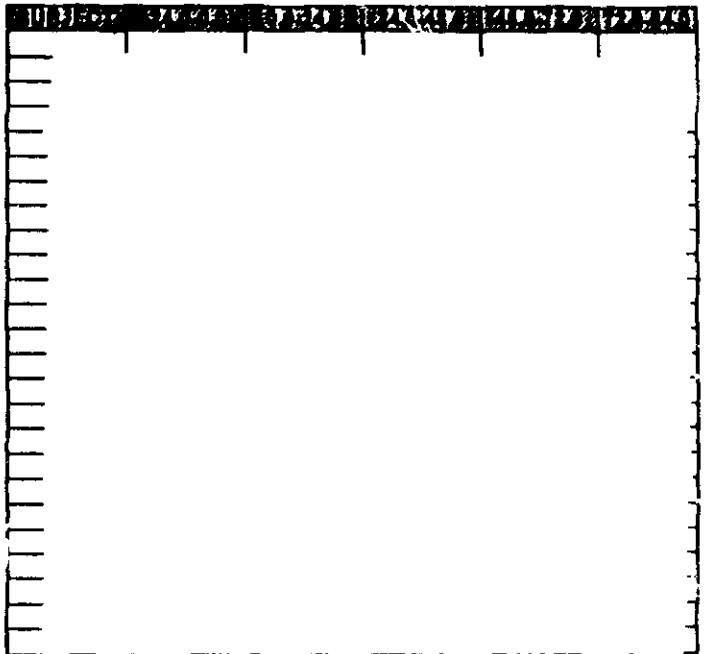
Mean	15.3	6353.2	1810.5	629.9	954.7	498.0	403.5	195.2	82.3	14.4	3.3
Std Dev	51.0	3653.4	1608.5	382.4	603.8	221.1	269.1	141.9	64.2	16.1	2.8
CV (%)	334	58	89	44	63	44	67	73	78	112	83
Min											
Max											

NOTE: "BLOQ" STANDS FOR BELOW LIMIT OF QUANTITATION
NOTE: "N.S." STANDS FOR NO SAMPLE
NOTE: "P.C." STANDS FOR POOR CHROMATOGRAPHY

Table
TR/3700/0002

Fosfomycin Concentrations in Feces Following a Single Dose Oral Administration of Monurol 3g Under Fasting Conditions (µg/mL)

Time in Hours After Dosing



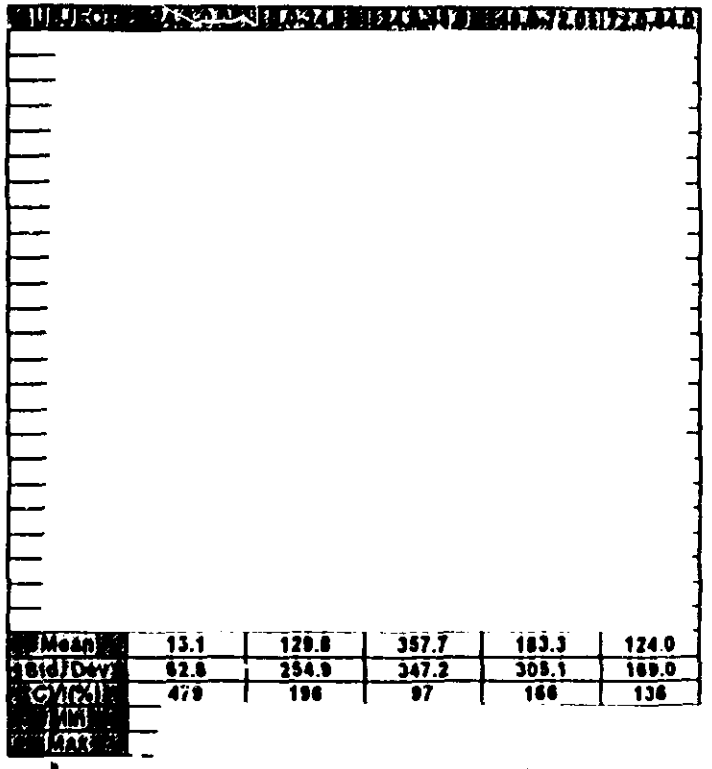
Mean	0.2	108.8	352.3	166.3	94.5
Std. Dev.	0.9	189.5	305.2	231.4	149.2
CV (%)	490	174	87	139	158
Min					
Max					

NOTE "BLOQ" STANDS FOR BELOW LIMIT OF QUANTITATION
NOTE "M S" STANDS FOR MISSING SAMPLES

Table 8
TR/3700/0002

Fosfomycin Concentrations in Feces Following a Single Dose Oral Administration of Monurol 3g Under Fed Conditions (µg/mL)

Time in Hours After Dosing



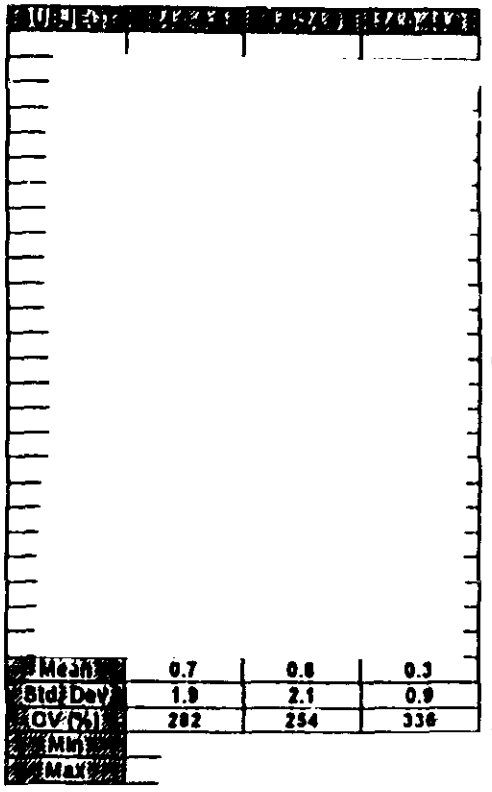
Mean	13.1	129.8	357.7	183.3	124.0
Std Dev	62.8	254.9	347.2	305.1	189.0
CV(%)	479	196	97	166	136
Min					
Max					

NOTE "BLOQ" STANDS FOR BELOW LIMIT OF QUANTITATION
NOTE "M.S" STANDS FOR MISSING SAMPLES

Table
TRJ3700/0002

Fosfomycin Concentrations in Feces Following a Single Dose Intravenous Bolus Administration of Monurol 3g (µg/mL)

Time in Hours After Dosing



Mean	0.7	0.8	0.3
Std Dev	1.9	2.1	0.9
CV (%)	282	254	336
Min			
Max			

NOTE "BLOQ" STANDS FOR BELOW LIMIT OF QUANTITATION
NOTE "M S" STANDS FOR MISSING SAMPLES

Table 10
Mean* Fosfomycin Serum Concentrations (μg/mL)
Following a Single 3 g Dose

Time After Dose (hr)	Treatment A (fasted)	Treatment B (postprandial)	Treatment C (intravenous)
0	0.0 (0.2) (1)	0.0 (0.1) (1)	0.0 (0.0) (0)
0.17	—	—	288.7 (89.0) (22)
0.25	0.8 (0.9) (13)	0.1 (0.2) (2)	229.1 (62.9) (22)
0.5	5.7 (3.3) (21)	0.5 (0.9) (7)	155.7 (43.8) (22)
1	17.7 (7.4) (23)	2.8 (2.1) (22)	102.5 (29.1) (22)
2	26.8 (7.8) (23)	9.8 (3.4) (24)	63.8 (18.2) (22)
3	22.3 (5.3) (23)	15.4 (4.1) (24)	41.4 (12.2) (22)
4	18.4 (4.5) (23)	17.3 (4.7) (24)	29.8 (9.8) (22)
6	10.9 (2.6) (23)	11.8 (3.4) (24)	15.8 (6.3) (22)
8	7.5 (1.7) (23)	8.7 (2.6) (24)	9.1 (4.0) (22)

*Data presented as means (±SD) followed by the number of subjects in parentheses.

Table (continued)
Mean* Fosfomycin Serum Concentrations (μg/mL)
Following a Single 3 g Dose

Time After Dose (hr)	Treatment A (fasted)	Treatment B (postprandial)	Treatment C (intravenous)
10	5.6 (1.3) (23)	6.2 (1.6) (24)	5.5 (2.6) (22)
12	3.9 (1.0) (23)	4.4 (1.3) (24)	3.4 (1.8) (22)
16	2.3 (0.9) (23)	2.5 (0.8) (24)	1.2 (0.9) (19)
20	1.5 (0.8) (22)	1.6 (0.7) (24)	0.5 (0.6) (11)
24	0.9 (0.7) (17)	1.0 (0.5) (22)	—
30	0.3 (0.4) (8)	0.4 (0.4) (12)	—
36	0.2 (0.4) (5)	0.2 (0.3) (6)	—

*Data presented as means (±SD) followed by the number of subjects in parentheses.

Table 11
Mean* Fosfomycin Urine Concentrations (μg/mL) Following a Single 3 g Dose

Time Interval (hours)	Treatment A (fasted)	Treatment B (postprandial)	Treatment C (intravenous)
-2.0—0.0	0.9 (1.8) (5)	0.3 (1.2) (3)	15.3 (51.0) (7)
0.0—2.0	649.2 (442.1) (22)	209.6 (127.2) (24)	6353.2 (3653.4) (21)
2.0—4.0	706.5 (466.4) (23)	428.1 (153.5) (24)	1810.5 (1608.5) (21)
4.0—6.0	594.2 (267.5) (23)	531.5 (187.2) (24)	829.9 (362.4) (22)
6.0—8.0	549.9 (302.4) (21)	537.7 (251.8) (23)	954.7 (603.8) (22)
8.0—10.0	478.5 (176.2) (23)	404.4 (221.3) (23)	498.0 (221.1) (21)
10.0—12.0	492.9 (212.2) (23)	351.8 (179.4) (23)	403.5 (269.1) (20)
12.0—16.0	265.0 (143.3) (23)	250.0 (123.9) (24)	195.2 (141.9) (22)
16.0—24.0	168.1 (108.9) (23)	163.5 (99.3) (24)	82.3 (64.2) (22)
24.0—36.0	62.2 (29.8) (23)	62.8 (30.2) (24)	14.4 (16.1) (21)
36.0—48.0	54.2 (45.5) (22)	54.1 (30.7) (24)	3.3 (2.8) (15)
48.0—60.0	30.6 (21.1) (22)	29.3 (23.3) (21)	—
60.0—72.0	21.6 (17.7) (22)	17.4 (17.2) (21)	—
72.0—84.0	10.8 (11.4) (21)	10.6 (10.7) (22)	—

*Data presented as means (± SD) followed by the number of subjects in parentheses

Table
Mean[a] Cumulative Amounts of Fosfomycin Excreted in Feces (mg) Following a Single 3 g Dose

Time After Dose (hours)	Treatment A (fasted)	Treatment B (postprandial)	Treatment C (intravenous)
0	0.22 (1.05)	10.61 (50.17)	0.83 (2.53)
24	48.70 (103.13)	115.07 (278.67)	1.24 (3.70)
48	347.64 (292.82)	346.51 (323.42)	1.34 (3.68)
72	458.66 (301.34)	469.59 (355.06)	-
84	530.64 (317.09)	565.64 (389.13)	-

[a]Data presented as means (± SD) followed by the number of subjects in parentheses.

Table 13
Summary of Fosfomycin Pharmacokinetics Parameters[a] Obtained Using Non-Compartmental Analysis

Parameter	Treatment		
	Fasted	Postprandial	I.V.
$AUC_{(0-t)}$ (μg·hr/mL)	172 (30.7) (17.9)	142 (32.1) (22.5)	498 (87.0) (17.5)
$AUC_{(0-\infty)}$ (μg·hr/mL)	184 (33.6) (18.2)	154 (34.2) (22.3)	504 (87.6) (17.4)
F_{abs}	0.37 (0.07) (19)	0.30 (0.05) (17)	-
F_{rel}	-	0.82 (0.13) (16)	-
C_{max} (μg/mL)	26.1 (9.1) (35)	17.6 (4.4) (25)	-
T_{max} (hr)	2.1 (0.42) (20)	4.0 (0.55) (14)	-
λ_z (p) (hr^{-1})	0.15 (0.06) (41.4)	0.13 (0.04) (32.8)	0.26 (0.06) (23.1)
$t_{1/2}$ (p) (hr)	5.7 (2.8) (49.5)	5.8 (1.9) (32.1)	2.7 (0.57) (21.1)
MRT (hr)	8.2 (2.54) (31.1)	9.9 (1.98) (19.9)	2.7 (0.60) (22.2)

Table (continued)

Summary of Fosfomycin Pharmacokinetics Parameters[a] Obtained Using Non-Compartmental Analysis

Parameter	Treatment		
	Fasted	Postprandial	I.V.
V_u (L)	136 (44.1)[b] (32.4)	201 (54.6)[b] (27.2)	16.5 (4.73) (28.7)
$Ae_{(0-84)\,u}$ (mg)	1128 (240) (21.3)	1082(195) (18.0)	2687 (404) (15.0)
$Ae_{(0-\infty)\,u}$ (mg)	1140 (238) (20.9)	1118 (201) (18.0)	2688 (404) (15.0)
$Ae_{(0-84)\,f}$ (mg)	530.6 (317.1) (59.8)	565.6 (389.1) (68.8)	1.34 (3.69) (275)
λ_z (u) (hr^{-1})	0.090 (0.125) (139)	0.080 (0.107) (134)	0.336 (0.253) (75)
$t_{1/2}$ (u) (hr)	16.6 (10.8) (65)	23.2 (41.9) (181)	3.1 (1.5) (48)
CL (L/hr)	16.9 (3.46)[c] (20.5)	20.4 (4.35)[c] (21.3)	6.1 (1.0) (16.4)
CL_R (L/hr)	6.3 (1.7) (27.0)	7.6 (2.2) (28.9)	5.5 (1.2) (21.8)

[a]Data are presented as mean (± SD) values and the %CV is in parentheses below these values.
[b]V_u calculated as V_u/F
[c]Total Clearance calculated as CL/F

Table 14

Summary of Fosfomycin Pharmacokinetics Parameters* Obtained Using Compartmental Analysis

Parameter	Treatment		
	Fasted	Postprandial	I.V.
B1 (hr^{-1})	4.352 (3.538) (81)	4.518 (3.521) (78)	4.708 (3.480) (74)
B2 (hr^{-1})	0.282 (0.099) (35)	0.288 (0.097) (34)	0.297 (0.089) (30)
λ_z (p) (hr^{-1})	0.642 (0.200) (31)	0.663 (0.175) (26)	0.684 (0.148) (22)
$t_{1/2\ \lambda z}$ (p) hr)	1.30 (0.84) (65)	1.16 (0.53) (46)	1.06 (0.24) (22)
λ_{01} (hr^{-1})	0.414 (0.296) (72)	0.215 (0.070) (32)	-
$t_{1/2\ ka}$ (hr)	2.13 (0.96) (45)	3.48 (0.91) (26)	-
Lagtime (τ) (hr)	0.205 (0.073) (36)	0.249 (0.002) (1)	0.063 (0.041) (64)
MRT-disposition (hr)	3.15 (1.29) (41)	3.02 (1.12) (37)	2.82 (0.65) (23)
MRT- total (hr)	6.44 (1.58) (25)	8.28 (1.29) (16)	2.89 (0.66) (23)
MRT- absorption (hr)	3.28 (1.34) (41)	5.26 (1.31) (25)	0.06 (0.04) (64)
MAT (hr)	3.79 (1.96) (52)	5.52 (1.46) (26)	-

Table 15
Summary of Fosfomycin Pharmacokinetics Parameters[a]: Comparison of Fasted and Postprandial

Parameter	Treatment		Significance[b]
	Fasted	Postprandial	
$AUC_{(0-t)}$ (µg•hr/mL)	172 (30.7) (17.9)	142 (32.1) (22.5)	p<0.05
$AUC_{(0-\infty)}$ (µg•hr/mL)	184 (33.6) (18.2)	154 (34.2) (22.3)	p<0.05
F_{abs}	0.37 (0.07)) (19)	0.30 (0.05) (17)	p<0.05
C_{max} (µg/mL)	26.1 (9.1) (35)	17.6 (4.4) (25)	p<0.05
T_{max} (hr)	2.1 (0.42) (20)	4.0 (0.55) (14)	p<0.05
λ_z (p) (hr^{-1})	0.15 (0.06) (41.4)	0.13 (0.04) (32.8)	NS
$t_{1/2,\lambda z}$ (p) (hr)	5.7 (2.8) (49.5)	5.8 (1.9) (32.1)	NS

[a]Data are presented as mean (± SD) values and the %CV is in parentheses below these values.
[b]Mean values were compared statistically by ANOVA with a level of significance of $P \leq 0.05$.

Table 16

Mean* Fosfomycin Serum Concentrations (µg/mL)
Following a Single 3 g Intravenous Bolus Dose: Male and Female Subjects

Time After Dose (hr)	Male Subjects	Female Subjects
0.17	261.2 (55.1)	350.5 (33.7)
0.25	215.6 (28.5)	268.3 (29.8)
0.5	146.3 (19.8)	182.7 (24.5)
1	96.7 (14.3)	119.6 (16.8)
2	63.5 (8.9)	70.6 (14.4)
3	42.0 (6.2)	44.8 (10.8)
4	31.5 (6.4)	30.8 (9.0)
6	17.4 (4.1)	15.5 (6.6)
8	10.4 (2.9)	8.6 (4.1)
10	6.6 (2.0)	4.8 (2.5)
12	4.2 (1.9)	2.7 (1.7)
16	1.5 (0.8)	0.8 (0.8)
20	0.7 (0.6)	0.2 (0.4)

*Data presented as means (±SD)

Table 18
Summary of Fosfomycin Pharmacokinetics Parameters[a] Following I.V. Treatment:
Comparison of Male and Female Subjects

Parameter	Gender		Significance[b]
	Male	Female	
$AUC_{(0-\infty)}$ (µg•hr/mL)	477 (72) (15)	535 (97) (18)	NS
$t_{1/2\,\lambda z}$ (hr)	3.08 (0.40) (13)	2.31 (0.44) (19)	p<0.05
V_{ss} (L)	19.5 (4.3) (22)	12.9 (1.7) (13)	p<0.05
$Ae_{(0-\infty),\,u}$ (mg)	2737 (518) (19)	2626 (209) (8)	NS
$Ae_{(0-84),\,f}$ (mg)	2.6 (5.0) (192)	0.1 (0.2) (200)	NS
CL (L/hr)	6.4 (1.0) (16)	5.7 (0.9) (16)	NS
CL_R (L/hr)	5.8 (1.5) (26)	5.1 (0.6) (12)	NS

[a]Data are presented as mean (±SD) values and the %CV is in parentheses below these values.
[b]Mean values were compared statistically by t-test with a level of significance of $P \leq 0.05$.

Table 17
Mean* Fosfomycin Cumulative Amounts of Fosfomycin Excreted in Urine (mg) Following a Single 3 g Intravenous Bolus Dose: Male and Female Subjects

Time of Urine Collection (hr)	Male Subjects	Female Subjects
0	0.40 (0.65) (163)	10.35 (27.49) (266)
2	1163 (346) (30)	1479 (200) (44)
4	1815 (350) (19)	2104 (217) (10)
6	2149 (376) ((17)	2356 (278) (12)
8	2388 (447) (19)	2477 (264) (11)
10	2450 (480) (20)	2556 (239) (9)
12	2571 (488) (19)	2571 (214) (8)
16	2657 (501) (19)	2606 (212) (8)
24	2716 (512) (19)	2622 (209) (8)
36	2734 (516) (19)	2625 (209) (8)
48	2736 (517) (19)	2626 (209) (8)

Data presented as means (± SD) followed by %CV in parenthesis.

TABLE

(Study Report #18)

TABLE - Fosfomycin concentrations in serum and prostatic tissue 3 hr (patients) and 12 hr (patients after single-dose oral administration of fosfomycin tromethamol and calcium fosfomycin at the dose of 3 g fosfomycin.

TREATMENT					
FOSFOMYCIN TROMETHAMOL				CALCIUM FOSFOMYCIN			
PAT. No.	FOSFOMYCIN CONCENTRATIONS		PT/S	PAT. No.	FOSFOMYCIN CONCENTRATIONS		PT/S
	SERUM	PROSTATIC TISSUE			SERUM	PROSTATIC TISSUE	
No.	mcg/ml	mcg/g		No.	mcg/ml	mcg/g	
1.				7.			
2.				8.			
3.				9.			
4.				10.			
5.				11.			
6.				12.			
13.				19.			
14.				20.			
15.				21.			
16.				22.			
17.				23.			
18.				24.			

PT/S fosfomycin concentration in the prostatic tissue-fosfomycin serum concentration ratio.

* means ± S.E.

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Figure
Study R/3700/0002
Semilogarithmic Plot of Mean Excretion Rate versus Midpoint Time
Treatment C: GC

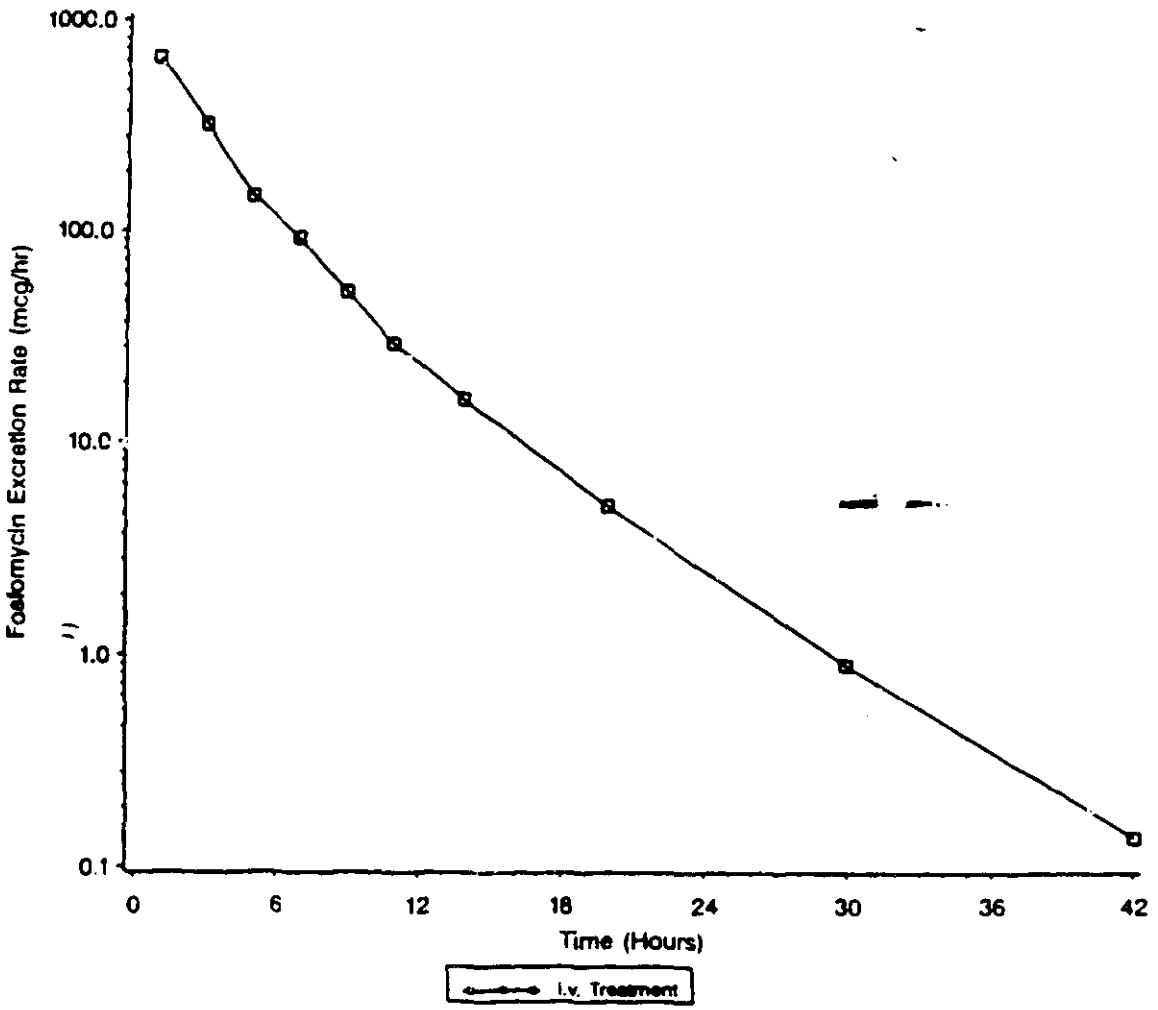


Figure 2
Study R/3700/0002
Rectilinear Plots of Mean Serum Fosfomycin Concentrations versus Time
Fasted and Postprandial

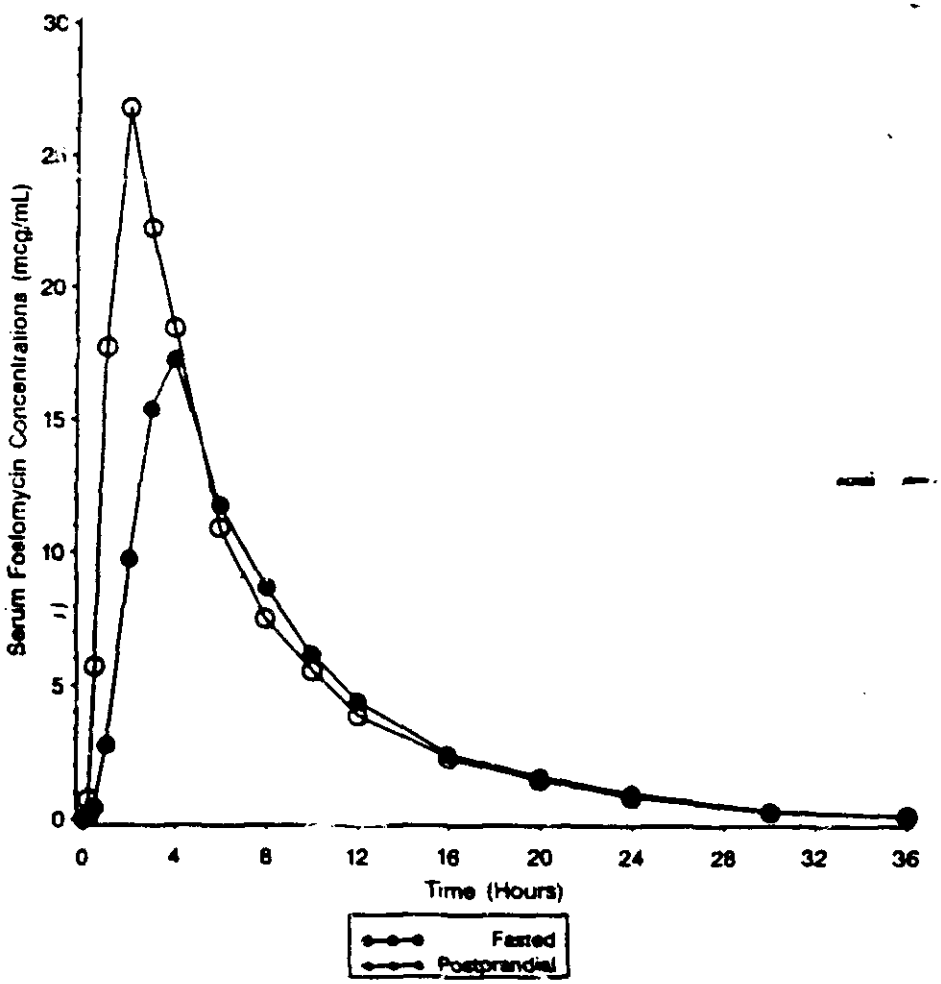


Figure 3
Study R/3700/3002
Rectilinear Plots of Mean Urinary Fosfomycin Concentrations versus Time
Fasted and Postprandial

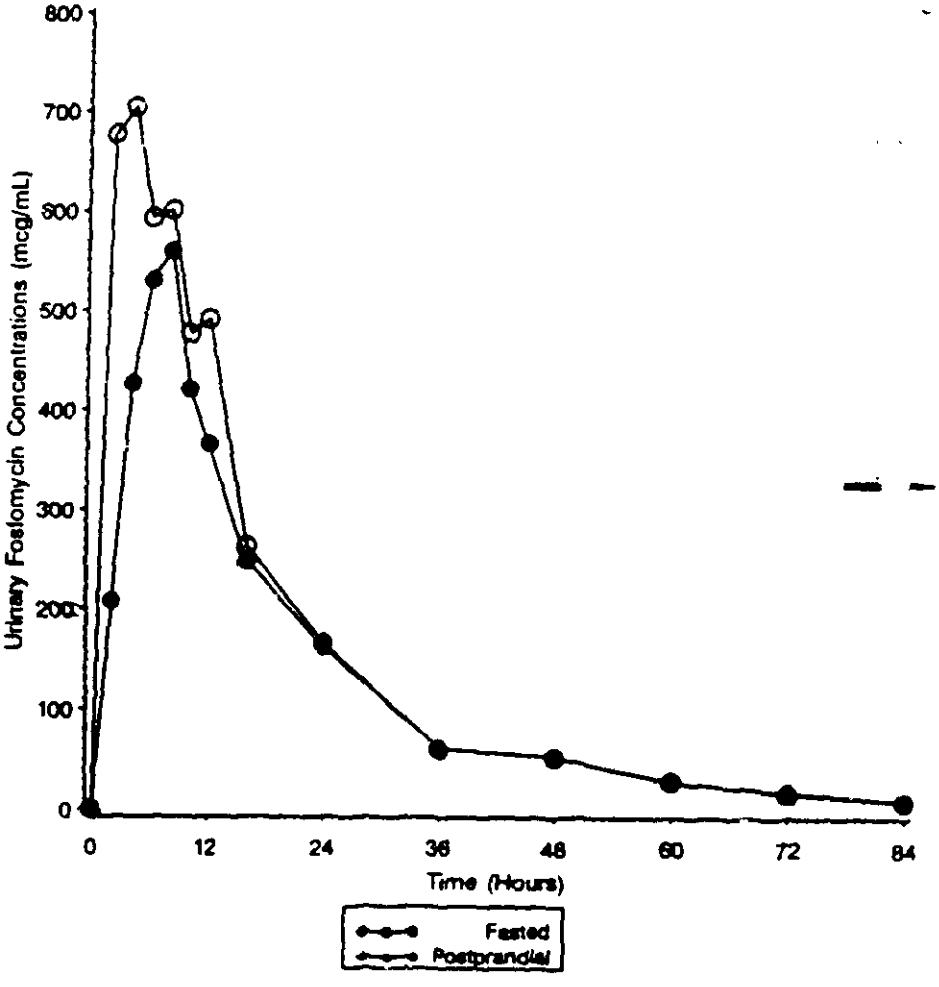


Figure 4
Study R/3700/0002
Rectilinear Plot of Mean Cumulative Amount Excreted versus Time
Fasted and Postprandial

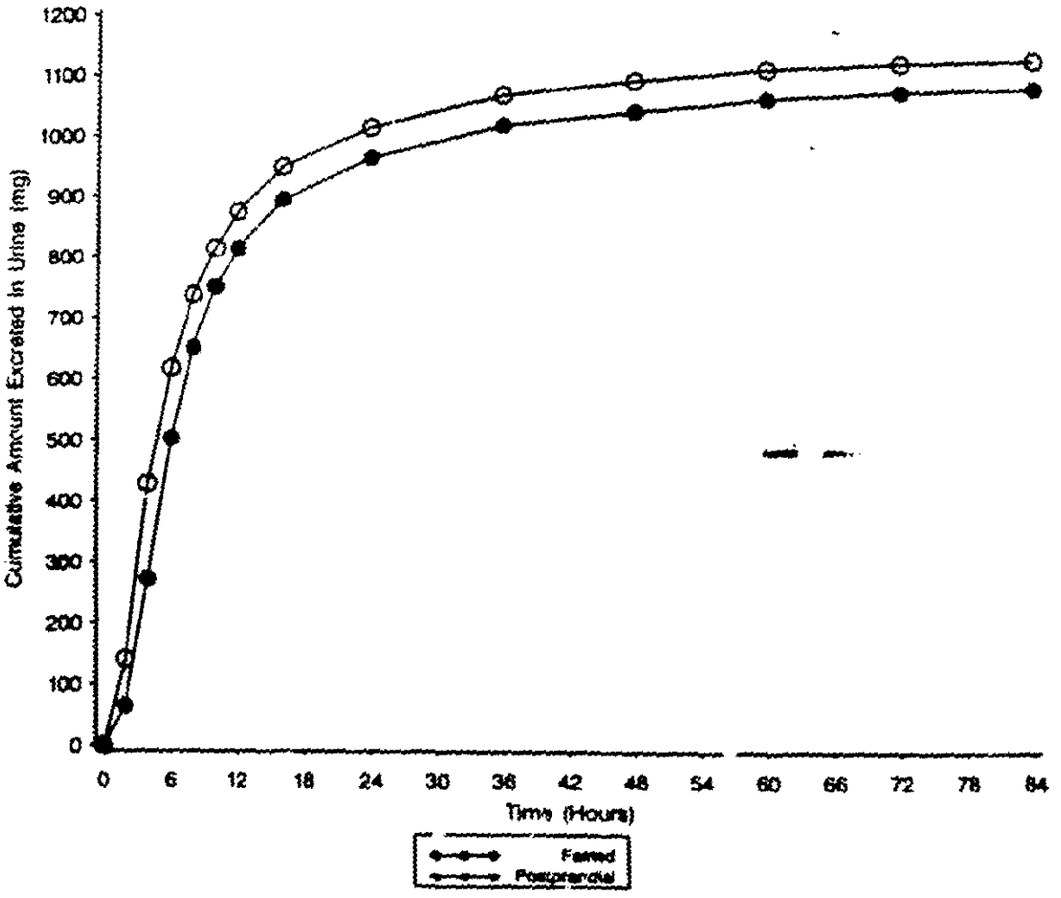


Figure 5
Study R/3700/0002
Rectilinear Plots of Mean Serum Fosfomycin Concentrations versus Time
Male and Female: I.v. Treatment

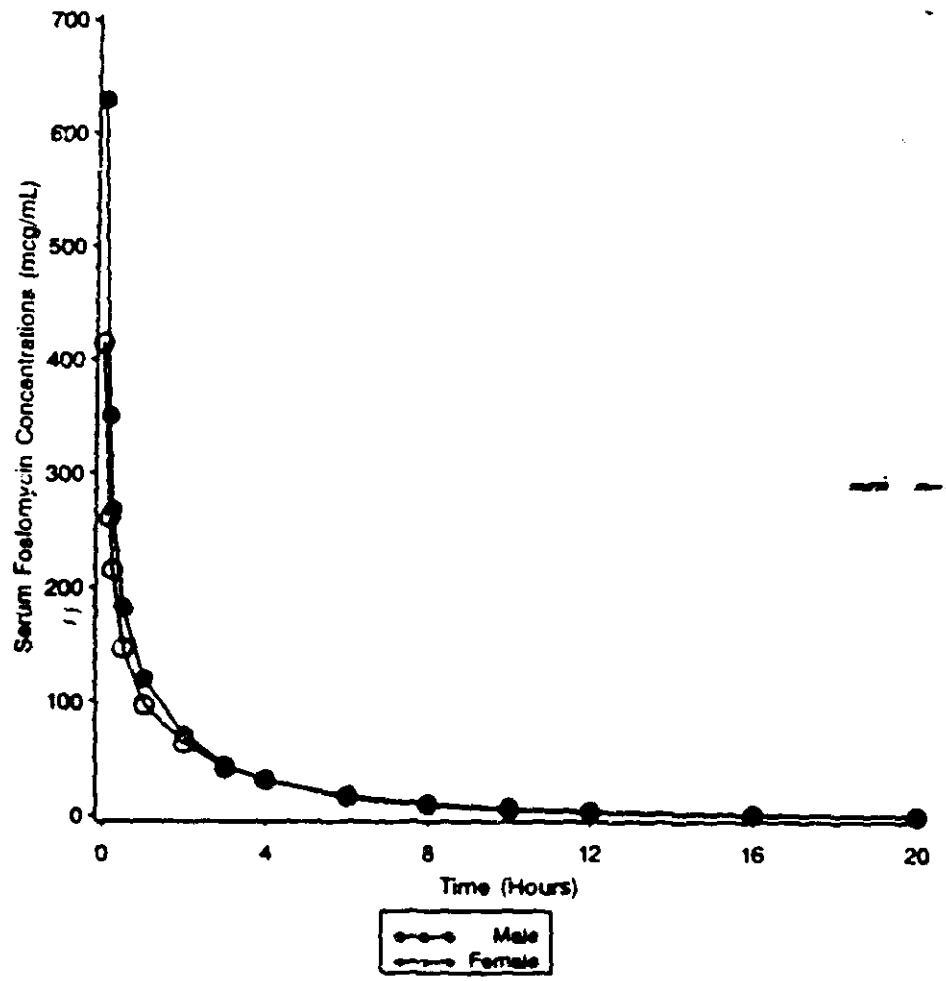
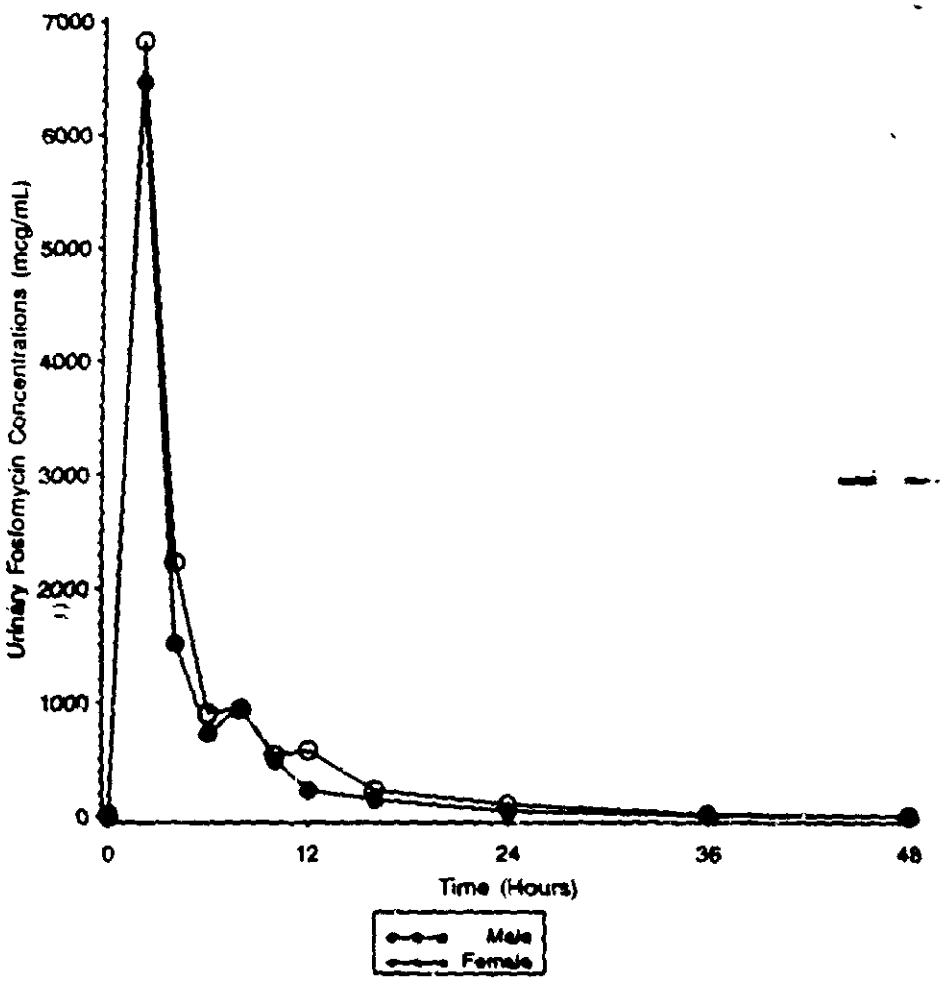


Figure 6
Study R/3700/0002
Rectilinear Plots of Mean Urinary Fosfomycin Concentrations versus Time
Male and Female: I.v. Treatment



TABLES AND FIGURES

(Study Report #2)

TABLE / Serum concentrations (µg/ml; means of 2 assays) of Fosfomycin in healthy subjects treated with Fosfomycin Trometamol orally, 2000 mg (as Fosfomycin acid). Individual data

TIME	SUBJECTS
0.0	
0.5	
1.0	
2.0	
3.0	
4.0	
6.0	
8.0	
10.0	
12.0	

TIME	SUBJECTS
0.0	
0.5	
1.0	
2.0	
3.0	
4.0	
6.0	
8.0	
10.0	
12.0	

ND: not detectable

NDA 50717

TABLE 2 Serum concentrations (µg/ml) (means of 2 assays) of Fosfomycin in healthy subjects treated with Fosfomycin Trometamol orally, 3000 mg (as Fosfomycin acid). Individual data

TIME	SUBJECTS											
0.0												
0.5												
1.0												
2.0												
3.0												
4.0												
6.0												
8.0												
10.0												
12.0												

TIME	SUBJECTS											
0.0												
0.5												
1.0												
2.0												
3.0												
4.0												
6.0												
8.0												
10.0												
12.0												

TABLE 3 Serum concentrations (µg/ml; means of 2 assays) of Fosfomycin in healthy subjects treated with Fosfomycin Trometamol orally, 4000 mg as (Fosfomycin acid). Individual data.

TIME	SUBJECTS
0.0	
0.5	
1.0	
2.0	
3.0	
4.0	
6.0	
8.0	
10.0	
12.0	

TIME	SUBJECTS
0.0	
0.5	
1.0	
2.0	
3.0	
4.0	
6.0	
8.0	
10.0	
12.0	

TABLE 4 Serum concentrations (µg/ml; means of 2 assays) of Fosfomycin in healthy subjects treated with Fosfomycin Sodium intravenously, 3000 mg (as Fosfomycin acid). Individual data.

TIME	SUBJECTS
0.017	
0.25	
0.50	
1.00	
2.00	
3.00	
4.00	
6.00	
8.00	
10.00	
12.00	

TIME	SUBJECTS
0.017	
0.25	
0.50	
1.00	
2.00	
3.00	
4.00	
6.00	
8.00	
10.00	
12.00	

TABLE Serum concentrations (µg/ml; means of 2 assays) of Fosfomycin in healthy subjects treated with Fosfomycin Trometamol orally, 2000, 3000 and 4000 mg (as Fosfomycinacid) and with Fosfomycin Sodium intravenously, 3000 mg (as Fosfomycin acid). Means ± SD of 12 subjects.

TIME	DOSE ADMINISTERED			
	ORALLY			INTRAVENOUSLY
	2000 mg	3000 mg	4000 mg	3000 mg
0.00	<0.710	<0.710	<0.710	-
0.017	-	-	-	370.643 ±92.051
0.25	-	-	-	194.432 ±23.521
0.50	4.271* ±2.324	5.464 ±4.066	6.285 ±1.148	149.528 ±5.726
1.00	11.026 ±5.667	15.415 ±8.043	20.282 ±7.198	100.998 ±46.403
2.00	14.397 ±5.778	21.015 ±4.510	30.853 ±5.629	62.141 ±6.924
3.00	11.827 ±4.292	17.309 ±3.869	23.520 ±4.593	41.608 ±5.559
4.00	10.170 ±4.101	13.252 ±3.353	18.389 ±3.956	30.121 ±6.360
6.00	6.471 ±2.653	8.655 ±3.387	11.411 ±3.121	14.897 ±2.844
8.00	4.947 ±2.296	6.509 ±2.393	8.269 ±2.563	8.150 ±2.106
10.00	3.640 ±1.607	4.803 ±1.506	6.558 ±2.064	4.552 ±1.496
12.00	2.809 ±1.247	3.926 ±1.458	5.315 ±2.019	2.764 ±1.292

* mean ± SD of 11 subjects

TABLE 6 Pharmacokinetic parameters of Fosfomycin Trometamol in healthy subjects treated with 2000 mg (as Fosfomycin acid) orally.Individual data

Param.	1os2000	2os2000	3os2000	5os2000	6os2000	7os2000	8os2000
T1/2 el	3.66	4.06	3.10	3.32	5.09	4.31	5.66
T1/2abs	0.80	0.72	0.44	0.41	0.28	1.20	0.91
Lag_t	0.00	0.00	0.00	0.00	0.35	0.00	0.00
Dose	2000.00	2000.00	2000.00	2000.00	2000.00	2000.00	2000.00
AUC_exp	116.08	103.53	90.14	91.83	147.17	89.54	65.88
Cmax	16.51	16.55	18.72	17.34	21.46	10.38	6.50
Tmax	3.00	2.00	2.00	1.00	2.00	3.00	2.00
Clr tot	17.23	19.32	22.19	21.78	13.59	22.34	30.36
Vd	91.02	113.10	99.25	104.21	99.74	139.06	248.14
MRT_exp	6.24	6.94	5.02	5.35	7.53	7.79	9.27
Vdss_ex	107.51	134.01	111.47	116.43	102.35	174.01	281.54
AUC_mod	114.22	100.35	84.60	89.52	133.00	88.83	64.28
MRT_mod	6.44	6.89	5.11	5.37	8.09	7.96	9.49
Vds_mod	112.83	137.36	120.79	120.06	121.73	179.18	295.12

Param.	9os2000	10os2000	11os2000	12os2000	MEAN	SEM
T1/2 el	3.38	3.53	3.98	4.51	4.05	0.24
T1/2abs	0.57	0.87	0.24	1.18	0.69	0.10
Lag_t	0.00	0.00	0.42	0.00	0.07	0.05
Dose	2000.00	2000.00	2000.00	2000.00	2000.00	0.00
AUC_exp	99.73	82.39	95.27	191.75	106.66	10.53
Cmax	18.95	13.26	16.01	20.27	16.00	1.33
Tmax	1.00	2.00	2.00	4.00	2.18	0.26
Clr tot	20.05	24.27	20.99	10.43	20.23	1.60
Vd	97.81	123.70	120.44	67.82	118.57	14.13
MRT_exp	5.41	6.49	6.25	8.15	6.77	0.40
Vdss_ex	108.47	157.54	131.27	85.02	137.24	16.34
AUC_mod	91.00	76.33	92.14	183.30	101.60	9.84
MRT_mod	5.70	6.35	6.50	8.20	6.92	0.41
Vds_mod	125.31	166.37	141.19	89.50	146.31	16.64

TABLE 7/Pharmacokinetic parameters of Fosfomycin Trometamol in healthy subjects treated with 3000 mg (as Fosfomycin acid) orally.Individual data

Param.	1os3000	2os3000	3os3000	4os3000	5os3000	6os3000	7os3000
T1/2 el	10.55	3.13	3.36	4.87	3.62	3.79	3.91
T1/2abs	0.27	0.79	0.33	0.34	0.35	0.90	0.93
Lag_t	0.34	0.00	0.00	0.48	0.00	0.00	0.00
AUC_exp	218.88	111.54	127.29	152.24	135.44	149.41	141.76
Cmax	16.11	21.61	25.25	21.24	27.46	21.64	21.14
Tmax	3.00	2.00	2.00	2.00	1.00	2.00	2.00
Clr tot	13.71	26.90	23.57	19.71	22.15	20.08	21.16
Vd	208.58	121.61	114.31	138.44	115.80	109.89	119.48
MRT_exp	15.49	5.75	5.35	7.85	5.60	6.71	7.23
Vdss_ex	212.30	154.54	126.17	154.66	124.00	134.77	152.95
AUC_mod	208.01	105.13	119.27	142.29	137.74	142.90	129.77
MRT_mod	15.96	5.66	5.33	7.99	5.74	6.78	6.98
Vds_mod	230.14	161.46	133.99	169.41	124.98	142.28	161.45

Param.	8os3000	9os3000	10os3000	11os3000	12os3000
T1/2 el	3.83	3.12	6.01	3.37	4.60
T1/2abs	0.79	0.49	0.35	0.59	0.82
Lag_t	0.00	0.00	0.45	0.00	0.00
AUC_exp	97.15	147.64	124.11	106.12	227.09
Cmax	15.45	28.85	13.36	24.20	25.28
Tmax	2.00	2.00	2.00	1.00	3.00
Clr tot	30.88	20.32	24.17	28.27	13.21
Vd	170.80	91.36	209.63	137.64	87.65
MRT_exp	6.71	5.08	9.88	5.22	7.59
Vdss_ex	207.11	103.15	238.89	147.44	100.33
AUC_mod	93.03	140.47	125.59	102.05	222.74
MRT_mod	6.67	5.20	9.63	5.72	7.82
Vds_mod	215.13	110.99	230.11	168.24	105.29

TABLE 8 Pharmacokinetic parameters of Fosfomycin Trometamol in healthy subjects treated with 4000 mg (as Fosfomycin acid) orally.Individual data

Param.	1os4000	2os4000	3os4000	4os4000	5os4000	6os4000	7os4000
T1/2 el	5.07	3.88	2.58	4.16	3.86	4.16	4.40
T1/2abs	0.45	0.67	0.74	0.37	0.55	0.61	0.94
Lag_t	0.00	0.00	0.00	0.39	0.00	0.00	0.00
AUC_exp	290.91	139.78	157.87	177.10	206.77	210.07	227.15
Cmax	34.83	23.69	35.08	29.35	37.45	34.32	31.26
Tmax	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Clr tot	13.75	28.62	25.34	22.59	19.34	19.04	17.61
Vd	100.65	160.36	94.34	135.44	107.80	114.40	111.85
MRT_exp	8.07	6.80	4.75	6.46	6.49	6.96	7.87
Vdss_ex	110.96	194.66	120.43	145.84	125.60	132.58	138.63
AUC_mod	280.96	130.70	147.82	161.97	198.24	200.06	209.97
MRT_mod	7.96	6.56	4.79	6.92	6.37	6.89	7.71
Vds_mod	113.39	200.90	129.66	170.95	128.50	137.72	146.87

Param.	8os4000	9os4000	10os4000	11os4000	12os4000
T1/2 el	3.84	3.34	3.68	3.18	4.83
T1/2abs	0.81	0.41	0.88	0.73	0.72
Lag_t	0.00	0.00	0.00	0.00	0.00
AUC_exp	140.41	183.28	122.51	167.15	253.85
Cmax	23.10	36.60	20.40	32.05	32.10
Tmax	2.00	2.00	2.00	2.00	2.00
Clr tot	28.49	21.82	32.65	23.93	15.76
Vd	158.00	105.22	173.38	109.87	109.87
MRT_exp	6.69	5.41	6.72	5.79	8.07
Vdss_ex	190.52	118.15	219.27	138.48	127.29
AUC_mod	134.80	171.26	113.12	147.13	238.78
MRT_mod	6.71	5.41	6.58	5.65	8.02
Vds_mod	199.07	126.28	232.55	153.53	134.27

TABLE 9 Pharmacokinetic parameters of Sodium Fosfomycin in healthy subjects treated with 3000 mg intravenously.Individual data.

Param.	1iv3000	2iv3000	3iv3000	4iv3000	5iv3000	6iv3000	7iv3000
T1/2 el	.276	.177	.730	.125	.242	.159	.175
T1/2abs	2.16	2.18	2.55	2.08	1.65	2.18	2.28
AUC_exp	487.00	372.34	402.60	448.45	424.73	464.65	548.26
Cmax	476.40	350.00	207.20	548.80	404.61	285.20	416.80
Tmax	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Clr tot	6.16	8.06	7.45	6.69	7.06	6.46	5.47
Vd	19.21	25.40	27.43	20.09	16.80	20.35	17.97
MRT_exp	2.29	2.53	2.47	2.31	1.82	2.93	2.92
Vdss_ex	14.14	20.39	18.42	15.45	12.88	18.94	15.97
AUC_mod	468.78	361.61	396.36	430.95	408.81	451.72	532.39
MRT_mod	2.38	2.64	2.67	2.46	1.92	2.91	2.86
Vds_mod	15.26	21.94	20.21	17.10	14.07	19.30	16.14

Param.	8iv3000	9iv3000	10iv3000	11iv3000	12iv3000
T1/2 el	.550	.108	.299	.248	.159
T1/2abs	2.32	1.50	2.39	2.05	1.99
AUC_exp	371.67	446.18	436.22	464.21	457.21
Cmax	380.75	421.50	303.00	353.55	299.90
Tmax	0.02	0.02	0.02	0.02	0.02
Clr tot	8.07	6.72	6.88	6.46	6.56
Vd	26.97	14.59	23.70	19.11	18.80
MRT_exp	2.37	2.14	2.77	2.40	2.88
Vdss_ex	19.17	14.41	19.06	15.49	18.90
AUC_mod	375.29	421.76	424.39	451.01	430.56
MRT_mod	2.39	1.96	2.83	2.48	2.62
Vds_mod	19.10	13.97	19.99	16.49	18.23

TABLE 10 Pharmacokinetic parameters (means±SD) of fosfomycin in healty subjects treated with Fosfomycin trometamol orally 2000, 3000 and 4000 mg (as Fosfomycin acid) and with Fosfomycin sodium intravenously 3000 mg (as Fosfomycin acid)

Parameter	F.T. 2000 mg	F.T. 3000 mg	F.T. 4000 mg	F.S. 3000 mg i.v.
T1/2 α(hr)				0.27±0.186
T1/2 el. (β)(hr)	4.05±0.79	4.51±2.07	3.92±0.69	2.11±0.09
T1/2 abs. (hr)	0.69±0.33	0.58±0.24	0.66±0.173	-
Lag-t (h)	0.07±0.16	0.11±0.20	0.03±0.10	-
AUC-exp (h*mg/L)	106.66±34.92	144.89±40.49	189.74±50.12	443.63±48.87
Cmax (mg/L)	16.00±4.41	21.80±4.81	30.85±5.61	370.64±92.04
Tmax (hr)	2.18±0.86	2.00±0.58	2.00±0.00	0.02±0.00
CL tot (L/h)	20.23±5.30	22.01±5.30	22.41±5.68	6.84±0.76
CLr (L/h)	425.52±303.43	500.43±311.97	495.45±341.24	195.72±150.41
Vd (L)	118.57±46.86	135.43±40.77	123.43±26.5	20.87±4.08
MRT-exp (h)	6.77±1.32	7.37±2.90	6.67±1.03	2.49±0.34
Vdss-exp (L)	137.24±54.19	154.69±43.68	146.86±34.95	16.93±2.45
AUC-mod(h*mg/L)	101.60±32.63	139.08±39.42	177.90±49.25	429.47±44.96
MRT-mod (h)	6.92±1.35	7.46±2.97	6.63±1.00	2.51±0.31
Vds-mod (L)	146.31±55.18	162.71±43.19	156.14±36.92	17.65±2.56

TABLE // Means±SD of some pharmacokinetic parameters distributed by sex

Parameter	Males	Female
2000 mg per os		
No. of cases	5	6
Cmax (mg/L)	15.60±6.02	16.31±3.13
Tmax (hr)	2.40±0.89	2.00±0.89
AUC-exp (h*mg/L)	118.14±51.19	97.09±10.03
T1/2 el. (β)(hr)	4.56±0.83	3.62±0.45
CL tot (L/h)	19.59±8.02	20.76±1.92
Vd (L)	130.50±69.03	108.63±17.88
MRT-exp (h)	7.67±1.09	6.00±1.00
Vdss-mod (L)	162.01±79.41	133.22±24.42
3000 mg per os		
No. of cases	6	6
Cmax (mg/L)	19.76±4.45	23.85±4.63
Tmax (hr)	2.16±0.40	1.83±0.75
AUC-exp (h*mg/L)	143.58±46.14	146.18±38.42
T1/2 el. (β)(hr)	4.37±1.01	4.65±2.89
CL tot (L/h)	22.49±6.20	21.52±4.74
Vd (L)	139.33±44.23	131.19±40.68
MRT-exp (h)	7.41±1.42	7.32±4.07
Vdss-mod (L)	170.44±46.21	154.96±42.76
4000 mg per os		
No. of cases	6	6
Cmax (mg/L)	27.16±5.56	34.54±2.45
Tmax (hr)	2.00±0.00	2.00±0.00
AUC-exp (h*mg/L)	173.95±50.27	205.52±46.98
T1/2 el. (β)(hr)	4.09±0.40	3.73±0.69
CL tot (L/h)	24.52±6.46	20.29±4.28
Vd (L)	141.90±26.13	104.95±6.49
MRT-exp (h)	6.94±0.57	6.39±1.34
Vdss-mod (L)	179.23±38.77	133.03±14.66
3000 mg i.v.		
No. of cases	6	6
Cmax (mg/L)	361.27±98.61	380.01±93.31
Tmax (hr)	0.01±0.00	0.01±0.00
AUC-exp (h*mg/L)	425.09±42.19	462.15±51.45
T1/2 el. (β)(hr)	2.18±0.14	2.03±0.39
CL tot (L/h)	7.11±0.74	6.55±0.69
Vd (L)	22.55±3.28	19.18±4.38
MRT-exp (h)	2.63±0.26	2.34±0.36
Vdss-mod (L)	19.27±1.64	16.01±2.29

TABLE Bioavailability data (in percent) in healthy subjects treated with Fosfomycin Trometamol orally, 2000, 3000, 4000 mg (as Fosfomycin acid). Individual data and means ± S.D.

	FOSFOMYCIN (mg)		
Subjects	2000	3000	4000
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	35.61	32.88	30.89
S.D.	11.17	7.96	7.10

TABLE Urine concentrations (mg/l) of healthy subjects treated with Fosfomycin Trometamol 2000 mg (as Fosfomycin acid) orally. Individual data.

TIME	SUBJECTS
0.0	
0- 2	
2- 4	
4- 6	
6-12	
12-24	
24-36	
36-48	
48-60	
60-72	

TIME	SUBJECTS
0.0	
0- 2	
2- 4	
4- 6	
6-12	
12-24	
24-36	
36-48	
48-60	
60-72	

ND: not detectable
NS: no sample.

TABLE 14 Urine concentrations (mg/l) of healthy subjects treated with Fosfomycin Trometamol 3000 mg (as Fosfomycin acid) orally. Individual data.

TIME	SUBJECTS
0.0	
0- 2	
2- 4	
4- 6	
6-12	
12-24	
24-36	
36-48	
48-60	
60-72	

TIME	SUBJECTS
0.0	
0- 2	
2- 4	
4- 6	
6-12	
12-24	
24-36	
36-48	
48-60	
60-72	

NS no sample.

TABLE 15 Urine concentrations (mg/l) of healthy subjects treated with Fosfomycin Trometamol 4000 mg (as Fosfomycin acid) orally. Individual data.

TIME	SUBJECTS										
0.0											
0- 2											
2- 4											
4- 6											
6-12											
12-24											
24-36											
36-48											
48-60											
60-72											

TIME	SUBJECTS										
0.0											
0- 2											
2- 4											
4- 6											
6-12											
12-24											
24-36											
36-48											
48-60											
60-72											

ND: not detectable

16

TABLE Urine concentrations (mg/l) of healthy subjects treated with Fosfomycin Sodium 3000 mg (as Fosfomycin acid) intravenously. Individual data.

TIME	SUBJECTS										
0.0											
0-2											
2-4											
4-6											
6-12											
12-24											
24-36											
36-48											
48-50											
60-72											

TIME	SUBJECTS										
0.0											
0-2											
2-4											
4-6											
6-12											
12-24											
24-36											
36-48											
48-60											
60-72											

ND: not detectable

040

6- 04887

TABLE 17 Urine concentrations of healthy subjects treated with Fosfomycin Trometamol orally, 2000, 3000 and 4000 mg as (as Fosfomycin acid) and with Fosfomycin Sodium intravenously, 3000 mg (as Fosfomycin acid). Means ± SD of 12 subjects.

TIME	DOSE ADMINISTERED			
	ORALLY			INTRAVENOUSLY
	2000 mg	3000 mg	4000 mg	3000 mg
0.00	<3.5	<3.5	<3.5	-
0-2	1074.675 ±883.83	1721.383 ±954.08	2764.350 ±1223.17	12529.466 ±3708.22
2-4	1419.748 ±1098.75	1532.338 ±838.32	2124.488 ±1064.56	5767.708 ±3194.89
4-6	1209.995* ±770.45	1300.650 ±509.26	1549.233 ±676.88	2900.292 ±898.43
6-12	407.240 ±206.82	560.354 ±206.59	755.625 ±342.01	883.729 ±450.63
12-24	213.752 ±137.27	334.312 ±131.52	491.623 ±230.70	131.944 ±71.13
24-36	74.114 ±25.38	131.713 ±45.57	230.646 ±131.59	10.071° ±4.88
36-48	44.661 ±20.58	90.928° ±41.96	181.796 ±94.76	-
48-60	13.735 ±10.33	42.567 ±24.79	77.038 ±54.23	-
60-72	11.686# ±5.94	33.912 ±33.52	51.855 § ±35.95	-

*: means ± SD. of 11 subjects (1 subject had no sample).
°: means ± SD. of 10 subjects (in 2 subjects not detectable values were found).
#: means ± SD. of 6 subjects (in 6 subjects not detectable values were found).
§: means ± SD of 11 subjects (in 1 subject a not detectable value was found).

18

TABLE Fecal concentration (mcg/g) of Fosfomycin after oral administration of Fosfomycin Trometamol 3000 mg (as Fosfomycin acid). Individual data.

Subject N°	Time (days)				
	-1	1	2	3	

* Faeces not excreted

TABLE 14 Fecal concentration (mcg/g) of Fosfomycin after intravenous aministration of sodium Fosfomycin 3000 mg (as Fosfomycin acid). Individual data.

Subject N°	Time (days)				
	-1	1	2	3	4

* Faeces not excreted

20

TABLE Fecal recovery of Fosfomycin after oral administration of Fosfomycin Trometamol 3000 mg (as Fosfomycin acid)

Subject N°	Time (days)					Total Recovery	
	−1	1	2	3	4	mg	%
Mean	0	103.6	451.8	182.1	103.7	841.2	28.0
SD		148.7	376.1	153.5	128.0	352.7	11.8

* Faeces not excreted

050

6- 04897

21

TABLE Fecal recovery of Fosfomycin after intravenous administration of Fosfomycin Sodium 3000 mg

Subject N°	Time (days)					Total Recovery	
	−1	1	2	3	4	mg	%

* Faeces not excreted

Urinary and faecal recovery in the same subjects after oral treatment is presented in table 31.

Table 32 presents the results of the statistical comparisons of bioavailability, plasma $AUC_{0-\infty}$, and urinary recovery for the 3 oral doses.

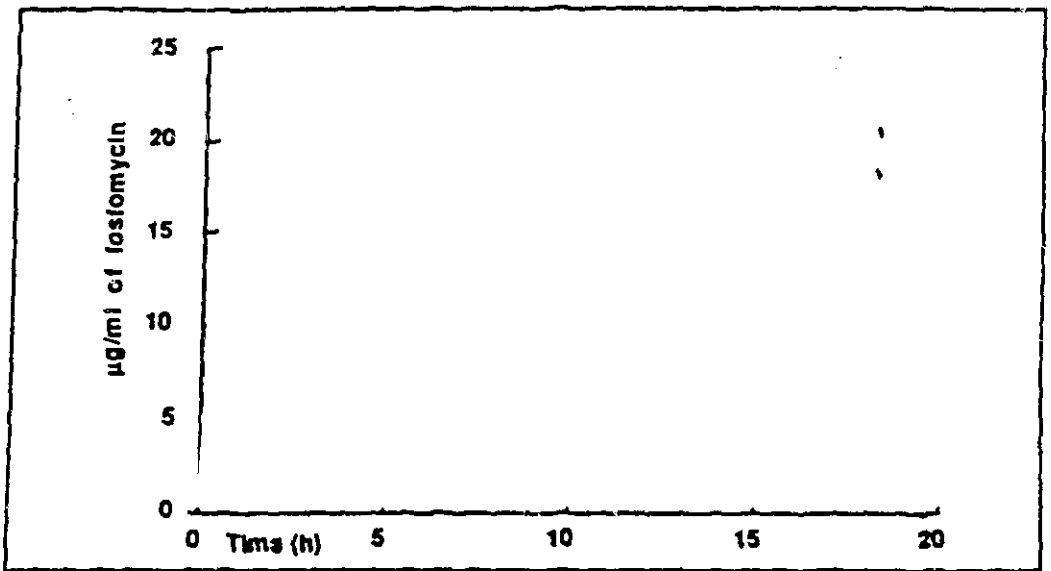


Fig. 1— Simulated fosfomycin concentrations after a single oral administration of 2 g of fosfomycin trometamol. Experimental data are also shown.

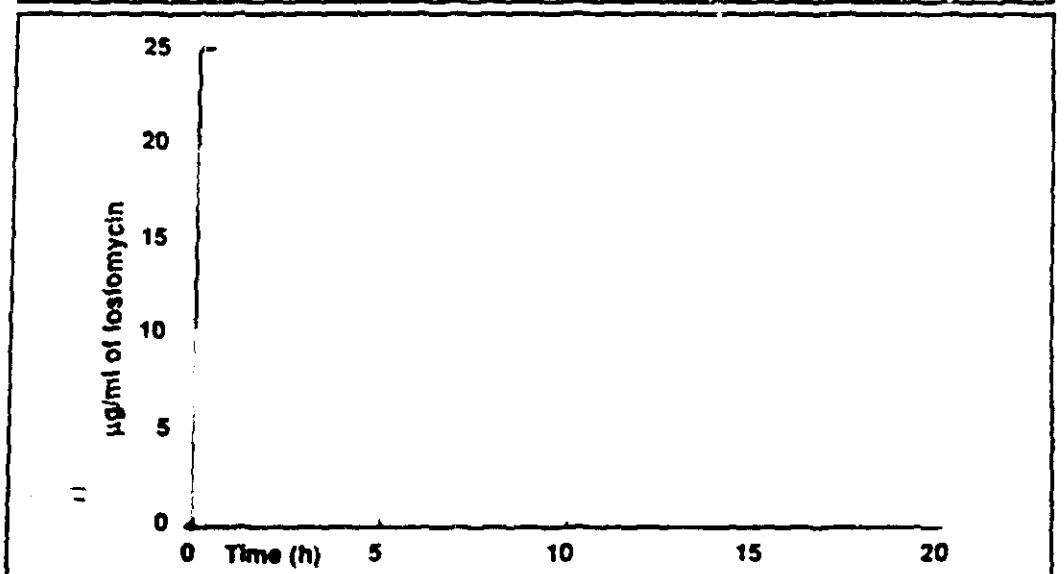


Fig. 2— Simulated fosfomycin concentrations after a single oral administration of 3 g of fosfomycin trometamol. Experimental data are also shown.

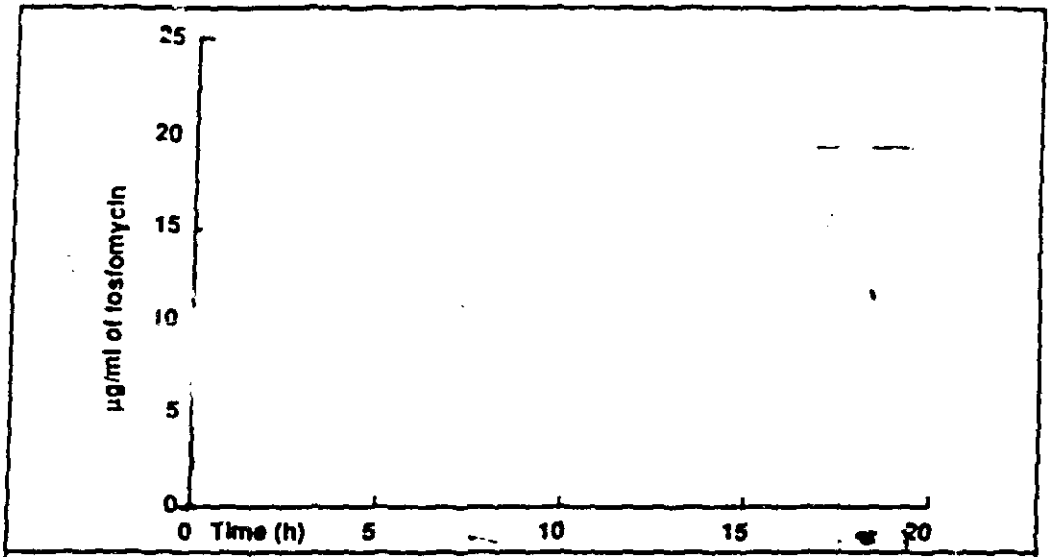


Fig. 3— Simulated fosfomycin concentrations after a single oral administration of 4 g of fosfomycin trometamol. Experimental data are also shown.

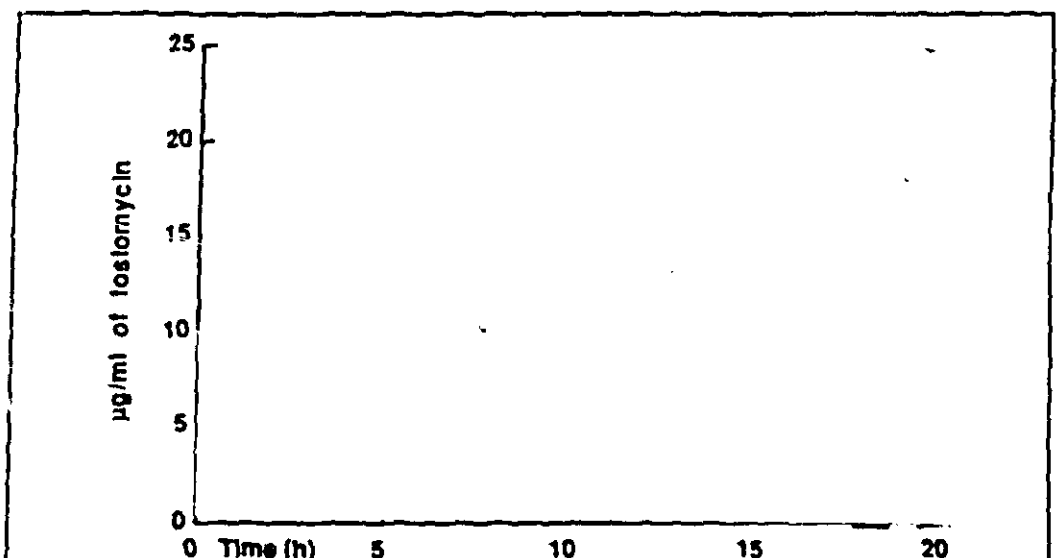


Fig. 4— Simulated fosfomycin concentrations after a single oral administration of 2 (continuous line), 3 (broken line), 4 g of fosfomycin (dotted line) trometamol.

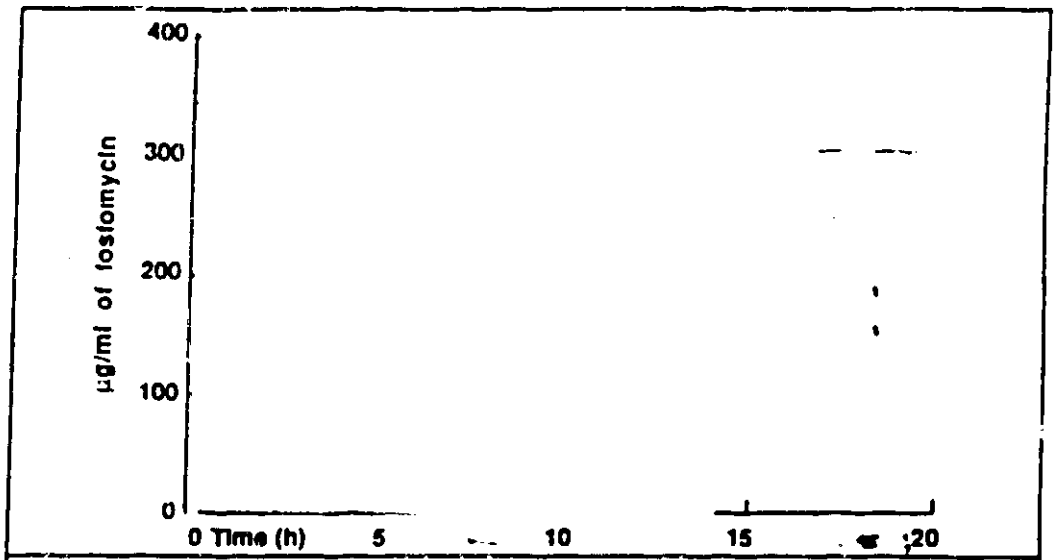


Fig. 5— Simulated fosfomycin concentrations after a single i.v. injection of 3 g of sodium fosfomycin. Experimental data are also shown.

8.3 Adverse Events

The adverse events observed during the study are presented in table 33

All the events spontaneously recovered without sequelae

8.3.2. Laboratory exams

8.3.2.1 Blood tests

The laboratory exams were repeated before each treatment and, as appears in tables 2–3, only few values lie outside the normal range, usually they are close to the limits, and in no case the abnormal findings could be correlated with the treatment. Patient n° 6 has a clearly abnormal SGOT value (196 U/L) recorded 3 weeks after having been treated with 4 g of the oral preparation. SGOT values slightly above the normal range were also recorded in the same patient at the first pre-treatment visit and after 3 g of fosfomycin trometamol per os. The other liver function tests (bilirubin and g-GT) were always normal in the patient.

8.3.2.2. Urine analysis

Endogeneous creatinine clearance values have been calculated. The values outside the normal ranges in no case have been considered clinically significant.

Some abnormal finding was present in the urine analysis before and during the treatment. None of them is related to the drug treatment.

Patient [redacted] had microscopic haematuria in the pre-treatment and after (Na Fosfo. i.v.) since menstruating.

TABLES

(Study Report #3)

TABLE Urinary recovery (mg) of fosfomycin in 12 elderly subjects after oral administration of fosfomycin trometamol (2 g as fosfomycin).

SUBJECT N°	TIME (h)						TOTAL RECOVERY	
	0	0-4	4-8	8-12	12-24	24-48	mg	%
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								

TABLE Urinary recovery (mg) of fosfomycin in 12 elderly subjects after oral administration of fosfomycin trometamol (3 g as fosfomycin).

SUBJECT N	TIME (h)							TOTAL RECOVERY	
	0	0-4	4-8	8-12		12-24	24-48	mg	%
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									

* not determined (sample missing)
** urinary recovery in 8-24 h interval

Table 5

Urinary concentration and total recovery % in elderly subjects after oral administration of fosfomycin trometamol (2 and 3 g as fosfomycin respectively). Mean values, standard error and analysis of variance.

	URINARY CONCENTRATION (mcg/ml)										TOTAL RECOVERY	
	TIME (h)											
DOSE	N	0-4	N	4-8	N	8-12	N	12-24	N	24-48	N	%
2 g	12	754.4 ± 168.7	12	1452.1 ± 166.6	12	768.3 ± 183.6	12	297.5 ± 68.7	12	59.0 ± 14.9	11	42.83 ± 2.50
3 g	12	1199.4 ± 175.1	12	1820.1 ± 210.0	10	924.9 ± 210.8	10	296.5 ± 53.9	12	106.7 ± 19.6	11	36.96 ± 1.77
ANOVA F		4.31		0.70		0.32		0.00		4.58		4.33
ANOVA p		0.07>p>0.05		>		>		>		0.06>p>0.05		0.07>p>0.05

TABLE AND FIGURE

(Study Report #7)

Urine Elimination

The fosfomycin concentrations in urine paralleled the serum concentrations (table III) as did, consequently, the total amount of fosfomycin eliminated in urine over the 48 h monitored (table III). The total elimination of the dose was 36.1 ± 6.0% when fosfomycin was taken alone, 41.2 ± 9.0% with cimetidine, and 27.7 ± 5.1% when metoclopramide was also

Table Urine concentrations (mg/l) of fosfomycin after oral doses of 50 mg/kg given as fosfomycin trometamol, either alone or with cimetidine or with metoclopramide

Urine collection interval, h	Fosfomycin alone		Fosfomycin + cimetidine		Fosfomycin + metoclopramide	
	mean	range	mean	range	mean	range
0–2	2,934 (1,927)		2,017 (1,615)		1,046 (606)	
2–4	4,415 (1,055)		4,883 (2,487)		2,545 (935)	
4–6	1,930 (1,251)		3,116 (1,310)		2,032 (900)	
6–8	1,629 (1,157)		1,705 (747)		1,483 (688)	
8–12	1,006 (394)		1,351 (411)		915 (196)	
12–16	7[illegible] (423)		792 (399)		689 (301)	
16–24	484 (203)		490 (249)		502 (378)	
24–36	121 (85)		82 (35)		169 (118)	
36–48	50 (73)		23 (22)		61 (39)	
Total urine recovery (% of dose, 48 h)	36.1 (6.0)		41.2 (9.0)		27.7 (5.1)	

[1] SD.

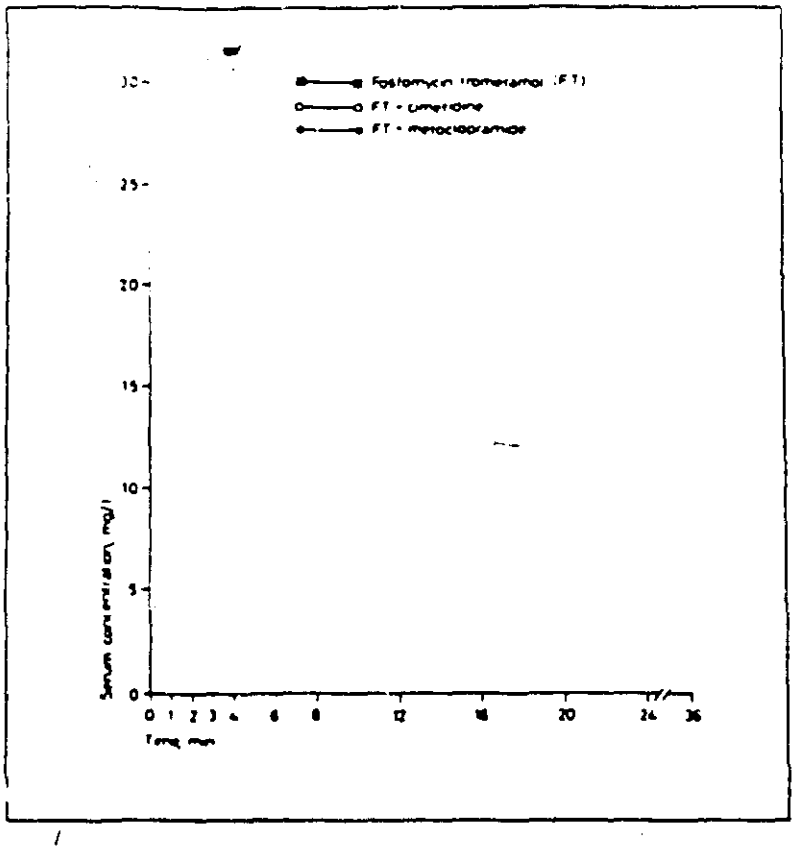


Fig. . Serum concentrations of fosfomycin given as fosfomycin trometamol, either alone or with cimetidine or with metoclopramide to 9 healthy volunteers. Detailed results are given in table I.

Results

Serum Concentrations

All predose sera lacked antibacterial activity. The fosfomycin serum concentrations were overlapping after the drug was administered alone and when it was taken together with cimetidine. In contrast, metoclopramide reduced the absorption: considerably lower serum concentrations resulted for the peak level and throughout most of the observation period

FIGURES

(Study Report #12)

Figure - Average serum fosfomycin concentrations following oral Z 1282 administration in children.

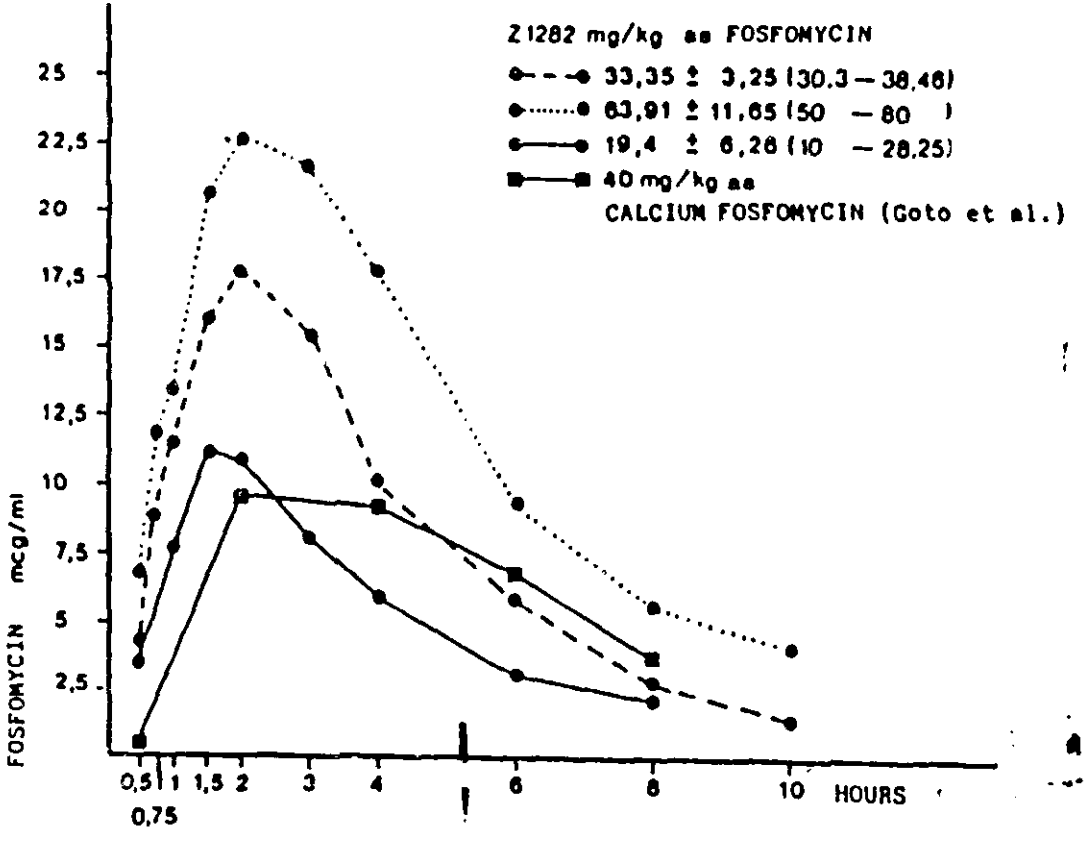


Figure 2 - Correlation between Z 1282 doses (mg/kg) and Cmax (mcg/ml) assessed.
Observation in children.

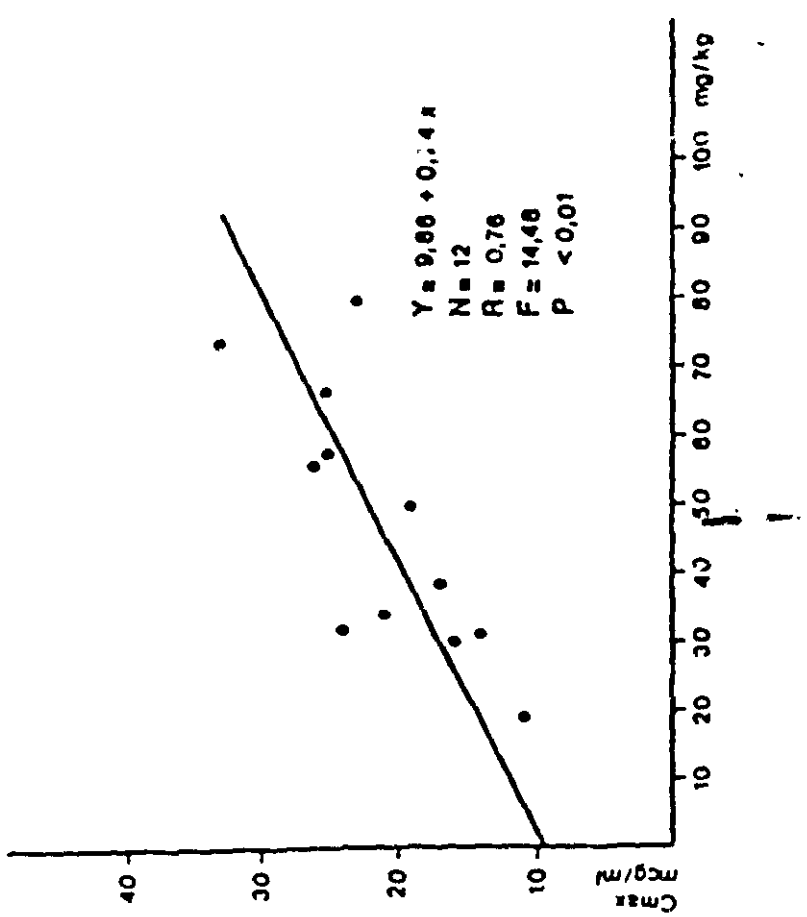


Figure 3 - Correlation between Z 1282 doses (mg/kg) and AUC (area below serum concentration curve).

Observations in children.

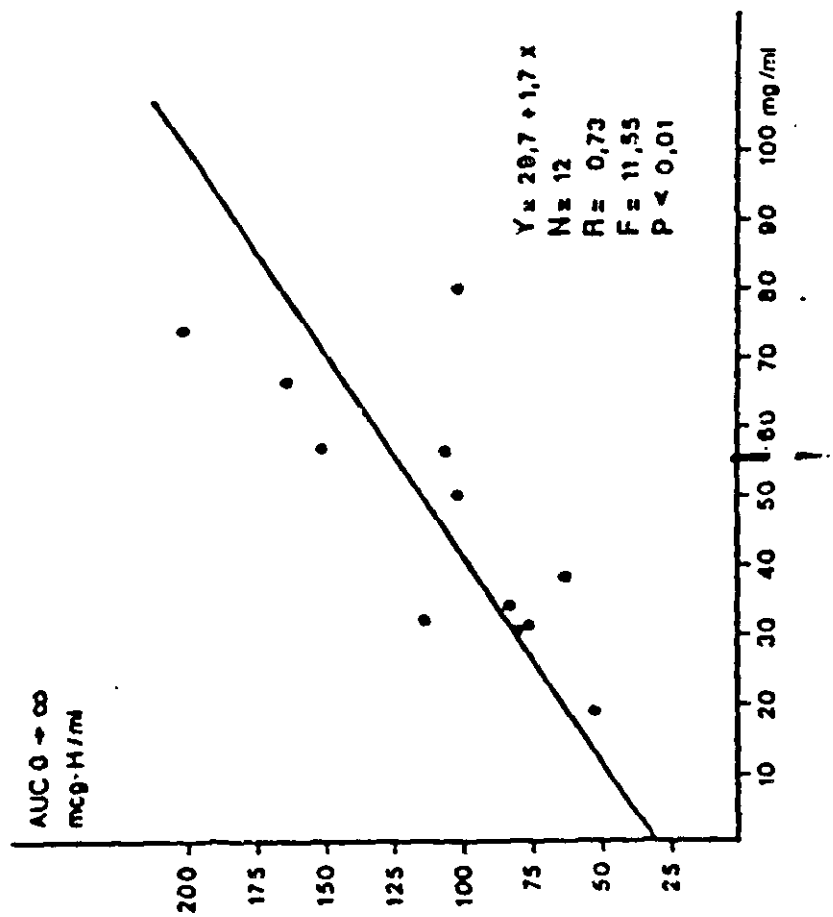
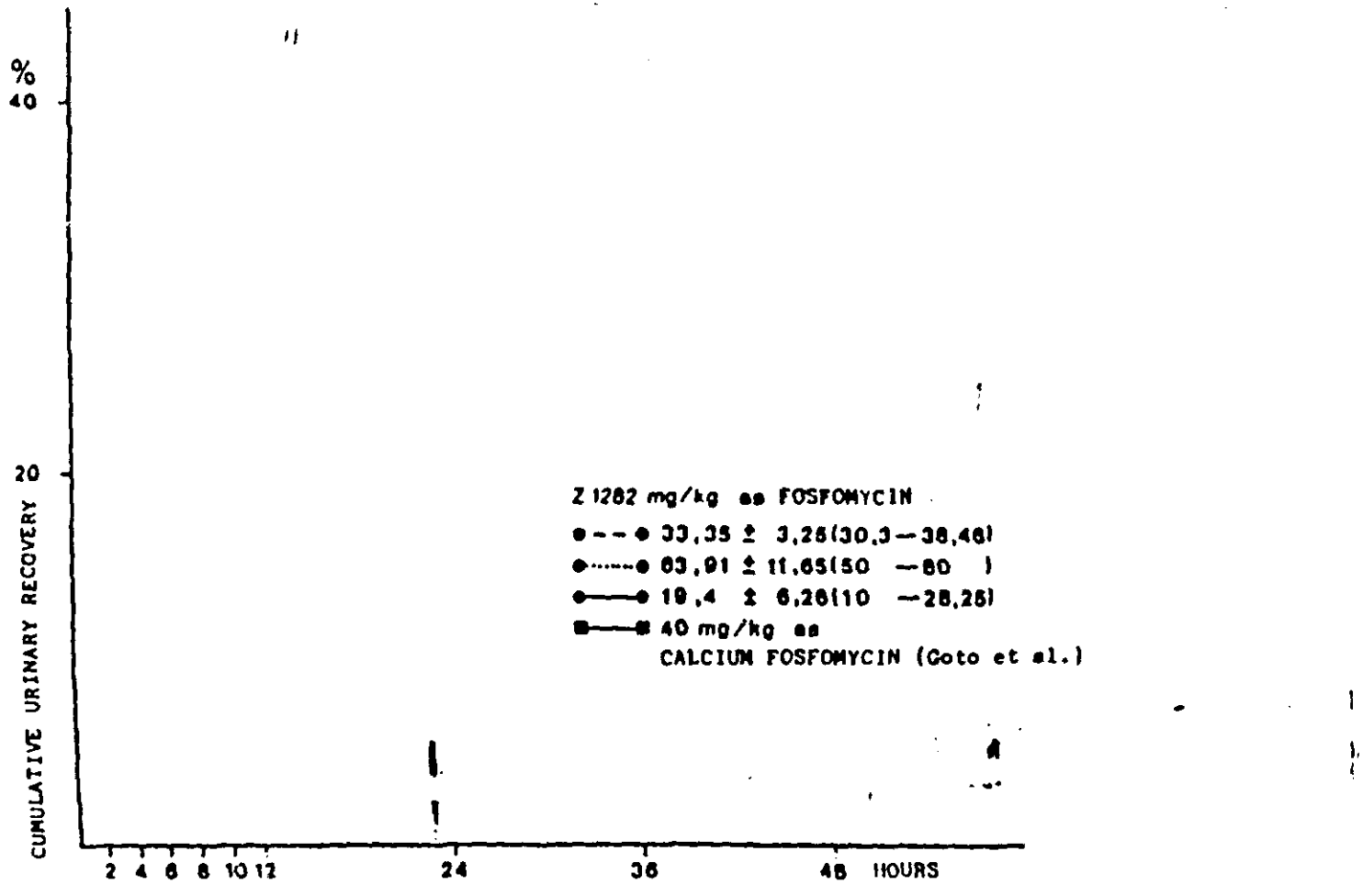


Figure - Fosfomycin urine recovery following single oral administration of Z 1282 in children.



TABLES

(Study Report #14)

TABLE - Fosfomycin concentrations (mcg/ml) in plasma of patients treated with single dose of Z 1202 equivalent to 3 g fosfomycin.

PATIENTS No.	NAME AND INITIAL OF SURNAME	COLLECTION INTERVALS IN HOURS								
		0,5	1	1,5	2	3	4	6	8	10
1										
2										
3										
4										
5										
6										
	average	6,92	13,97	19,67	27,85	31,9	27,45	19,92	18,62	11,44
	s.d.	4,50	8,82	7,27	5,10	11,02	42,98	4,52	5,32	3,18

TABLE - Pharmacokinetic Parameters

PATIENT No.	CREAT.CLEAR. ml/min	T/2 el. h	AUC0-oo ng/ml h	CMAX ng/ml	AUC 0--10 ng/ml h	TMAX h	Ka (h^{-1})	T/2 (h)	LAG TIME (h)
1									
2									
3									
4									
5									
6									
average	94,33±	3,69±	263,71±	33,07±	200,39±	3±	0,62±	1,33±	0,34±
s.d.	8,64	1,45	76,40	10,12	56,86	0,63	0,31	0,56	0,10

67590 -9

TABLES

(Study Report #15)

Table . Comparison of fosfomycin trometamol and calcium fosfomycin pharmacokinetic parameters obtained in healthy young (YS) and elderly subjects (ES) after a single oral dose of the two forms (mean values ± SD)

Parameters	Fosfomycin trometamol			Calcium fosfomycin		
	YS	ES	p[1]	YS	ES	p[1]
Dose, mg	2,032 ± 444	1,809 ± 276	0.28 NS	3,025 ± 661	2,694 ± 412	0.28 NS
C_{max}, μg/ml	18.48 ± 10.27	22.01 ± 8.71	0.52 NS	7.42 ± 4.29	5.91 ± 1.69	0.38 NS
t_{max}, h	1.61 ± 0.33	2.16 ± 0.72	0.13 NS	1.41 ± 0.67	2.58 ± 0.54	0.005 S
AUC, μg·h/ml	102.80 ± 42.12	221.60 ± 94.86	0.02 S	49.97 ± 20.44	116.00 ± 66.31	0.06 NS
t½ elimination, h	5.37 ± 2.56	8.28 ± 5.51	0.30 NS	4.81 ± 1.90	11.80 ± 6.86	0.05 NS
Urinary elimination 24 h, % of dose	57.7 ± 30.2	27.5 ± 10.6	0.02 S	17.9 ± 21.2	9.4 ± 3.1	0.28 NS
C_{cr}, ml/min/1.73 m²	179.6 ± 25.1	48.8 ± 17.0	< 0.001 S	83.0 ± 18.3	34.4 ± 18.7	0.01 S

[1] Unpaired *t* test: S = significant; NS = non-significant.

2

Table . Fosfomycin trometamol pharmacokinetic parameters in healthy subjects and in the different groups of uraemic patients after administration of the same oral dose (mean values ± SD)

Parameters	Healthy subjects	Uraemic patients				p[1]
		group I	group II	group III	group IV	
Dose, mg	2,032 ± 444	1,792 ± 410	1,667 ± 368	1,811 ± 38	1,836 ± 240	> 0.1 NS
C_{max}, µg/ml	18.48 ± 10.27	26.02 ± 10.00	35.66 ± 10.33	27.44 ± 8.39	37.92 ± 7.94	< 0.02 S
t_{max}, h	1.61 ± 0.23	2.38 ± 1.42	4.38 ± 1.20	5.06 ± 1.33	7.92 ± 3.84	< 0.001 S
AUC, µg·h/ml	102.80 ± 42.12	388.5 ± 184.7	1,266.3 ± 457.4	2,108.6 ± 824.0	2,367.0 ± 855.8	< 0.001 S
$t_{½}$ elimination, h	5.37 ± 2.56	10.76 ± 4.55	24.54 ± 11.72	50.25 ± 12.94	39.38 ± 19.63	< 0.001 S
Urinary elimination 24 h, % of dose	37.7 ± 30.2	31.6 ± 10.5	24.0 ± 17.3	11.0 ± 4.6	-	< 0.004 S
C_{cr}, ml/min/1.73 m²	179.6 ± 25.1	43.3 ± 32.5	10.1 ± 3.9	5.4 ± 1.3	-	< 0.001 S

[1] Analysis of variance: S = significant, NS = non-significant.

6- 06619

TABLE

(Study Report #17)

TABLE - CONCENTRATIONS OF FOSFOMYCIN, TROMETAMOL IN VARIOUS TISSUES, IN THE URINE AND SERUM OF PATIENTS AT DIFFERENT TIMES AFTER ADMINISTRATION OF THE DRUG.

PATIENTS	TIME	CONCENTRATION (ug/g) BLADDER	PERICYSTIUM	PROSTATE	SEMINAL VESICLES	TIME	CONCENTRATION (ug/ml) URINE	SERUM
	3					-		
	3					3		
	3					1 2 3		
	3					1		
	3					3(Rdx) 3(Rsx)		
	3					3(Rdx) 3(Rsx)		
	3					3(Rdx) 3(Rsx)		
	24					2 19 24(Rdx) 24(Rsx)		
	24					2 18 24(Rdx) 24(Rsx)		
	24				-	1 2 18 24(Rdx)		
	24				-	2 19 24(Rdx) 24(Rsx)		

• Female

FDA Corresp.

MAR 24 1997

Division of Anti-Infective Drug Products

CONSUMER SAFETY OFFICER REVIEW OF FINAL PRINTED LABELING (FPL)

Application Number: NDA 50-717

Name of Drug: Monurol® (fosfomycin tromethamine) 3 gram Sachet

Sponsor: Forest Laboratories, Inc. (U.S. Agent for Zambon Corporation)

Material Reviewed

Submission Date: February 4, 1997

Receipt Date: February 5, 1997

Background and Summary Description: Original NDA submitted on September 28, 1994. Non-approval letter was issued on September 20, 1995. Application resubmitted on June 28, 1996 and approved on December 19, 1996 with approved marked-up labeling. Monurol® is indicated for the treatment of uncomplicated urinary tract infections (acute cystitis) in women.

Review

The final printed labeling for NDA 50-717 is consistent with the labeling approved December 19, 1996. There are several minor editorial differences between the two sets of labeling, some of which need revision. At the time of the next printing, the following changes should occur:

Conclusions

Based on the review of the FPL, an acknowledge and retain (A&R) letter is recommended. The letter should include a request for the changes, #'s 1-3 and 5-7 as noted above, to be revised at the time of the next printing.

Bill Duvall Miller
Consumer Safety Officer

Janet Soreth
Medical Officer

cc:
Original NDA 50-717
HFD-520/Div. Files
HFD-520/CSO/B. Duvall-Miller
HFD-520/ActDivDir/D. Feigal
HFD-520/SMO/J. Soreth 5/7/97

Concurrence:
HFD-520/SCSO/J. Bona 5/11/97
HFD-520/SMO/J. Soreth 5/7/97
HFD-520/ActDivDir/D. Feigal
9 May 97

draft: bdm/March 3, 1997/M:\LABREV\50717.ORI
r/d Initials:
final: 1330m 5/11/97

CSO REVIEW

NDA 50-717

MAY 12 1997

Forest Laboratories, Inc.
Attention: Foma Rashkovsky
Acting Director, Regulatory Affairs
One Meadowlands Plaza
East Rutherford, NJ 07073

Dear Mr. Rashkovsky:

We acknowledge the receipt of your February 4, 1997 submission containing final printed labeling in response to our December 19, 1996 letter approving your new drug application for Monurol® (fosfomycin tromethamine) 3 gram Sachet.

We have reviewed the labeling that you have submitted in accordance with our December 19, 1996 letter, and we find it acceptable.

Several minor editorial changes were noted in the review of your final printed labeling. At the time of the next printing, the following changes to the label should occur:

If you should have any questions, please contact Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-717
HFD-520/Div. Files
HF-2/Medwatch (with labeling)
HFD-104/Office Director (with labeling)
HFD-520/CSO/B. Duvall-Miller (with labeling)
HFD-520/SCSO/J. Bona
HFD-40/DDMAC (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)

Concurrence:
HFD-520/SCSO/J. Bona 3/11/97
HFD-520/SMO/J. Soreth 3/4/97
HFD-520/ActDivDir/D. Feigal
8 Mar 97

Drafted by: bdm/March 3, 1997/M:\A&R\N50717.FPL
Initialed by:
final: BDM 3/11/97

ACKNOWLEDGE AND RETAIN (AR)

NDA 50-717

APR 17 1997

Forest Laboratories, Inc.
Attention: Foma Rashkovsky
Acting Director, Regulatory Affairs
One Meadowlands Plaza
East Rutherford, NJ 07073

Dear Mr. Rashkovsky:

Please refer to your February 19, 1997 submission containing final printed secondary trade packaging in response to our December 19, 1996 letter approving your new drug application for Monurol® (fosfomycin tromethamine) 3 gram Sachet.

We have reviewed the packaging that you have submitted in accordance with our December 19, 1996 letter, and we find it inadequate. Please incorporate the following changes for resubmission and review:

1. To your statement

please add the information

taken directly from your package insert. This information is needed to insure that patients receive appropriate treatment for their medical condition.

2. To your statement

please add the information

If you have any questions, please contact Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

4/17/97

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-717
HFD-520/Div. Files
HFD-104/T. Nearing
HFD-520/CSO/B. Duvall-Miller
HFD-520/Chem/J. Timper
HFD-40/J. Spearmon/DDMAC (with labeling)

Concurrence:
HFD-520/SCSO/J. Bona
HFD-520/SMO/J. Soreth
HFD-520/ActDivDir/D. Feigal

Drafted by: bdm/March 26, 1997/M:\NONA&R\50717.1
Initialed by:
final:

GENERAL CORRESPONDENCE (GC)

RECORD OF TELEPHONE CONVERSATION

DATE: December 1, 1994

TO: Ms. Tammy Replogle of Forest Laboratories
Telephone Number (212)224-6810

FROM: Maureen Dillon-Parker of FDA 12/1/94
Telephone Number (301)443-0257

SUBJECT: Clinical, Statistical, Biopharmaceutical, and Chemistry Reviewers Requested Information

NDA NUMBER/DRUG NAME: 50-717/Monurol (fosfomycin tromethamine)

SPONSOR/APPLICANT: Forest Laboratories/Zambon
150 East 58th Street
New York, N.Y. 10155-0015

The attached Clinical, Statistical, Biopharmaceutical, and Chemistry Reviewers recommendations were discussed with Ms. Replogle and then forwarded via facsimile. Ms. Replogle stated that she would have the appropriate disciplines address the recommendations. She stated that she would phone if there were questions and that they would do their best to respond by the deadline.

The conversation ended amicably.

cc: Orig NDA 50-717
HFD-520
HFD-520/SMO/Albrecht
HFD-520/MO/Soreth
HFD-520/SPHARM/Osterberg
HFD-520/PHARM/Joshi
HFD-520/SCHEM/Roy
HFD-520/CHEM/Timper
HFD-520/SMICRO/Sheldon
HFD-520/MICRO/Sorrey
HFD-521/PROJ MGR/MDillonParker/N50717.TC

TELECON (Attached - facsimile [3 pages])

RE: MONUROL
SPONSOR: FOREST/ZAMBON
NDA 50-717

The following is broken down by each discipline in need of additional information. So that we may review this application in a timely manner, it is requested that the information requested by the Clinical, Chemistry and Biopharmaceutics Reviewers, be provided as soon as possible, but no later than December 16th.

CLINICAL

In follow-up to the recent CANDA meeting, please be reminded that the following was requested by the Clinical Reviewer:

1. Reasons for sponsor non-evaluability, given in detail.
2. Day relative to start of therapy for all follow-up visits and cultures taken.
3. Designation of visits numerically (e.g., 1=entry; 2=first follow-up fosfomycin, on-therapy cipro; etc.)

CHEMISTRY

The following information is requested:

a) provide the full stability data currently available for the drug substance and drug product;

b) provide three copies of the method validation package for the drug substance suitable for collaboration by the FDA laboratories.

BIOPHARMACEUTICS

(1) Please provide further information on the disposition of fosfomycin tromethamine with regards to:

a. the fate of the remaining % of a dose following oral adminstration;

b. specific information on the metabolite(s).

(2) Detailed reports (formulation used, raw data, assay validation) of the studies submitted from publications and other incompleted reports should be provided for review.

STATISTICS

Please see the 2 pages attached titled **APPENDIX II**. Responses to Appendix II should be received no later than January 6, 1995.

PLEASE CONTACT MAUREEN DILLON-PARKER at 301-443-0257, if you have further questions. Thank you.

APPENDIX II:

1. For studies MON-US-01 and MON-US-02, a tabular summary of the percentage of patients included for in each analysis population (ITT and evaluable) by center. A possible table shell is as follows:

center	FT evaluable/enrolled (%)	COMPARATOR evaluable/enrolled (%)
1 2 . . .		
all centers combined		

2. For studies MON-US-01 and MON-US-02, a tabular summary by treatment of the patient reasons for exclusion from the ITT and evaluable populations. This should be provided for all patients combined, and then by center within each reason. Separate sets of tables should be for the ITT and evaluable patient populations. Possible table shells are as follows:

For all patients:

reason	FT # with reason/enrolled (%)	COMPARATOR # with reason/enrolled (%)
reason1 reason2 . . .		

By center within each reason (one table per reason):

center	FT # with reason/enrolled (%)	COMPARATOR # with reason/enrolled (%)
1 2 . . .		

3. For studies MON-US-01 and MON-US-02, an explanation for why some patients who were included in the ITT and the evaluable analysis populations do not have bacteriologic or clinical evaluations at the primary efficacy visit.

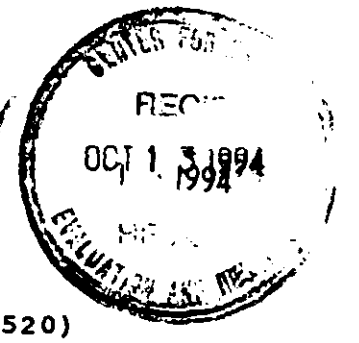
4. For studies MON-US-01 and MON-US-02, subset efficacy analyses by age (≤65, >65) and race (Black, White, Other) in the evaluable patient population.

5. For the Integrated Summary of Safety, subset safety analyses by race (Black, White, Other).

6. Verification that the patients from investigators Harnack, Costantini, and Iravani did not participate in both studies MON-US-01 and MON-US-02.

7. Electronic datasets of the efficacy and safety data for studies MON-US-01 and MON-US-02. Files compatible with SAS version 6.08 are preferred. Complete documentation of these datasets, including file contents, file layouts, sample printouts, detailed variable definitions, and variable codes, should also be provided.

8. Word processing files of the final study reports (including tables), protocols (if available), and the proposed label. Files compatible with WordPerfect version 6.0 are preferred. The files should be provided on 3.5 inch diskettes.



MEMO OF RECORD

Date: October 12, 1994

To: M.Dillon-Parker, Project Manager. DAIDP (HFD-520)

From: S.R. Joshi, D.V.M., Ph.D. 10/13/94

Thru: R.E.Osterberg, Ph.D., Supervisory Pharmacologist 10/13/94

Subject: NDA ~~20-477~~ 50-717; MONUROL™ (Fosfomycin Tromethamine)

The above NDA contains a 13-week oral (gavage) study in the rat.

The applicant has not submitted, in its entirety, the histopathology report of the study. The report consists of two volumes: **volume 1, pp 1-420; volume 2, pp 1-272.** The sponsor has submitted 8 pages [5-02407 to 5-02415] only. Furthermore, the legends in the Figures [Tables] are too small to be legible.

Please request the applicant to submit the above mentioned histopathology report in its entirety with the legends in a legible format.

I have telephoned the contact person, Dr. Rosen.

Thanks.

cc: NDA 20-477(orig)
HFD-520
HFD-520/MO/Soreth

N-20-477.MEM

NDA 50717

NDA50-717

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50-717

Trade Name: MONUROL SACHET

Generic Name:Fosfomycin Tromethamine

Sponsor: Forest Laboratories, Inc.

Approval Date: December 19, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-717

MEDICAL REVIEW(S)

Medical Officer's Review of Original NDA 50-717
Fosfomycin

Applicant: Forest Laboratories, Incorporated, as agent for Zambon Corporation
Date of Submission: September 28, 1994
Review Completed: July 7, 1995; revised August 8, 1995

Material reviewed: Original 99 volume submission, inclusive of 50 volumes of clinical and statistical data, case report tabulations and case report forms. In November and December 1994, and January 1995, a computer-assisted version of the new drug application (CANDA) was also submitted. This included text files for word-processing, data files in a relational database for the pivotal studies, and case report form images on optical disk.

Related IND:

Name of Drug:

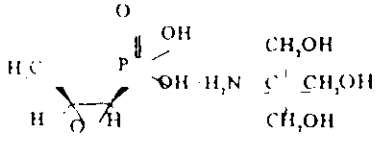
Generic: Fosfomycin Tromethamine
Code No: Z1282
Trade: Monurol® Sachet

***Medical Officer's Comment**: During its early drug development outside the United States, fosfomycin tromethamine was known as fosfomycin trometamol (European trade name Monuril®). Throughout this review, fosfomycin tromethamine will be referred to as fosfomycin or FT.*

Chemical Name: mono-acid salt of 2-ammonium-2 hydroxy-methyl-1,3-propanediol (2R-cis)-(3-methyloxiranyl) phosphonate

Molecular Formula: $C_7H_{18}NO_7P$,

Chemical Structure



Pharmacologic Category: Phosphonic acid derivative which is antibacterial for the urinary tract

Dosage Form and Route of Administration: fosfomycin tromethamine, 3 g single dose sachet (3 g existing as the free base, hereafter designated as 3 g of fosfomycin) to be given orally.

Proposed Package Insert:

Medical Officer's Comment: In the two pivotal trials submitted with this NDA, the applicant has studied women 18 years of age or older.

Resume:

(The following is excerpted from the applicant's "Background of Clinical Investigations" of the NDA and Introductory Statement of the IND):

Each year, one in ten women will seek medical treatment for acute symptoms of increased urinary frequency and dysuria. Most women with cystitis respond well to oral antibiotic therapies when those antibiotics are taken as directed. Current standard antibacterial therapy for uncomplicated urinary tract infections is a 7-10 day course of treatment. With this regimen, however, more frequent and/or serious side effects are reported. There is also a greater chance for the development of resistant microorganisms and alteration of colonic and vaginal flora compared to single-dose therapy. Currently, in the United States, there is no approved short-term antibiotic therapy given as a single dose for the treatment of UTI. A single dose antibiotic that was both safe and effective would, therefore, be a significant therapeutic breakthrough in the treatment of uncomplicated urinary tract infections.

Medical Officer's Comment: The IND for fosfomycin was filed in 1990. At that time, there were no approved antimicrobials for short-term treatment of uncomplicated lower urinary tract infections (cystitis) in women. Since then, two products have been approved for a 3-day course of therapy:

norfloxacin (Noroxin®)	*400 mg q12h for 3 days, and*
ofloxacin (Floxin®)	*200 mg q12h for 3 days.*

In each case, the short-term treatment was clinically and microbiologically equivalent (95% confidence interval met) to standard therapy for 7-10 days.

Fosfomycin trometamol is a novel antimicrobial agent, a derivative of phosphonic acid, which is produced by strains of *Streptomyces*. It was first described in 1969. Two salts of fosfomycin were in clinical use in 1979 when Zambon Research Laboratories, headquartered in Italy, started its drug development project: a disodium salt (parenteral formulation) and a calcium salt (oral formulation). The disodium salt has been used for many years in Europe for the treatment of a wide variety of infections. However, this parenteral formulation is unsuitable for oral administration since it produces gastric irritation.

The calcium salt for oral use is relatively insoluble and poorly absorbed, resulting in low plasma and urinary concentrations. The development of another formulation of fosfomycin by Zambon was pursued in order to provide a well-absorbed, oral alternative. In the form of the tromethamine salt (a monobasic salt of fosfomycin with tromethamine), the antibiotic is highly soluble and well-absorbed after oral administration.

Fosfomycin tromethamine is bactericidal, blocking bacterial cell wall synthesis through the inhibition of the enzyme piruvyl transferase. Besides its primary mode of action, fosfomycin inhibits synthesis of penicillin binding protein involved in the final stage of peptidoglycan polymerization at sub-inhibitory concentrations. In addition, the ability of fosfomycin to reduce the adherence of bacteria to uroepithelial cells enhances its chemotherapeutic potential.

Fosfomycin tromethamine is active at low concentrations against the most common gram-positive and gram-negative urinary tract pathogens, including *E. coli*, *Citrobacter* species, *Proteus* species, *Klebsiella* species, *Enterobacter* species, and the majority of strains of *Staphylococci* and *Streptococci*. Fosfomycin has been shown to be very active (MIC $\leq$ 2 µg/ml) against *E. coli*. Resistance has not been a major problem in countries where fosfomycin tromethamine is most frequently used. Cross-resistance with other agents, such as beta lactams and aminoglycosides, has rarely been demonstrated.

Numerous acute, subacute, chronic and reproductive toxicity studies have been conducted in animals with no remarkable findings to report.

The pharmacokinetic and bioavailability profile of fosfomycin tromethamine is based upon the results of eighteen human studies (two pivotal studies and sixteen supportive studies). After a single 3 g oral dose of FT under fasting conditions, maximum serum fosfomycin concentrations of µg/ml are achieved within hours. The half-life for elimination of fosfomycin is prolonged following oral administration to hours as compared to a serum half-life of hours following intravenous administration. Detectable levels of fosfomycin are present in the blood 36 hours after drug administration. Oral bioavailability under fasting conditions is 33% - 37%. Food decreases the rate and extent of absorption. The absolute bioavailability of FT when administered orally as a 3 g dose with food is 30%.

Fosfomycin is excreted unchanged in urine. Urine fosfomycin concentrations are significantly higher than serum drug concentrations. Following administration of a single oral dose of FT, concentrations of μg/ml are attained within hours. Pharmacokinetic studies have demonstrated urinary levels of μg/ml after hours. Urinary bactericidal concentrations exceeding the MIC_{90} for *E. coli* (μg/ml) for hours following a single g oral dose of have been demonstrated.

Plasma levels and urinary excretion of fosfomycin tromethamine after a 3 g dose in healthy elderly subjects are comparable to those observed in healthy volunteers. In elderly patients with diminished renal function, however, the half-life of fosfomycin is prolonged (from about hours) and the urinary excretion is decreased by %. Renal impairment alters the pharmacokinetic profile of fosfomycin tromethamine, but with single dose therapy, no dosage adjustment is recommended for patients with mild to moderate renal insufficiency.

Fosfomycin trometamol has been extensively investigated in preclinical and clinical studies outside of the United States. More than 5000 patients have been treated with the drug thus far. Open trials were first conducted with single and multiple dose regimens in patients with uncomplicated urinary tract infections.

Initial studies abroad showed comparable cure rates for both single and multiple dose regimens, and subsequent trials, open as well as controlled, used only the single dose regimen. A total of 25 foreign controlled clinical trials were conducted involving 1649 patients treated with FT in dosages ranging from g per day for days. Of the 1649 subjects enrolled, approximately 54% were adult non-pregnant women, 15% were pregnant women, 25% were adult men, 6% were children. A total of 16 foreign uncontrolled clinical trials were also conducted, involving 3930 patients. Of those, 3581 (91%) received fosfomycin tromethamine as single dose therapy. The remaining 349 patients (9%) received fosfomycin tromethamine in dosages ranging from mg/kg to g per day, for durations of one day up to twice weekly dosing over 9 months. Of the 3930 subjects enrolled, approximately 68% were adult non-pregnant women, < 1% were pregnant women, 28% were adult men, 3% were children.

Fosfomycin (as Monurol®) was first approved on July 12, 1986 in Italy. It is currently approved for marketing in 19 countries, as listed below:

Country	Dosage	Marketing Authorization
Belgium	2 gram* and 3 gram	1/9/89
Bolivia	2 gram and 3 gram	10/20/89**
Brazil	2 gram and 3 gram	3/15/90
Chile	3 gram	9/3/93**
Columbia	2 gram and 3 gram	12/4/87
Denmark	2 gram and 3 gram	6/18/93
Ecuador	3 gram	4/13/90**
France	3 gram	7/25/89
Germany	2 gram and 3 gram	1/2/92
Holland	2 gram and 3 gram	4/4/90
Ireland	2 gram and 3 gram	8/16/93
Italy	2 gram and 3 gram	7/12/86
Korea	3 gram	6/8/92**
Luxembourg	3 gram	7/31/89
Mexico	2 gram and 3 gram	7/4/93**
Spain	2 gram and 3 gram	11/26/90
Slovakia	3 gram	4/16/93
Switzerland	2 gram and 3 gram	6/2/88
United Kingdom	2 gram and 3 gram	3/10/92

* Pediatric formulation

** Indicates countries where product is not currently marketed

In addition, countries in which applications for marketing are pending include

Country	Dosage
Austria	2 gram and 3 gram
Bohemia	3 gram
Greece	2 gram and 3 gram
Hungary	3 gram
Indonesia	3 gram
Israel	2 gram and 3 gram
Portugal	2 gram and 3 gram
Taiwan	3 gram
Turkey	2 gram and 3 gram

The drug has not been withdrawn from marketing in any country for reasons related to safety or ineffectiveness.

In general, the recommended doses for Monurol® abroad are as follows:

1) **Adults** - One 3 gram sachet as a single dose preferably taken at night after emptying the bladder. In more serious cases such as in the elderly, bed ridden patients, those patients with recurrent infections, or else suffering from infections of microorganisms sensitive to high concentrations of antibiotic - a second sachet may be taken after 24 hours.

   In the case of prophylactic treatment of potential urinary tract infection following surgical intervention or TURP, two doses of Monurol may be taken, administering the first dose approximately 3 hours before surgical intervention and the second dose given 24 hours following the first.

2) **Children** - One sachet 2 grams as a single dose.

Among its approved indications are the single dose treatment of uncomplicated urinary tract infections, asymptomatic bacteriuria of pregnancy, postoperative urinary infections, and prophylaxis of urinary infections in surgical and transurethral diagnostic maneuvers.

Two double-dummy, double-blind active controlled clinical studies, identified as MON-US-01 and MON-US-02, have been completed in adult women only in the United States. These are the pivotal clinical studies submitted in support of this NDA. The studies were designed to assess the safety and efficacy of a single oral dose of fosfomycin tromethamine compared to a multiple dose regimen of either ciprofloxacin or trimethoprim/sulfamethoxazole in women 18 years of age or older with uncomplicated urinary tract infections.

Manufacturing and Controls
(Please see the manufacturing and controls review by Mr Jim Timper)

Drug Substance:

Physical and Chemical Properties

Appearance/General Characteristics:
White or near white crystalline powder, characteristic citrus fruit flavor

Solubility:
- Very soluble in water
- Slightly soluble in 95% methanol
- Slightly soluble in ethanol
- Insoluble in acetone
- Insoluble in ether
- Insoluble in chlorinated solvents

Melting Point: between 116°C and 122°C
pH: between 4.0 and 5.0
(5% w/v aqueous solution)

Site of Manufacture and Control Operations

The manufacturer of fosfomycin tromethamine is:
Zambon Group S.p.A.
Fine Chemical Division
Via Dovaro-Almisano di Lonigo 36045
Vicenza, Italy

Drug Product:

Quantitative Composition	3g sachet
Fosfomycin Trometamol (equivalent to fosfomycin base 2000 mg and 3000 mg, respectively)	mg
Mandarin Flavor	mg
Orange Flavor	mg
Saccharin, BP	mg
Sucrose, EP	mg
Purified Water, EP	
TOTAL WEIGHT	mg

Site of Manufacture

The drug product will be manufactured by: Alternate packager/labeler of bulk drug product:

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
Manufacturing Plant 1
3721 Laclede Avenue
St. Loius, MO 63108

Stability

The finished drug product, packaged in a sachet, is tested for the following:

Appearance of container	Four-layered sachets
Controls of sachet tightness	Complies with test
Appearance	Granular powder
Color	White
Odor	Characteristic of Mandarin
Residual moisture	Less than %
15% solution in tap water	Homogeneous and opalescent
Solubility	Soluble in seconds
pH	4.0-5.0
HPLC assay of fosfomycin	Limit %
-Degradation products	
> glycolic derivative	NMT %
> 1-hydroxy-2-trometamoyloxy-n propyl fosfonic acid	NMT %
> tromethamine fosfate ester	NMT %
> trometamoyloxy fosfomycin dimer	NMT %

On the basis of stability results for three batches manufactured at an expiration date of 2 years has been proposed.

Medical Officer's Comment. As noted in Mr. Timper's review, stability data submitted thus far supports a 1 year expiration date, not 2 years.

Pharmacology and Toxicology Preclinical Trials

(Please see review by the pharmacologist, Dr Sewa Joshi)

The following information is excerpted from volume 1.3 of the NDA submission, pages 179-239, and volumes 1.1 and 1.5, pages 26-75 and 1-35, respectively, of the IND submission:

Fosfomycin trometamol has been extensively investigated in preclinical studies. Acute studies using oral, intraperitoneal, and intravenous administration have been completed in mice and rats; in rabbits and dogs, oral and intravenous administration acute studies have been completed. Subacute and chronic studies, ranging in duration from 15 days to 26 weeks, have been conducted using rats and dogs. Segment I, II, and III reproduction studies have been conducted, as well as an array of mutagenicity assays. A pharmacokinetic study in dogs using oral fosfomycin tromethamine was also conducted.

Overall, high doses of fosfomycin tromethamine were tolerated best when administered orally. No adverse effects were observed in the mouse (5000 mg/kg) and in the rat (5000 mg/kg) Watery stools in rabbits, and diarrhea with anorexia in dogs, were manifest beginning 2-3 days after oral doses of 2000 mg/kg. There was no mortality Diarrhea and high mortality (60%) in rats were observed only when single oral doses were administered in a range from mg/kg (LD_{50}: 14,553 mg/kg). In the mouse, no gastrointestinal upset or mortality was observed with oral doses up to 10,000 mg/kg.

> ***Medical Officer's Comment**: The proposed marketing dosage of 3 grams as a single dose is the equivalent of 60 mg/kg in a 50 kg woman. As pointed out in the pharmacology review by Dr. Joshi,*
> *"The <u>lowest</u> no-adverse effect level (NOAEL) of 100 mg/kg/day reported in a 4-week dog study is 1.67 times the human dose. However, the actual safety margin would be larger since the comparison was based upon a subchronic toxicology study whereas human exposure is based upon single dosage use. [In other subchronic studies, the NOAEL was generally 1,000 mg/kg/day or about 10.7 times the human dose.]"*

High doses of fosfomycin tromethamine were toxic when administered parenterally to mice, to rats, and to rabbits Signs of respiratory distress, cyanosis, decreased motility, incoordination, catatonia, tremors, epistaxis, hypothermia, piloerection, polyuria, exophthalmos, and blepharoptosis were observed variably either during dosing or soon thereafter Mortality was high LD_{50} values are shown below

Table LD_{50} of Single Dose Fosfomycin Tromethamine in Different Species

Animal	Route	LD_{50}(mg/kg) *males*	LD_{50}(mg/kg) *females*
Mouse	po	> 5000	> 5000
	ip*	4441	4344
Rat	po	14,553	> 5000
	ip	4539	4342
Rabbit	po	> 2000	> 2000
Dog	po	> 2000	> 2000

*intraperitoneal

Mice, rats, and rabbits were most sensitive to fosfomycin tromethamine when it was administered intravenously. In companion non-GLP studies, the acute LD_{50} level in male mice was 1652 mg/kg; in male rats, 1364 mg/kg.; and, in male rabbits, 1360 mg/kg. Cumulative mortality was high (male mice: 72/150, 48%; male rats: 38/70, 54%; male rabbits: 4/6, 67%).

Male dogs tolerated fosfomycin tromethamine well when infused intravenously at doses of 130 mg/kg (injected over a 15 mirute period) and 260 mg/kg (injected over a 3 hour period), respectively. There were no adverse effects. No significant changes in heart rate or arterial blood pressure were noted. There were no deaths and drug-related effects or changes in blood pH, pO_2, and pCO_2.

No drug-related deaths occurred in any subacute or chronic studies with doses up to 4000 mg/kg/day.

> *Medical Officer's Comment: Results from two sub-acute toxicity studies deserve mention. Both rats and dogs showed elevations in liver-associated enzymes when administered high doses daily for 4 weeks (32,000 mg/kg and 1000 mg/kg, respectively). The table below outlines these studies:*

Subacute Toxicity Studies
Multiple Dose Regimen

Study ID/ Design	Route of Administration	Specie/Strain	Animal/Sex/ Group	Dosage Levels	Findings
#88-3324 4 Week Study	Oral gavage-once daily for 4 weeks	Rat, Sprague Dawley CD	60 males 60 females 15/sex/group	mg/kg/day 0 200 800 3200	No adverse effect level: 200 mg/kg/day No drug-related side effects or deaths occurred during study. A dose-related **increase in cholesterol** was noted **in the high-dose groups**, as well as increased liver and kidney weights **increases in SGPT and SGOT** were noted **in 3200 mg/kg/d group**, suggestive of effect on liver function
#88-3324 4 Week Study	Oral gavage -once daily for 4 weeks	Dog, Beagle	16 male 16 female 4/sex/group	mg/kg/day 100 300 1000 Control= empty capsule	No adverse effect level 100 mg/kg/day No drug-related side effects Decrease in body weights of high dose males and 300 and 1000 mg/kg/d females. **Increase in AST and decrease in testes weights seen in high dose mal at study termination.** Animals were sacrificed; on postmortem exam, there was no gross or microscopic evidence of adverse, treatment-related effects due to fosfomycin.

All mutagenicity assays were negative

Acute and subacute studies were conducted in 1989 according to Good Laboratory Practice (GLP) regulations. However, many of the original toxicology and reproduction studies were not conducted using GLP guidelines. In 1993, a study evaluating fosfomycin and developmental toxicity (embryo-fetal toxicity and teratogenic potential) was conducted in compliance with GLP requirements (Protocol No 406-004). Fosfomycin trometamol was administered orally to New Zealand Rabbits. Dosages of 0 (vehicle), 250, 500 and 1000 mg/kg/day were administered to 20 pregnant rabbits/group. The maternal no-observable-adverse-effect-level (NOAEL) for fosfomycin was less than 250 mg/kg/day. The 250, 500 and 1000 mg/kg/day dosages caused abortions, reduced body weight and food consumption, the 500 mg/kg/day dosage also caused 2 deaths, and the 1000 mg/kg/day caused one premature delivery. ***MO Comment:*** *As Dr. Joshi notes in his review, "The fetal NOAEL for fosfomycin tromethamine could not be determined from this study... The applicant's proposed Pregnancy Category B [no terata effects] should be changed to Pregnancy Category C. The terata effects noted were: wavy ribs and delayed retarded ossification of bones in the rat, increased abortions, fetal resorptions and reduced fetal body weights in the rabbit."*

Microbiology

(Please see review by the microbiologist, Mr. Peter Dionne.)

The following is excerpted from the applicant's volume 1.3, pages 277-282, of the NDA submission and from preclinical studies reported in volume 1.5 of the IND submission:

Mode of Action

Fosfomycin tromethamine is a bactericidal agent which inhibits bacterial cell wall synthesis by

Fosfomycin tromethamine is active in low concentrations against the most common gram-negative and gram-positive bacteria involved in urinary tract infections. Its antimicrobial spectrum includes *E. coli*, *Citrobacter* species, *Proteus* species, *Klebsiella* species, and the majority of strains of *Staphylococci* and *Streptococci*. All these organisms are considered causative agents in lower urinary tract infections, *E. coli* accounting for at least 70-90% of the incidence in community-acquired urinary tract infections.

Early work on fosfomycin showed it to be very active (MIC $\leq$2 mcg/ml) against 73 investigated strains of *E. coli*. The table below presents these data, as well as MICs against other uropathogens:

Table MICs of Fosfomycin Trometamol Against 245 Urinary Pathogens (in presence of G6P*)

Organism	Number Tested	MIC Range mcg/ml	MIC_{50}	MIC_{90}
Citrobacter spp.	18		0.5	2
Enterobacter spp.	14		8	16
E. coli	73		0.5	2
Klebsiella spp.	12		16	64
Proteus indole-positive	18		128	>512
P. mirabilis	22		2	64
P. aeruginosa	34		32	256
Serratia spp.	14		16	>512
Staphylococcus spp.	19		4	64
S. faecalis	21		32	64

*Glucose-6-phosphate (G6P); in media with G6P, fosfomycin's activity is potentiated.

In initial pre-clinical studies in the United States, the in vitro antibacterial activity of fosfomycin tromethamine, in terms of fosfomycin base content, was determined against 352 bacterial isolates from a wide variety of geographic locations. The isolates represented 25 species often associated with urinary tract infections. The investigators performed broth microdilution susceptibility tests according to the procedures of the National Committee for Clinical Laboratory Standards. However, they fortified the media with 25 μg/ml of glucose-6-phosphate (G-6-P) to reverse the antagonistic effect of high phosphate and glucose content in the cation adjusted Mueller Hinton broth (CAMHB) or agar. Fosfomycin inhibited the growth of 91% of the 352 bacterial isolates at concentrations ≤128 μg/ml. Against the same isolates, norfloxacin, nalidixic acid, trimethoprim, and trimethoprim/ sulfamethoxazole inhibited, respectively, 94%, 73%, 76%, and 91% at their published NCCLS breakpoints. Susceptibility test results were virtually identical when dilution tests were performed in CAMHB or on Mueller Hinton agar containing 25 μg/ml of glucose-6-phosphate.

To determine more definitively the in vitro spectrum of fosfomycin tromethamine against

bacteria isolated in the United States, agar dilution MICs were obtained against 2,167 bacterial isolates of 21 species associated with urinary tract infection. Fosfomycin inhibited 91% of the 3,176 bacterial isolates at concentrations ≤128 μg/ml. Among the *Enterobacteriaceae*, resistance was very uncommon. *Morganella morganii* and *Enterobacter agglomerans* were exceptions to that generalization. Among 1,597 *Escherichia coli* isolates, there were no resistant strains and only two had "intermediate" MICs of 128 μg/ml. Very few non-enteric gram-negative bacilli were resistant to 256 μg/ml. *Staphylococcus saprophyticus* isolates were variable in their susceptibility to fosfomycin, i.e., only 52% of 128 strains were susceptible to 64 μg/ml, 12% were intermediate, and 36% were resistant.

Susceptibility Criteria:

Due to the high and prolonged urine concentration of fosfomycin following single oral doses of three grams of fosfomycin (as the tromethamine salt), microorganisms that are inhibited by μg/ml were initially considered to be susceptible to fosfomycin. However, due to technical considerations regarding the relationship of MIC to zone diameters obtained from disk diffusion studies, it was deemed necessary to consider isolates with MICs of μg/ml to be intermediate. An intermediate zone diameter range of mm, and a concomitant MIC of μg/ml, were required to avoid excessive interpretive errors with the disk method, especially with respect to *Staphylococcus saprophyticus*.

Data from two studies showed that susceptibility test disks containing 200-μg of fosfomycin base (375.4 μg of fosfomycin tromethamine) and 50 μg of G-6-P delineated susceptible from resistant isolates, in accord with proposed MIC criteria. The species tested were: *Escherichia, Enterobacter, Klebsiella, Serratia, Morganella, Providencia, Acinetobacter, P. aeruginosa*, other *Pseudomonas* species, *X. maltophilia*, *Enterococcus*, and *S. saprophyticus*. Investigators proposed a three-category system to avoid interpretive errors at the mm zone diameter and μg/ml MIC level. Thus, the following interpretive zone diameter categories are proposed:

	Inhibition Zone Diameter (mm)	MIC (μg/ml) in Dilution Tests
Susceptible	≥16	≤ 64
Intermediate	13-15	128
Resistant	≤ 12	≥ 256

With these criteria, major errors (which indicate false negative disk tests with susceptible MICs) were minimal, being only 2.8%. When this three-category system was applied to commercially prepared disks there were three (2%) false-resistant disk test results. When these MICs and disk zone diameters were evaluated with respect to bacteriologic and clinical outcomes obtained during clinical evaluations of fosfomycin in women with cystitis, the experimentally derived MIC and disk zone susceptibility criteria were supported.

Human Pharmacokinetics and Bioavailability

(Please see the Biopharmaceutics review by Dr Dan Wang.)

The following is excerpted from the applicant's biopharmaceutics summary in volume 1.3 of the NDA submission:

After single oral doses of fosfomycin tromethamine ranging from g there is a dose-dependent response in terms of peak plasma concentration, lower doses being more completely absorbed than higher doses Mean peak plasma concentrations generally occur at 2-3 h after the dose and range from mg/L g dose) to mg/L g dose). The bioavailability of fosfomycin from Monurol expressed as the proportion of the oral dose recovered in the urine varies from about % at lower g) to % at the g dose

Fosfomycin is not bound to plasma proteins The volume of distribution following intravenous administration is about 17 - 21 liters Following oral dosing with FT, plasma concentrations decline with a half-life of about hours The apparent volume of distribution has been calculated to range from liters Following administration of FT with food, the apparent volume of distribution increased to 60 liters There appears to be no transformation of fosfomycin to active metabolites

Following intravenous administration of fosfomycin, more than 90% of the dose is recovered unchanged in urine. Fecal recovery accounts for less than 0.1% of the administered i.v. dose. Following oral administration, urinary recovery of fosfomycin was 38% under fasting conditions and 37% when the dose was administered with food. Compared to i.v. administration, oral fosfomycin tromethamine recovery in feces increased to about 18% (fasting) and 19% (fed).

> ***Medical Officer's Comment:*** *For the oral formulation fosfomycin tromethamine, urinary and fecal recovery account for approximately 60% of the dose administered. The applicant was asked in a fax of December 1, 1994, to provide further information on the fate of the remaining 40%. In a response dated December 15, 1994, they stated: "No data is available to document the fate of the remaining 40% of the dose... Fosfomycin is a strong acid. In the milieu of the intestinal tract, ionization of fosfomycin is likely. We believe in the ionized state, fosfomycin is likely to be reactive leading to its degradation."*

Following the i.v. administration of disodium fosfomycin, approximately half the dose is excreted in the urine in the first 2 hours. After dosing with oral fosfomycin tromethamine (FT), excretion of fosfomycin is slower, presumably reflecting the longer observed plasma half-life In the first 12 hours after a 3 g dose of FT, urinary concentrations of fosfomycin are very high, peaking at 300 - 3000 µg/ml at 2 - 4 hours and declining to 120 - 970 µg/ml at 8 - 12 hours and 9 - 600 µg/ml at 12 - 36 hours In a study conducted in the United States, urinary fosfomycin concentrations were found to be lower than those determined in pK studies abroad, but the total amount of fosfomycin excreted in urine was similar

Medical Officer's Comment: The applicant attributes the lower figures in U.S. subjects (healthy volunteers) to their having been well-hydrated. However, foreign pK studies were conducted in healthy volunteers as well, who were presumably well-hydrated.

Concentrations above the MIC are maintained for at least 84 hours for *E. coli* following oral administration regardless of food. Plasma and urinary concentrations of fosfomycin are similar when healthy adults (who received 3 g) are compared with children given a 2 g dose. In healthy, elderly subjects, urinary concentrations similar to those obtained in healthy young volunteers are noted. In pregnant women, plasma levels and urinary excretion after a 3 g dose of fosfomycin tromethamine are nearly the same before and after delivery and are similar to those observed in healthy volunteers.

Drugs modifying gastrointestinal motility (metoclopramide) and secretion (cimetidine) were coadministered with fosfomycin tromethamine to determine their effect on the kinetics of fosfomycin. The results of the study indicate that cimetidine does not have a significant effect on fosfomycin kinetics. In contrast, metoclopramide significantly lowered serum and urinary concentrations of fosfomycin.

In general, the human pharmacokinetic studies performed with fosfomycin can be divided into two categories:

1. Bioavailability studies to define rate and extent of absorption relative to an intravenous injection and pharmacokinetic studies in young healthy volunteers and healthy elderly subjects (Studies 1-10).

2. Supportive studies in elderly subjects with renal impairment, pregnant women and in children (Studies 11-18).

The study designs were varied depending upon the study objective and the scientific endpoint. The table lists of each of the human pharmacokinetic and bioavailability studies along with the objectives and summary conclusions. These studies have been categorized as above and are presented in order of decreasing importance within each class.

Table: Human Pharmacokinetics and Bioavailability Study Summary

Study No	Investigator/ Location	Study Title	Study Design	No. of Subjects	Analytical Method/Matrix	Results and Conclusions
A. Pharmacokinetic and Bioavailability Studies in Healthy Volunteers						
1	Kissei USA	A study to characterize the Pharmacokinetics/Bioavailability of Fosfomycin Following a Single 3 Gram Dose Administered Orally as Fosfomycin Tromethamine (Monurol™) to Fasted and Fed Volunteers or Intravenously as the Disodium Salt to Fasted Volunteers	single-dose crossover for oral fasted and fed phases followed by i.v. phase healthy volunteers	24 12F, 12M	GC/npd and microbiological serum, urine and feces	Absolute bioavailability of FT was 37% following oral administration under fasting conditions and 30% following oral administration with food. Food decreased both rate and extent of absorption. Following I.V. administration of 3 g of FNa, over 90% of fosfomycin is excreted renally and less than 0.1% excreted in the feces. Upon oral administration, the urinary recovery of fosfomycin was 38% and 37% respectively following fasted and fed conditions. Fecal excretion of fosfomycin following oral administration was 18% and 19% respectively following fasted and fed conditions. Following I.V. administration, there was a statistically significant but not clinically relevant difference between female and male subjects for the half-life of elimination and volume of distribution at steady state. All other pharmacokinetic parameters were similar in both genders. Comparison of serum concentration data, urinary excretion and fecal excretion data and pharmacokinetic parameters (AUC and C_{max}) from GC/npd assay and microbiological assay indicated that results from both assays were similar.

Table I: Human Pharmacokinetics and Bioavailability Study Summary (continued)

Study No.	Investigator/ Location	Study Title	Study Design	No. of Subjects	Analytical Method/Matrix	Results and Conclusions
2	Thorsteinsson Iceland	Fosfomycin Pharmacokinetics and Bioavailability of Fosfomycin Trometamol after Oral Administration	single-dose crossover healthy volunteers	12 6F, 6M	microbiological/ serum, urine and feces	The absolute bioavailability of FT was 32% Fosfomycin kinetics were linear over the dose range tested. The mean urinary recovery after the intravenous administration of 3g of FNa was 92% The mean urinary recovery after the oral administration of 3g FT was 39%
3	Greene U.K.	Urinary Recovery of Fosfomycin after Taking Fosfomycin Trometamol (Monurol) by Mouth in Elderly Subjects	single-dose crossover healthy elderly volunteers	12 6F, 6M	microbiological urine	Following oral doses of 2 g and 3 g in the elderly subjects aged 75 years and over, there is a difference in the amount of fosfomycin recovered in urine during the first and last fractions and the total percent recovered. There is no correlation between creatinine clearance, age and total percent recovery
4	Nelson U.K.	Comparative Pharmacokinetics of Fosfomycin Trometamol, Sodium Fosfomycin and Calcium Fosfomycin in Humans	single-dose crossover healthy volunteers	13 3F, 10M	microbiological/ serum and urine	Absolute bioavailability of FT was 37% Fosfomycin kinetics were linear over the dose range tested. Double the FT dose doubled the AUC. Improved rate and extent of oral absorption compared to calcium fosfomycin (FCa). Half the dose of FT produced double the serum concentration of FCa
5	Bergogne-Berezin France	Trometamol-Fosfomycin (Monuril) Bioavailability and Food-Drug Interaction	single-dose crossover healthy volunteers	10 6F, 4M	microbiological/ serum and urine	With food Cmax was reduced by 36% AUC was reduced by 28% and Tmax was prolonged, however, urinary concentrations were only reduced for the first two hours and comparable fasting and fed after 2 hours indicating that FT can be administered without regard to meals.
6	Borgia Italy	Relative Bioavailability of Fosfomycin and of Trometamol After Administration of Single Dose by Oral Route of Fosfomycin Trometamol in Fasting Conditions and After a Meal	single-dose crossover healthy volunteers	6 5F, 1M	GC/MS serum and urine	No statistically significant difference in any FT pharmacokinetic parameters, except Cmax which was statistically lower under fed condition. Urinary concentrations of FT were less then 10% lower fed than fasting at all intervals indicating that FT can be administered fasting or fed.

Table I: Human Pharmacokinetics and Bioavailability Study Summary (continued)

Study No.	Investigator/ Location	Study Title	Study Design	No. of Subjects	Analytical Method/Matrix	Results and Conclusions
7	Bergan Norway Italy	Pharmacokinetics of Fosfomycin and Influence of Cimetidine and Metoclopramide on the Bioavailability of Fosfomycin Trometamol	single-dose crossover healthy volunteers	9 9M	microbiological/ serum and urine	Cimetidine had no significant effect on pharmacokinetics of FT when given concomitantly FT had lower AUC and increased half-life when metoclopramide was given concomitantly
8	Borgia Italy	Fosfomycin Absorption Following Oral Treatment with FZ 588 by Zambon Farmaceutici S p A., Observations in Healthy Volunteers	single-dose single treatment healthy volunteers	5 4F, 1M	microbiological/ serum and urine	Average FT Cmax was 33 μg/mL, AUC_{∞} was 172 μg hr/mL and urinary recovery over 48 hrs was 47%
9	Borgia Italy	Z 1282 (FZ 588) A New Fosfomycin Derivative with Much Improved Bioavailability by Oral Route	single-dose crossover healthy volunteers	6 3F, 3M	microbiological/ serum and urine	Rate and extent of absorption and urinary recovery of fosfomycin from FT were 3-4 times that of FCa Serum levels of FT increased in proportion to increasing doses. Urinary recovery was independent of dose
10	Segre Italy	Pharmacokinetic Profile of Fosfomycin Trometamol (Monuril)	single-dose crossover healthy volunteers single-dose crossover healthy volunteers	5 5M 4 4M	GC/MS and microbiological/ serum and urine	The absolute bioavailability of FT was 44% Serum levels of FT appear to increase less than in proportion to increasing dose Urinary recovery decreases as dose increases. Data is inconsistent with other studies

Table 1: Human Pharmacokinetics and Bioavailability Study Summary (continued)

Study No.	Investigator Location	Study Title	Study Design	No. of Subjects	Analytical Method/Matrix	Results and Conclusions
B. Supportive studies in Populations at Increased Risk						
11	De Cecco Italy	Urinary Tract Infections in Pregnancy: Monuril Single-Dose Treatment versus Traditional Therapy	single-dose crossover pregnant women	4 4F	microbiological/ plasma and urine	Plasma and urinary concentrations of FT following a single 3g dose were comparable during and after pregnancy.
2	Carcioli Italy	Trometamol Salt of Fosfomycin (Monuril): Preliminary Pharmacokinetic and Clinical Experience in the Treatment of Urinary Tract Infections in Children	single-dose parallel children	23 7F, 16M	microbiological serum and urine	FT half-life (approx. 2 hr) was comparable to that in adults. Cmax and AUC were dose proportional in the dose range tested (0.5 to 2g). Two g of FT provided serum and urinary levels comparable to 3 g of FT in adults.
13	Pavesio Italy	Pharmacokinetics in Children of a New Fosfomycin Derivative with Improved Bioavailability	single-dose crossover	6	GC/MS plasma and urine	FT was more bioavailable than FCa (AUC was 2-fold greater and Cmax was 2.5 times higher). Urinary concentration was higher with FT.
14	Salvioli Italy	Oral Bioavailability of Z 1282 in Elderly Patients	single-dose single treatment elderly	6 5F, 1M	GC/MS plasma and urine	Mean Cmax and AUC of FT were slightly higher than values observed in other studies in healthy volunteers.
15	Fillastre France	Comparative Pharmacokinetics of Fosfomycin Trometamol versus Calcium Fosfomycin in Elderly Subjects and Uraemic Patients	single-dose crossover in healthy volunteers parallel in elderly and chronic renal impaired patients	5 healthy volunteers 5M, 8 healthy elderly 4F,4M 23 chronic renal impairment patients 5F, 18M	microbiological/ serum and urine	Bioavailability of FT in healthy volunteers was greater than FCa. FT was less well absorbed based upon urinary recovery and renal clearances were lower in elderly subjects compared to young volunteers for both drugs. In uremic patients, Cmax was higher with longer Tmax, half-life was longer and urinary elimination decreased in relation to degree of renal impairment.

Table I: Human Pharmacokinetics and Bioavailability Study Summary (continued)

Study No.	Investigator/ Location	Study Title	Study Design	No. of Subjects	Analytical Method/Matrix	Results and Conclusions
[illegible]	[illegible]	Renal, Plasmatic and Urinary Concentrations of Fosfomycin After an Oral Single Dose of Trometamol or Calcic Fosfomycin	single-dose parallel patients	45 15T, 7M 11F, 12M	microbiological and GC/MS plasma, urine and tissue	FT produced higher plasma and urine concentrations as well as higher concentration in kidney tissue than FCa. Urinary concentrations following FT were 3 times greater than those produced by FCa
	[illegible] Italy	Study of Fosfomycin Trometamol Kinetics for the Purpose of Evaluating the Concentrations of this Antibacterial Agent in Various Human Tissue	single-dose single treatment patients	11 2F, 9M	microbiological/ serum, urine, tissue	The fosfomycin concentration after FT was 21.7 µg/mL in the serum, 11.6 µg/mL in the prostate, 9.8 µg/mL in the pericystium and 8.8 µg/mL in seminal vesicle
[illegible]	[illegible] Italy	Fosfomycin Serum and Prostatic Tissue Concentrations Following the Administration of Fosfomycin Trometamol, a New Fosfomycin Derivative with High Bioavailability by the Oral Route	single dose parallel patients	24 24M	microbiological/ serum, urine and tissue	The fosfomycin concentrations in the serum and prostatic tissue after FT were 7 times higher at 3 hrs and more than 3 times higher at 12 hrs than FCa

Summary of Foreign Clinical Trials

(The following is excerpted from the applicant's Summary of the Clinical Data and Introduction to the Clinical/Statistical Report.)

Based on the results of pharmacokinetic and in vitro susceptibility studies, fosfomycin was studied as single dose therapy in lower urinary tract infections. An open, uncontrolled trial of 365 patients was conducted by Moroni et al. in 1983-84 (84 males and 281 females, thirteen of whom were pregnant) in an in-patient and out-patient setting. Patients received either a single 3 gram dose of fosfomycin trometamol (198 patients) or 3 grams of fosfomycin trometamol once daily for 2-3 days (167 patients). The study enrolled patients with a variety of urinary tract infections, including asymptomatic bacteriuria, lower uncomplicated symptomatic UTIs, lower complicated symptomatic UTIs, recurrent lower symptomatic UTIs and cystopyelitis (Table 1). Two hundred twenty-one strains, of which 134 were *Escherichia coli*, were isolated from the urine by urine cultures.

> *Medical Officer's Comment: The bacteriologic and clinical efficacy definitions used in this study were not stated. The timing of post-therapy visits for in-patients and out-patients also was not specified.*

The applicant states that,

"A high success rate was observed using the single dose regimen in asymptomatic bacteriurias and in lower uncomplicated symptomatic UTIs -- 78.1% and 89.5%, respectively. In these cases, multiple doses did not increase the success rate any further.

"Excellent results were also observed using single dose in recurrent lower symptomatic UTI in which a 75% success rate was achieved, in fact, only slightly lower than the one obtained using multiple doses (80.6%). In remaining syndromes, elevated success rates were observed only with the multiple dose regimen.

"As table 2 illustrates, there were approximately three times more side effects among patients receiving multiple dose (9.2%) compared to a single dose (3.1%).

"This study concluded that fosfomycin trometamol is safe and effective in the treatment of UTI. The single dose regimen was shown to ensure high success rates in asymptomatic bacteriurias and in lower uncomplicated symptomatic UTIs. In these patients multiple doses added no advantage."

TABLE 1: Fosfomycin Trometamol and UTI Treatment in Adults: Bacteriological Results According to UTI Clinical Presentation

UTIS	Single 3 gram Dose		Multiple 3 gram Dose	
	# of Patients	Cure Rate (%)	# of Patients	Cure Rate (%)
Asymptomatic Bacteriuria	32	78 1	16	68 7
Lower Uncomplicated Symptomatic	114	89 5	87	89 6
Lower Complicated Symptomatic	21	57 1	28	82 1
Recurrent Lower Symptomatic	28	75 0	31	80 6
Cystopyelitis	3	66 6	5	100 0
TOTAL	198	80 8*	167	85 0*

*$X^2 = 1.6$, $P>0.05$
Adapted from Moroni M. Eur Urol 1987, 13 (suppl 1) 101-104 Table IV, p 103.

TABLE 2: Fosfomycin Trometamol and UTI Treatment in Adults: Safety Evaluation

Regimen	# of Patients	# of Patients with Side Effects					
		Diarrhea	Itch	Nausea	Pyrosis	Skin Rash	TOTAL (%)
Single Dose	233	4	1	1	0	1	3 1
Multiple Dose	227	18	0	2	1	0	9 2

Adapted from Moroni M. Eur Urol 1987, 13 (suppl 1) 101-104 Table VII, p 103

A total of 25 controlled clinical trials were conducted outside of the United States. Each study was conducted in support of foreign approvals of fosfomycin tromethamine. A total of 1649 patients analyzed for safety were treated with FT in dosages ranging from 1 to 3 g per day for 1 to 4 days. Of the 1649 subjects enrolled, approximately 54% were adult non-pregnant women, 15% were pregnant women, 25% were adult men, 6% were children. Two percent of this population (men and women) were considered to be elderly.

A total of 505 patients were treated with FT at doses of 3-6 g in the two studies conducted in the United Kingdom and identified as MON-UK-05 and MON-UK-10. Of the 505 patients, 350 were adult women with uncomplicated UTI (MON-UK-10) and 155 were adult men (MON-UK-05) who received prophylactic therapy for infection associated with transurethral resection procedures.

In 16 completed, uncontrolled, foreign clinical trials, a total of 3930 patients were treated with fosfomycin. Of those, 3581 (91%) received fosfomycin tromethamine as a single dose therapy. The remaining 349 patients (9%) received fosfomycin tromethamine in dosages ranging from 60 mg/kg to 4 g per day, for durations of one day up to twice weekly dosing over 9 months. Of the 3930 subjects enrolled, approximately 68% were adult non-pregnant women, < 1% were pregnant women, 28% were adult men, 3% were children. Eight percent of this population (men and women) were considered to be elderly.

Medical Officer's Comment: *No raw data from the 25 controlled and 19 uncontrolled European trials with single or multiple dose fosfomycin regimens are available for review. Of the 25 controlled trials conducted abroad, I have reviewed the final reports for all adult studies and commented on study design, number of evaluable patients, timing of follow-up visits, and definitions used for bacteriologic efficacy. These summary tables are found below:*

TABLE: CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE
CONDUCTED OUTSIDE THE UNITED STATES

Principal Investigator, Country	Completion Status (Start Date & End Date)[1]	Study Design	Treatment Dose (SD = single dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
A. W. Asscher [illegible] Nottingham Med. Sch. Nottingham NG7 2UH U.K.	Complete (Dates not given -- Article 1988, Report Jan 1991)	Randomized, double blind, double dummy Indication: UTI. *MO Comment: bacterial persistence defined as* <u>*> 100,000 cfu/mL*</u> *of the original pathogen*	Oral FT 3 g SD vs Trimethoprim (TMP) 200 mg SD	FT 35 TMP 40	FT 16-72 yrs (mean = 39.2 yrs) TMP 16-67 yrs (mean = 33.0 yrs)	<u>Total</u> 75 F (100%)	34 FT evaluable 32 TMP evaluable <u>7 days posttherapy</u> clin cure 72% FT 68% TMP bact erad 78% FT 61% TMP Failures not carried forward into 6 week posttherapy visit
F. Bultet Urologic Dept Sint-Maatenziekenhuis [illegible] Belgium	Complete (Dates not given -- Article 1990)	Randomized, placebo controlled, double blind Indication: prophylactic use in transurethral prostatectomy	Oral FT 3 g x 2 doses vs. Placebo (PL): 3 g x 2 doses	FT: 31 PL: 30	FT: 50-83 yrs (mean = 69 yrs) PL: 48-76 yrs (mean= 66.1 yrs)	<u>Total</u> 61 M (100%)	<u>Positive culture</u> <u>24h and 48h post-op</u> 0/31 FT 6/30 placebo Significant bacteriuria defined as ≥ 100,000 cfu/mL

- Fosfomycin tromethamine = fosfomycin trometamol.
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TABLE: CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE CONDUCTED OUTSIDE THE UNITED STATES

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose [SD = single dose]	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
J B J Boerema Medical Research Bureau Keizerkarelplein 32 B Nijmegen Netherlands	Complete (1987 - 1988)	Randomized, double blind, multicenter. Indication uncomplicated UTI. *MO Comment: Protocol does not define a "positive culture" posttherapy*	Oral FT 3 g SD vs. Norfloxacin (NFX) 400 mg bid x 7 days	FT: 79 NFX: 79	FT: 17-45 yrs (mean = 30 yrs) NFX: 16-46 yrs (mean = 30 yrs)	Total 158 F (100%)	61 FT evaluable 50 NFX evaluable study day 7 bact erad 98% FT 96% NFX clin cure 76% FT 96% NFX There is no visit for NFX patients 5-9 days posttherapy study day 42 bact erad 93% FT 90% NFX clin cure 96% FT 100% NFX Failures are not carried forward 15/79 (19%) FT patients reported diarrhea

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CONDUCTED OUTSIDE THE UNITED STATES

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J B J Boeremа Medical Research Bureau Keizerkaraplein 32 B Nijmegen, Netherlands	Complete (1986 - 1987)	Randomized, double blind Indication uncomplicated UTI *MO Comment* *Enrolled symptomatic and asymptomatic patients. Significant bacteriuria at entry defined as ≥ 10^5cfu/ml Gram + or ≥ 10^5cfu/ml Gram - bacteria.* Eradication = < 10^4 cfu/ml Gram +, < 5 x 10^4 Gram -.	Oral FT: 3 g SD vs. Amoxycillin (AMOX): 3 g SD	FT: 24 AMOX: 21	FT: 21-68 yrs (mean = 40.9 yrs) AMOX: 25-63 yrs (mean = 40.6 yrs)	Total: 45 F (100%)	16 FT evaluable 14 Amox evaluable 3-9 days postherapy bact erad 88% FT 57% Amox clin cure 93% FT 77% Amox 12-57 days postherapy bact erad 71% FT 33% Amox clin f/u not reported

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CONDUCTED OUTSIDE THE UNITED STATES

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose [SD = single dose]	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
A. Brunelli Divisione Pediatrica Ospedale M. Bufalini Via Ghirotti 326 I- 47023 Cesena, Italy	Complete (Dates not given -- Publication 1988)	Indication: Pediatric recurrent UTI	Oral FT: 1-2 g SD vs. Nitrofurantoin: 5 mg/kg/day vs. Cotrimoxazole: 40 mg/kg/day vs. Nalidixic acid: 50 mg/kg/day vs. Cephalosporins: 40 mg/kg/day	Total: 5	Total: 5-11 yrs	Total: 5 F (100%)	Protocol not reviewed CRFs: not available
P. Careddu Pediatric Clinic I Univ. of Milan Milan, Italy	Complete (1986 - 1987)	Randomized, comparative: Indication: Pediatric UTI	Oral FT: 2 g SD vs. Pipemidic acid (PA): 200/400mg bid x 7 days	FT: 24 PA: 27	1 - 14 yrs FT: (mean = 6.7 yrs) PA: (mean = 6.6 yrs)	FT: 2 M (8%) 22 F (92%) PA: 3 M (11%) 24 F (89%)	Protocol not reviewed CRFs: not available

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Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose [SD = single dose]	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
J. Ruiz Castañe Dept. of Urology Fundazione Puigvert Barcelona Spain	Complete (1986 - 1987)	Randomized, controlled Indication: uncomplicated UTI. *MO Comment: Significant bacteriuria not defined at entry or follow-up*	Oral FT: 3 g SD vs. Amoxicillin (AMOX): 3 g SD	FT: 25 AMOX: 34	Age not specified	Total 59 F (100%)	23 FT evaluable 23 Amox evaluable 96% bacteriologic cure for both drugs after 3 days, 7-10 days and 21-28 days. Clinical efficacy not reported. CRFs not available
J. Cooper Earnswood Medical Centre, Crewe Cheshire CW 2JR UK	Complete. (1987 - 1988)	Randomized, open, controlled. Indications: bacterial & nonbacterial dysuria & frequency *MO Comment: Definition for bacteriologic eradication not specified.*	Oral FT: 3 g SD vs. Clavunalate-potentiated Amoxycillin (AMOX/C): 375 mg q8h x 5 days	FT: 72 AMOX/C: 69	FT: 17-78 yrs (mean = 45.4 yrs) AMOX/C: 18-75 yrs (mean = 50 yrs)	Evaluable FT: 2 M (3%) 64 F (97%) AMOX/C: 2 M (3%) 63 F (97%)	33 FT evaluable 29 Amox/C evaluable 5-10 days posttherapy bact erad 85% FT 72% Amox/C clin cure 85% FT 79% Amox/C 4-6 wks posttherapy bact erad 81% FT 65% Amox/C

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Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose (SD = single dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
A. Corbusier Dept. of Urology Univ. Clinics of Brussels Belgium	Complete (1985 - 1986)	Multicenter, randomized. Indication: lower uncomplicated UTI. *MO Comment:* *Significant bacteriuria at entry defined as > 10^5 cfu/ml. Bacteriologic eradication defined as < 10^5 cfu/ml*	Oral FT: 3 g SD vs. Amoxycillin (AMOX) 3 g SD	FT: 48 AMOX: 48	FT: (mean = 36.9 yrs) AMOX: (mean = 42.2 yrs)	Total: 96 F (100%)	41 FT evaluable 43 Amox evaluable No visit 5-9 days post overall erad 3-4 wks 78% FT 70% Amox CRFs: not available
P. Crocchiolo Dept. of Infectious Diseases Ospedale Maggiore 20075 Lodi, Italy	Complete (1986 - 1987)	Multicenter, open, randomized, controlled. Indication: lower UTI. *MO Comment* *Bacteriologic eradication not defined*	Oral FT: 3 g SD vs. Cotrimoxazole (CTX) 960 mg/day x 3 days	FT: 38 CTX: 35	FT: (mean = 43.6 yrs) CTX: (mean = 45.1 yrs)	Total: 73 F (100%)	19 FT evaluable 17 CTX evaluable study day 5-10 bact erad: 100% FT 88% CTX clin cure: 92% FT 83% CTX study day 25-30 bact erad: 89% FT 76% CTX Safety: 2/19 FT pts reported diarrhea CRFs: not available

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CONDUCTED OUTSIDE THE UNITED STATES

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose (SD = single dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
T. Dejonckheere H. Hart Ziekenhuis Dept. of Gynaecology Wilgenstraat 2 8800 Roeselare Belgium	Complete (1987 - 1988)	Randomized, controlled Indication: post-op catheter-associated UTI in gyn surgery *MO Comment:* **Bacteriologic eradication** *defined as sterile culture or original pathogen grown at < 10^4 cfu/ml*	Oral FT: 3 g SD vs Norfloxacin (NFX): 400mg bid x 3 days	FT: 32 NFX: 32	FT: 44-57 yrs (mean = 50.4 yrs) NFX: 41-53 yrs (mean = 47.5 yrs)	Total 64 F (100%)	30 FT evaluable 26 NFX evaluable 7 days post bact erad: 96% FT 89% NFX 1 month post bact erad: 92% FT 95% NFX Failures not carried forward CRFs not available
F. DiSilverio Urological Pathology Univ. "La Sapienza" Via Porro 20 Rome, Italy	Complete (Dates not given – Abstract 1990)	Randomized, double blind, placebo controlled. Indication: prophylactic transurethral surgery.	Oral FT: 3 g x 2 doses vs. Placebo (PL): 3 g x 2 doses (3g, 3hrs before and 3g, 24 hrs after surgical procedure)	FT: 40 PL: 24	FT: 50-82 yrs (mean = 65 yrs) PL: 36-85 yrs (mean = 66 yrs)	FT: 36 M (90%) 4 F (10%) PL: 21 M (88%) 3 F (12%)	35 FT evaluable 20 PL evaluable urine culture + 6-8 days postop 3% FT 25% placebo 25-30 days postop 3% FT 20% PL CRFs not available

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Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose [SD = single dose]	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
G. Ferraro Dept. of Biomedical Sciences & Technologies First School of Internal Medicine Univ. of Milan Ospedale Policlinico Milan, Italy	Complete. (Dates not given -- Article 1990)	Open, controlled, randomized. Indication: uncomplicated UTI in the elderly. *MO Comment: Bacteriologic efficacy definitions not stated.*	Oral FT, 3 g SD vs. Norfloxacin (NFX) 400 mg bid x 7 days	FT 30 NFX 30	Total mean = 68.4 yrs	Total 15 M (25%) 45 F (75%)	30 FT evaluable 30 NFX evaluable No 5-9 day visit 25-35 day post bact erad 77% FT 73% NFX No significant modifications of fecal flora noted in either group CRFs not available

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Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose [SD = single dose]	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
A. Jardin Hôpital Kremlin Bicetre Service Urologie 18 Av. du Général Leclerc F-94275 Kremlin Bicetre France	Complete (1987 - 1988)	Open, multicenter, parallel. Indication: lower UTI	Oral FT: 3 g SD vs Pipemidic acid (PA) 800 mg bid x 5 days	FT 206 PA 180	16 - 75 yrs FT (mean = 39.1 yrs) PA (mean = 41.5 yrs)	Total 386 F (100%)	150 FT evaluable 146 PA evaluable 5-10 days post bact erad 84% FT 91% PA 28 days post bact erad 93% FT 93% PA Failures not carried forward CRFs not available

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Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose (SD = single dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
P. Marone Infectious Disease Clinic-IRCCS Policlinico S. Matteo Univ. of Pavia Italy	Complete (Dates not given -- Paper 1988, Report 1991)	Multicenter, open, randomized, controlled. Indication: UTI in pregnant women *MO Comment: Bacteriological efficacy definitions not stated. 90% of patients in each arm in 2nd or third trimester*	Oral FT 3 g SD vs Amoxycillin (AMOX) 3 g SD	FT 30* AMOX 31	FT 19-37 yrs (mean = 27.3 yrs) AMOX 19-36 yrs (mean = 26.7 yrs)	Total 61 F (100%)	24 FT evaluable 24 Amox evaluable Authors lumped 3, 15, and 30 days post Bact eradi 71% FT 71% Amox Clinical efficacy not assessed beyond 3 days post Safety analysis minimal. No drug related side effects reported in either arm No obstetrical follow-up or fetal infant follow up reported CRFs not available

Fosfomycin tromethamine = fosfomycin trometamo.

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TABLE: CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE
CONDUCTED OUTSIDE THE UNITED STATES

Principal Investigator, Country	Completion Status (Start Date & End Date)[3]	Study Design	Treatment Dose (SD = single dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
[illegible] Stahler [illegible] Diakonie Hospital Schulgasse 29 D-8440 Straubing-FRG Germany	Complete (1986 - 1987)	Multicenter, single-blind, randomized Indication uncomplicated UTI *MO Comment Patients stratified by colony count, significant = $\geq 10^5$ low = 10^3-10^4 no bacteriuria $\leq 10^3$ *Bacteriologic efficacy definitions not stated* *Patients with no bacteriuria too low for statistical analysis*	Oral FT 3 g SD vs Ofloxacin (OFX) 200 mg SD vs Cotrimoxazole (CTX) 1 92 g SD	FT 266 OFX 131 CTX 134 Unknown 31	Total 18-75 yrs	Total 562 F (100%)	224 FT evaluable [2] 113 OFX eval 109 CTX eval bacteriologic erad up to 4 weeks post 82% FT 81% OFX 79% CTX Same figures for clinical efficacy reported Most common FT side effect diarrhea (6%) CRFs not available

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TABLE: CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE CONDUCTED OUTSIDE THE UNITED STATES

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose (SD = single dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No (%)	Medical Officer's Summary and Comments
[illegible] Dept. of Internal Medicine Infectious Diseases and Immunopathology Ospedale Policlinico "F. Sforza" [illegible] Milan Italy	Complete (Dates not given -- Publication 1988)	Open, randomized, controlled Indication: UTI in the elderly *MO Comment: All patients were hospitalized. Significant bacteriuria not defined for inclusion criteria or follow-up assessment*	Oral FT: 3 g every 72 hrs x 4 doses vs Norfloxacin (NFX): 400 mg bid x 10 days	FT: 6 NFX: 6	Total: mean = 64 yrs	Total 4 M (33%) 8 F (67%)	6 FT evaluable 6 NFX evaluable No 5-9 day post visit 25-35 days post bact erad: 6/6 FT 5/6 NFX One adverse reaction in FT: "mild transient gastric disturbance" CRFs: not available
P. Perno Dept. of Pharmacology [illegible] Italy	Complete (Dates not given -- Publication 1988)	Randomized, open, multicenter. Indication: prophylactic use in transurethral prostatectomy *MO Comment: Post-op bacteriuria defined as > 10^5 cfu/ml*	Oral FT: 3 g x 2 doses vs. Amoxycillin (AMOX): 3 g x 2 doses vs Cotrimoxazole (CTX): 1 920 g x 2 doses (Dosing: one dose 3hrs before surgery and second dose 24hrs after surgery)	FT: 329 AMOX: 283 CTX: 288	FT: 43-92 yrs (median = 68 yrs) AMOX: 42-88 yrs (median = 69 yrs) CTX: 44-89 yrs (median = 69 yrs)	Total 900 M (100%)	329 FT evaluable 283 Amox evaluable 288 CTX evaluable Cumulative incidence of significant postop bacteriuria at 2 weeks 16% FT 25% Amox 27% CTX Adverse events reported in 4% FT, 6% Amox, 8% CTX CRFs: not available

[illegible] fosfomycin trometh[illegible] = fosfomycin trometamol

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CONDUCTED OUTSIDE THE UNITED STATES

Principal Investigator, Country	Completion Status (Start Date & End Date)[1]	Study Design	Treatment Dose (SD = single dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
[illegible]	Complete (Dates not given -- Report 1988)	Open, randomized, multicenter, parallel Indication: lower UTI *MO Comment: Entry criteria specified ≥ 10^5 Bact eradication < 10^5*	Oral FT: single dose 3 g SD vs Norfloxacin (NFX): 400 mg bid x 5 days	FT: 38 NFX: 30	FT mean = 36.7 yrs NFX mean = 43.5 yrs	Total 68 F (100%)	33 FT evaluable 30 NFX evaluable 3-4 days post bact erad: 94% FT 87% NFX clin cure: 70% FT 80% NFX 25-30 days post bact erad: 73% FT 78% NFX 9 FT and 4 NFX reported adverse events: 5 9 FT had diarrhea CRFs: not available
[illegible] Pediatric Dept [illegible]	Complete (1986 - 1987)	Multicenter, open, randomized Indication: pediatric UTI	Oral FT: 1 or 2 g SD vs Netilmycin (NET): 5mg/kg IM, SD	FT: 71 NET: 64	Total 1 month to 16 yrs	FT 21M (30%) 50F (70%) NET 24M (37.5%) 40F(62.5%)	*Not reviewed* Report Section 8, Volume 61, pp. 8.0 - 8.1 CRFs: not available

- Fosfomycin tromethamine = fosfomycin trometamol
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- [illegible] patients first treated with amoxicillin who were switched to FT after persistence or relapse was seen. A total of 37 patients were exposed to FT in this trial

TABLE CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE
CONDUCTED OUTSIDE THE UNITED STATES

Principal Investigator, Country	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose (SD = single dose)	Number Entered Each Treatment	Age Range (Mean or Medi. n), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
[illegible]	Complete (Dates not given -- Article 1988)	Multicenter, randomized, controlled Indication pregnant women, UTI *MO Comment Significant bacteriuria ≥ 10^5 cfu/ml at entry Eradication defined as ≤ 10^5 cfu/ml*	Oral FT 3 g SD vs Pipemidic acid (PA) 400 mg bid x 7 days	FT 209 PA 156	FT (mean = 27.98 yrs) PA (mean = 28.29 yrs)	Total 365 F (100%)	177 FT evaluable 136 PA evaluable 15 days post bact erad 95% FT 95% PA 30 days post bact erad 94% FT 94% PA 185 FT and 138 PA followed until delivery %FT sp AB 2.7 stillbirth 1 low BW 4.3 malform 0.5

Fosfomycin tromethamine = fosfomycin trometamol

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There were seven patients first treated with amoxicillin who were switched to FT after persistence or relapse was seen A total of 37 patients were exposed to FT in this trial

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CONDUCTED OUTSIDE THE UNITED STATES

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose (SD = single dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
[illegible]	Complete (1987 - 1988)	Randomized, controlled Indication uncomplicated UTI *MO Comment: Significant bacteruria ≥ 10^5 cfu/ml at entry. Eradication defined as < 10^5 cfu/ml*	Oral FT 3 g SD vs Norfloxacin (NFX) 400 mg bid x 3 days	FT 20 NFX 20	FT 15-73 yrs (mean = 43.1 yrs) NFX 18-65 yrs (mean = 52.8 yrs)	Total 40 F (100%)	16 FT evaluable 16 NFX evaluable 5-10 days post bact erad 88% FT 88% NFX clin cure 89% FT 89% NFX 1 month post bact erad 81% FT 56% NFX One adverse event in each arm diarrhea FT heavy stomach NFX CRFs not available

[1] Fosfomycin trometh[illegible] = fosfomycin trometamol
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Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose [SD = single dose]	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
C. Richaud Dept. of Urology Hospital Nord Chemin des bourrély 13015 Marseille France	Complete (1988 - 1989)	Multicenter, double blind, double dummy, randomized Indication: lower UTI. *MO Comment: Significant bacteriuria ≥ 10^5 c.u./ml at entry. Eradication defined as < 10^3 cfu/ml. However, persistence defined as ≥ 10^3 [sic].*	Oral FT: 3 g SD vs. Pefloxacin (PFX): 800 mg SD	FT: 31 PFX: 31	FT: (mean = 57.2 yrs) PFX: (mean = 51.4 yrs)	Total: 62 F (100%)	29 FT evaluable 28 PFX evaluable 8-10 days post bact erad: 90% FT 93% PFX 28-35 days post bact erad: 86% FT 89% PFX Similar clinical efficacy reported CRFs: not available
F.P. Selvaggi Dept. of Surgery - Surgical Nephrology Univ. of Bari Italy	Complete (1986 - 1987)	Multicenter, randomized, double blind, double dummy. Indication: uncomplicated UTI. *MO Comment: Significant bacteriuria defined as "> 10 bacteria /ml". Efficacy definitions not stated.*	Oral FT: 3 g SD vs. Norfloxacin (NFX): 800 mg SD	FT: 45 NFX: 44	FT: 16-66 yrs (median = 39 yrs) NFX: 17-70 yrs (median = 33 yrs)	Total: 89 F (100%)	28 FT evaluable 25 NFX evaluable 7 days post bact erad: 75% FT 84% NFX No side effects reported in 89 patients enrolled CRFs: not available

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H. Thiounn Dept. of Gynecology and Obstetrics Univ. Hospital Liege, Belgium	Completion status not indicated Preliminary results published in Article 1990. (study assumed to be complete)	Randomized, controlled Indication: pregnant women, UTI	Oral FT: 3 g SD vs. Nitrofurantoin (NTF): 100 mg bid x 7 days	FT: 13 NTF: 10	Age not specified	Total: 23 F (100%)	All evaluable for efficacy and safety 15 days post bact erad: 84% FT 90% NTF Study ongoing. No patient had delivered by the time of this publication. CRFs: not available

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[2] The name and country of the first listed investigator or author is presented here.
[3] If start and end dates were not given, the date of a document or publication is presented here. Study completion assumed unless stated otherwise.

TABLE: CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE
CONDUCTED OUTSIDE THE UNITED STATES

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose (SD = single dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F), No. (%)	Medical Officer's Summary and Comments
MON UK 05 4 Study Centers United Kingdom	Complete (July 30, 1991 - September 17, 1993) Final report is not available.	Randomized, placebo-controlled, double-blind, group comparative, Phase III multi-center clinical trial. Indication: Antimicrobial prophylaxis during transurethral resection of the prostate	FT: 3 g x 2 doses Placebo	FT/Placebo 155 / 154	FT: mean = 69.3 yrs. CONTROL: mean = 68.6 yrs.	116M(100%) 114M(100%)	*Final study report not available* Report: Synopsis, Section 8, Volume 62, pg. 8-02290 CRFs: not available
MON UK 10 United Kingdom	Complete (May 1991 - September 1993) Final report is not available	Phase III, active-controlled, randomized, group comparative Indication: Lower UTI *MO Comment:* *Eradication defined as ≤ 10 cfu/ml.*[4]	Oral FT 3 g SD Trimethoprim (TMP) 200mg BID x 5 days	FT - 350 evaluable TMP-180 evaluable	FT: mean = 39.1 yrs. TMP: mean = 39.0 yrs.	350F(100%) 180F(100%)	176 FT evaluable 87 Tmp evaluable 7-9 days post bact erad 69% FT 74% TMP day 26-30 post bact erad 69% erad 81% erad Diarrhea was most commonly reported FT adverse event. CRFs: not available

1. Fosfomycin tromethamine = fosfomycin trometamol.
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3. If start and end dates were not given, the date of a document or publication is presented here. Study completion assumed unless stated otherwise.

TABLE D: NON-CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE CONDUCTED OUTSIDE THE UNITED STATES[*]

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose [SD = single dose; MD = multiple dose]	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F) No. (%)	NDA Volume and Page for Study Report and CRFs
G. Ambrosioni Ospedale Maggiore C.A. Pizzardi Bologna, Italy	Complete (14 Nov. 1983 - 10 May 1984)	Open, non-controlled Indication: Pediatric-- lower UTI	Oral FT (a) 2 g SD (b) 2 g x 2 doses	Total (a + b) 16	1-9 yrs (mean = 5.5 yrs)	5 M (31%) 11 F (69%)	Report Section 8, Volume 63, Pg 8-03716 CRFs not available
R. Arione Dept. A. Amedeo Di Savoia Hosp. Turin, Italy	Complete (Dates not given -- Article 1987)	Open, non-controlled Indication: lower UTI	Oral FT 3 g SD	26	12-83 yrs (mean = 52.3 yrs)	5 M (19%) 21 F (81%)	Report Section 8, Volume 62, pg 8-03543 CRFs not available
Ross R. Bailey Dept. of Nephrology Christchurch Hosp. Christchurch New Zealand	Complete (1987 - 1988)	Open, non-controlled Indication: women with lower UTI	Oral FT 3 g SD	25	18-74 yrs (mean = 31.6 yrs)	25 F (100%)	Report Section 8, Volume 62, pg 8-03504 CRFs not available

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TABLE D: NON-CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE CONDUCTED OUTSIDE THE UNITED STATES*

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose (SD = single dose; MD = multiple dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F) No. (%)	NDA Volume and Page for Study Report and CRFs
P. Careddu Pediatric Clinic I Univ. of Milan Milan, Italy	Complete (Dates not given -- Article 1987)	Non-controlled Indication: prophylaxis in children with urinary tract abnormalities	Oral FT 1-2 g 2x/week for 3 weeks -9 months	10	4-11 yrs (mean = 7.7 yrs)	1 M (10%) 9 F (90%)	Report Section 8, Volume 63, pg 8-03737 CRFs not available
F. Dibisceglie Inst. of Urological Pathology Univ. La Sapienza Rome, Italy	Complete (July 1987-Jan 1988)	Open, prospective non-controlled Indication: prophylactic - transurethral surgery, urological maneuvers	Oral FT 3 g x 2 doses (3h before and 24h following procedure)	712	15-94 yrs (mean = 59 yrs)	521 M (73%) 191 F (27%)	Report Section 8, Volume 63, pg 8-03774 CRFs not available

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TABLE D: NON-CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE CONDUCTED OUTSIDE THE UNITED STATES*

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose (SD = single dose; MD = multiple dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F) No. (%)	NDA Volume and Page for Study Report and CRFs
F. DiSilverio Inst. of Urological Pathology Univ. La Sapienza Italy	Complete (Dates not given -- Publication 1987)	Open, non-controlled Indication *prophylaxis* after ESWL & ureter-pyeloscopy	Oral FT 3 g x 2 doses (3h before and *24h following* procedure)	30	22-76 yrs (mean = 42 yrs)	21 M (70%) 9 F (30%)	Report Section 8, Volume 62, pg 8-03781 CRFs not available
A.P. MacGowan Dept. of Medical Microbiology Southmead Hospital Westbury on Trym Bristol, BS10 5NB United Kingdom	Complete (Dates not given -- Article 1990)	Open, non-controlled Indication UTI	Oral FT 3 g SD	20	47-88 yrs (mean = 72 yrs)	5 M (25%) 15 F (75%)	Report Section 8, Volume 62, pg 8-03670 CRFs not available

* Fosfomycin trometh**a**mine = fosfomycin trometamol

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TABLE D: NON-CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE CONDUCTED OUTSIDE THE UNITED STATES*

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[1]	Study Design	Treatment Dose (SD = single dose; MD = multiple dose)	Number [illegible]ered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F) No. (%)	NDA Volume and Page for Study Report [illegible] and CRFs
M. Marioni L. Sacco Hospital Milan, Italy	Complete (1983 - 1984)	Open, non-controlled, multicenter Indication uncomplicated UTI	Oral FT (a) 3 g SD (b) 3 g x 2-3 days	(a) 223 (b) 227	Not given	Total (a + b) 84 M (19%) 281 F (62%) 85 NI (19%) (13 Pregnant)	Report Section 8, Volume 62, pg 8-03507 CRFs not available
M. Neuman Dept. of Gastroenterology Hospital Cochin Paris, France	Complete (1984 - 1985)	Open, non-controlled Indication uncomplicated UTI	Oral FT (a) 3 g SD (b) 4 g SD (c) 4 g x 2-3 days	(a) 28 (b) 12 (c) 8	Not given	Total (a + b + c) 1 M (2%) 47 F (98%)	Report Section 8, Volume 62, pg 8-03549 CRFs not available
Neuman Dept. of Gastroenterology Hospital Cochin Paris, France	Complete (Dates not given -- Publication 1988)	Open, non-controlled Indication: lower UTI	Oral FT (a) 3 g SD (b) 3 g + 2 g	(a) 12 (b) 8	Inclusion criteria 19-70 yrs	2 M (10%) 18 F (90%)	Report Section 8, Volume 62, pg 8-03553 CRFs not available

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TABLE D: NON-CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE CONDUCTED OUTSIDE THE UNITED STATES*

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose (SD = single dose; MD = multiple dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F) No. (%)	NDA Volume and Page for Study Report and CRFs
P. Perdo Dept. of Pharmacology Univ. of Florence Florence, Italy	Complete (Dates not given -- Article 1988)	Open, non-controlled Indication: prophylactic - cystoscopy, transurethral resection	Oral FT: 3 g x 2 doses (3g 3hrs before and 3g 24hrs after surgical procedure)	N=283	mean = 62.7 yrs	231 M (82%) 52 F (18%)	Report Section 8, Volume 62, pg 8-03744 CRFs not available
L. Roland Inst. of Internal Medicine (ISMI) Univ. of Genoa Genoa, Italy	Complete (Dates not given -- Publication 1988)	Open, non-controlled Indication: UTI in elderly women	Oral FT: 3 g SD	27	51-85 yrs (mean = 54.7 yrs)	27 F (100%)	Report Section 8, Volume 63, pg 8-03636 CRFs not available
Swiss Multicenter Switzerland	Complete (1988 - 1989)	Open, non-controlled, multicenter Indication: UTI or urinary tract procedures	Oral FT: (a) 3 g SD (b) 3 g x 2 doses	(a) 2148 (b) 10	Total Inclusion criteria 16-75 yrs Actual mean M = 52 yrs F = 42 yrs	Total 207 M (10%) 1913 F (89%) 38 (2%) Not Indicated	Report Section 8, Volume 62, pg 8-03563 CRFs not available

* Fosfomycin tromethamine = fosfomycin trometamol

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TABLE D: NON-CONTROLLED STUDIES OF FOSFOMYCIN TROMETHAMINE CONDUCTED OUTSIDE THE UNITED STATES*

Principal Investigator, Country[1]	Completion Status (Start Date & End Date)[2]	Study Design	Treatment Dose (SD = single dose; MD = multiple dose)	Number Entered Each Treatment	Age Range (Mean or Median), Years	Sex (M/F) No. (%)	NDA Volume and Page for Study Report and CRFs
R. Lombardo Inst. of Pediatric Clinic Catania, Italy	Complete (Dates not given -- Paper 1986)	Open, non-controlled Indication lower UTI	Oral FT 2 g SD	10	3-12 yrs	M and F, numbers not indicated	Report Section 8, Volume 63, pg 8-03732 CRFs not available
I. A. Varese Nephrologic and Microbiologic Dept Children's Hospital Torino, Italy	Complete (March 1984 - July 1984)	Open, non-controlled Indication UTI in children	Oral FT (a) 2 g SD (b) 3 g SD (c) 1 g SD (d) 0.5 g SD (e) 2 g MD	(a) 30 (b) 2 (c) 3 (d) 2 (e) 6	1 month - 15 yrs (mean = 5.7 yrs)	9 M (21%) 34 F (79%)	Report Section 8, Volume 63, pg 8-03680 CRFs not available
I. A. Varese Nephrologic and Microbiologic Dept Children's Hospital Torino, Italy	Complete (1984 - 1985)	Open, non-controlled Indication uncomplicated UTI in children	Oral FT: 60-160 mg/kg SD	5?	1 month - 16 yrs (mean = 6 yrs)	Sex not indicated	Report Section 8, Volume 63, pg 8-03712 CRFs not available

* Fosfomycin tromethamine = fosfomycin trometamol.

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Clinical Trials Conducted in the United States

The investigational plan for the U.S. clinical development of the 3 g single dose regimen of fosfomycin included two double-blind/double-dummy, randomized, active-controlled, multicenter studies that compared the safety and efficacy of a single 3 g dose of fosfomycin with an approved comparator in adult female patients with acute uncomplicated urinary tract infections (cystitis). In each study, the same single 3 g dose regimen of fosfomycin was used. In MON-US-01 the active comparator was ciprofloxacin 250 mg, administered every 12 hours for seven days, in MON-US-02, trimethoprim/sulfamethoxazole, 160 mg/800 mg, given every 12 hours for ten days.

APPLICANT'S PROPOSED PACKAGE INSERT

PROTOCOL MON-US-01 Volume 1 54-1 55

Title

Single Dose Fosfomycin Tromethamine Versus Multiple Dose Ciprofloxacin for the Treatment Of Uncomplicated Urinary Tract Infections In Female Patients

Study Design

The study was a multi-center, randomized trial with double-blind, double-dummy design comparing the efficacy and safety of Monurol® (fosfomycin) Sachet and Ciprofloxacin Tablets in the treatment of adult women with acute cystitis

Study Population

Inclusion Criteria

- non-pregnant females ≥ 18 years of age

Medical Officer's Comment: In this pivotal U.S. trial, there were no patients enrolled less than 18 years of age. The applicant is seeking approval for cystitis for patients over 12 years of age

- clinical signs and/or symptoms of a UTI (e.g., dysuria, frequency, urgency) with onset of symptoms ≤ 96 hours prior to study entry
- one positive pre-treatment urine culture within 48 hours of enrollment in the study

Urine for culture was obtained by the clean-voided midstream catch method (N.B. Although urine obtained via catheter was allowed by protocol, in practice this was not done.) A single specimen containing $\geq 10^5$ CFUs of a uropathogen per milliliter of urine was considered a positive culture. If more than one organism was cultured, there must have been a minimum urine colony count of $\geq 10^5$ organisms per milliliter of at least one organism. Each organism cultured must have been present in a colony count of $\geq 10^5$ organisms per milliliter to have been considered an evaluable pathogen for eradication.

- susceptibility testing to both fosfomycin and ciprofloxacin

Study medication was started before the results of the urine culture were available to the investigator. If culture results showed that no organism was isolated, or that the organism isolated was not present in sufficient quantities or was not a known uropathogen, the patient (at the discretion of the investigator) was either removed from the study and treated according to the discretion of the investigator or completed the protocol-described treatment course and, in some cases, all study requirements. In either case, the patient was considered a screening failure and was not evaluable for efficacy analysis. The patient was evaluated for safety.

Exclusion Criteria

Patients were excluded from study participation for reasons that would jeopardize either patient safety or the reliability and accuracy of the efficacy data. The following patients were excluded:

- women who were pregnant, nursing, or not using a medically accepted, effective method of birth control;
- patients with recurrent urinary tract infections (greater than 3 UTIs within the preceding year);
- patients with evidence of factors predisposing to the development of urinary tract infections, including calculi, stricture, primary renal disease (e.g., polycystic renal disease), or neurogenic bladder;
- patients with the onset of symptoms for this episode of UTI for more than 96 hours;
- patients with a temperature ≥101°F, flank pain, chills, or any other manifestations suggestive of upper urinary tract infection;
- patients with known or suspected hypersensitivity to fosfomycin, nalidixic acid, ciprofloxacin, or other quinolones;
- patients with clinical evidence of severe renal impairment as determined by estimated creatinine clearance of < 30 ml/min;
- patients with clinical or laboratory evidence of hepatic dysfunction;
- patients who received theophylline, probenecid, or metoclopramide;
- patients with known or suspected CNS disorders such as severe cerebral arteriosclerosis or epilepsy, or other factors which would predispose the patient to seizures;
- patients with acute symptomatic vaginitis. *MO Comment: The applicant did not explain why patients with vaginitis were excluded from the study. If a patient had a positive urine culture (≥ 10^5 cfu/ml of a uropathogen and UTI symptoms), I included her in my analysis.*
- patients who had received treatment with other antimicrobials within 48 hours prior to entry;
- patients who had received any investigational compound within the previous two weeks;
- patients with granulocytopenia (<500/mm^3 polymorphonuclear leukocytes);
- patients with presence or evidence of another significant underlying disease which precluded evaluation of response to therapy, including states of immunosuppression;
- patients who did not have the ability to give written informed consent;
- patients who, in the opinion of the investigator, could not be relied upon for follow-up; or
- patients who within 96 hours prior to enrollment or during the trial, received urinary agents classified by the Physicians' Desk Reference as analgesics or anti-spasmodics.

Entry Procedures

Baseline assessments included complete history and physical examination, urinalysis, urine culture and sensitivities, blood chemistries (sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, uric acid, alkaline phosphatase, total bilirubin, SGPT, SGOT, and cholesterol) and hematologies (hemoglobin, red blood cells, hematocrit, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, and prothrombin time). Pyuria on urinalysis was routinely assessed at baseline but not an absolute criterion for inclusion. Urine culture results were routinely not known and the time of study entry. Patients were randomized to either treatment with fosfomycin or ciprofloxacin on a 1:1 schedule. Both the investigator and the patient were blinded to the treatment arm (all patients took either a dummy "fosfomycin" sachet or dummy "ciprofloxacin" tablets).

Study Drug Regimens and Information

The two treatment groups were:

Fosfomycin (FT) Group:	Fosfomycin, 3 g single dose plus placebo tablets every 12 hours for 7 days
Ciprofloxacin (CIPRO) Group:	Ciprofloxacin, 250 mg every 12 hours for 7 days plus one placebo sachet taken on the first day of dosing

Fosfomycin was supplied as single sachet packets containing 3 g of fosfomycin or identically appearing placebo. Ciprofloxacin tablets were obtained from , in bulk. They were packed in individual blister cards, each containing fourteen (14) 250 mg tablets of active drug or identically appearing placebo. The control agent, ciprofloxacin, was not altered in any way but it was repackaged so that it could be blinded for this study. Ciprofloxacin 250 mg was administered every 12 hours for seven days (a dosage recommendation in the approved manufacturer's Package Insert).

Each sachet and each blister card was labeled to show the sponsor, patient identification, patient number, directions for use, and storage conditions. The label consisted of identical fixed and tear-off portions. The portion of the label that was torn-off when medication was dispensed was affixed to the appropriate page of the case report form. All unused study medication was returned to the sponsor.

The study drugs used were the following:

Fosfomycin tromethamine, 3 g sachet (Batch Nos. 01268 and 11608)

Ciprofloxacin, 250 mg tablet (Batch Nos. SP-01-32 and KQ-9-33. Manufactured by

Placebo sachet (Batch No. 01495) Placebo tablets (Batch No. RM-14-92)

Evaluation Procedures

Study Day	Visit Name	Assessments
Day 0:	Visit 1	Baseline assessments included urinalysis, urine culture, complete history and physical examination, blood chemistries and hematologies.
Days 2-4:	Visit 1A	Patients were contacted by phone. If symptoms persisted, patients returned to clinic.
Days 5-9:	Visit 2	Visit with re-evaluation including history and physical examination, MSU culture, and urinalysis. This visit represents *either* the 5-9 day post-treatment visit for patients who received fosfomycin *or* an end-of-therapy/ just-off-therapy visit for patients who received ciprofloxacin.
Days 11-15:	Visit 3	Visit with re-evaluation including history and physical examination, MSU culture, and urinalysis. This visit represents *either* the 5-9 day post-treatment visit for patients who received ciprofloxacin *or* a 2-week post-therapy visit for patients who received fosfomycin.
Days 35-49:	Visit 4	Visit with re-evaluation including history and physical examination, MSU culture, and urinalysis. This is the 4-6 week post-therapy follow-up.

Outline of Study Procedures and Visits (MON-US-01)

	VISIT				
ASSESSMENT/ OBSERVATION	1 Baseline Day 0*	1A* Day 2-4	2 Day 5-9	3 Day 11-15	4 4-6 Week Post-Therapy
Inclusion/Exclusion	✓				
Informed Consent	✓				
Medical History	✓				
Physical Examination	✓				✓
Vital Signs	✓	✓	✓	✓	✓
Clinical Evaluation	✓	✓	✓	✓	✓
Pregnancy Test[b]	✓				
Bacteriology Quantitative Urine Culture and Susceptibility	✓	✓	✓	✓	✓
Urinalysis	✓	✓	✓	✓	✓
Hematology	✓		✓	✓	
Chemistry	✓		✓	✓	
Adverse Events	✓	✓	✓	✓	✓

[a] Study days are recorded throughout this report as shown above. Day 0 = Day of first dosing. Note that the protocol identifies days of dosing as Day 1.

[b] Visit 1A was an optional visit. Either a telephone contact or a visit was conducted at this time.

[c] Urine beta-hCG and serum pregnancy test were to be performed on all females of child bearing potential.

Applicant's Evaluability

The applicant performed two analyses for efficacy and defined evaluability in each as follows:

1. Intent-to-Treat (ITT)
Patients was analyzed in the efficacy analyses of the intent-to-treat (ITT) population if they were not screening failures (i.e., if they had a uropathogen $\geq 10^5$ cfu/ml). *Medical Officer's Comment: The applicant's ITT analysis is a modified intent-to-treat analysis since screening failures are not included.*

2. Evaluable Population
Patients was analyzed in the efficacy analysis of the evaluable population if they were
a- not screening failures
b- if they were found to have uropathogens that were susceptible to both antibiotics
c- if they were compliant with taking study medication (i.e., took $\geq$ 10 tablets of study medication)
d- if there were no protocol violations. Such protocol deviations of study inclusion or exclusion criteria that precluded patients from efficacy parameter analyses included:
   1- > 3 UTIs within the past year,
   2- active symptoms of vaginitis, *MO Comment: I didn't exclude patients with vaginitis from my analysis.*
   3- predisposing factors for UTI,
   4- administration of antimicrobial 48 hours prior to study,
   5- administration of analgesic/antispasmodic, *MO Comment: Only a few patients were excluded for this reason.*
   6- UTI symptoms occurred > 4 days, and
   7- other (evaluability reviewed prior to breaking the blind)

e- if the medical monitor deemed them appropriate for analysis
N.B. The medical monitor did not disqualify patients from analysis solely because of deviations from entry or study criteria. Patients were excluded from the efficacy analysis in the EVALUABLE population if, in the opinion of the medical monitor (after blinded review of medical and surgical histories), extenuating circumstances that compromised the validity of patient data warranted said exclusion.
Medical Officer's Comment: *The medical officer examined those cases made unevaluable by the medical monitor due to "extenuating circumstances that compromised the validity of patient data". These were all patients, who in the opinion of the investigator, met inclusion and exclusion criteria and were appropriate for enrollment in an uncomplicated UTI treatment trial. The medical officer reviewed the information and excluded only patients with clear-cut risks for complicated UTI (history of stones, strictures, neurogenic bladder, etc.)*

Medical Officer's Evaluability

The following criteria were used by the Medical Officer to define evaluability for efficacy:

1 women ≥ 18 years of age with clinical signs and symptoms of acute cystitis,

2 a positive urine culture (defined as growth of a uropathogen ≥ 10^5 cfu/ml);

3. medical history, physical examination and laboratory assessments (including urine culture) at

Visit 1	Day 0	Entry
Visit 2	Days 5-9	This visit represents *either* the 5-9 day post-treatment visit for patients who received single-dose fosfomycin *or* an end-of-therapy/ just-off-therapy visit for patients who received a seven-day course of ciprofloxacin. ***MO Comment:*** *The applicant accepted day 5-11 for visit 2, and I did the same for the sake of consistency in timing of visits. Throughout the rest of this review, "days 5-11" will be used to describe visit 2.*
Visit 3	Days 12-18	This visit represents *either* the 5-11 day post-treatment visit for patients who received ciprofloxacin *or* a 2-week post-therapy visit for patients who received fosfomycin. ***MO Comment:*** *Study days "12-18" were derived by simply adding the "5-11" day follow-up to a 7-day long course of cipro (i.e., 5+7=12, 11+7=18).*
Visit 4	Days 35-49	This is the 4-6 week post-therapy follow-up. ***MO Comment:*** *The applicant did not require this long-term follow-up for a patient to be included in their evaluable pool or modified ITT analysis. The majority of patients did have a long-term follow-up at least 25 days after the last dose of antibiotic. I required this long-term follow-up for patients to be included in my efficacy analysis.*

4. evidence of compliance

MO Comment: Since all patients were administered fosfomycin in the physician's office, there was 100% compliance with the sachet. The applicant excluded from the evaluable pool fosfomycin-treated patients who did not take all their "dummy" cipro tablets. I included these patients in my efficacy analysis. For patients treated with cipro, compliance was defined, per protocol, as taking ≥ 10 tablets of study medication

Outcome Assessments

Applicant's Bacteriologic Efficacy Definitions[1]

Bacteriological Cure:

A patient was defined to have a bacteriological cure if the following criteria were satisfied:

1. A culture was taken within the following appropriate time windows (Primary Evaluation Windows), when the initial treatment occurred on Day 0:

Study Drug	Time Window	Visit Number
Fosfomycin	Days 5-11	Visit 2
Ciprofloxacin	Days 12-18	Visit 3

2. All of the uropathogens, found at baseline at levels $\geq 10^5$ cfu/mL, were reduced to levels $\leq 10^4$ CFU/ml as evaluated in the Primary Evaluation Window. If more than one sample was taken within the window, the worst case was used.

   MO Comment: I used the term bacteriologic eradication and defined it as all uropathogens, found at entry at $\geq 10^5$ cfu/mL, reduced to $< 10^4$ cfu/mL by the "5-11 day" post-treatment visit (visit 2 for FT patients, visit 3 for Cipro patients).

Bacteriological Failure:

1. A patient who met Criterion #1 above and failed to meet Criterion #2 above was a bacteriological failure.
   MO Comment: A failing patient can present outside of the above time windows, since clinical symptoms may re-appear at any time and prompt an unscheduled visit. This information needs to be captured, and it is a critical difference between the applicant's analysis and mine, as illustrated by patient She presented with UTI symptoms 12 days after receiving a single-dose of fosfomycin. A urine culture from that visit was positive (>100,000 cfu/mL of the original pathogen, K. pneumoniae). The discontinuation reason noted by investigator was "treatment failure". The applicant assessed the patient's bacteriologic outcome as "no sample", and clinical evaluation as "no evaluation". I classified the patient as a bacteriologic persistence/clinical failure.

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[1] *MO Comment: I will note in comments any differences in definitions of microbiologic outcome assessments between the applicant and me.*

Applicant's Bacteriologic Efficacy Definitions (continued)

Bacteriological Failure: (continued)

2. For ciprofloxacin patients, the results from the Visit 2 culture were used if the Visit 3 culture was not available. In that circumstance, if during Visit 2, one or more of the uropathogens found at baseline at levels $\geq 10^5$ CFU/ml were at levels $>10^4$ CFU/ml and if the patient had an overall clinical evaluation of treatment of uncomplicated UTI that was classified as either improvement or failure, the patient was considered to have a bacteriological failure

MO Comment: Patients on ciprofloxacin, evaluated on day 5, could have as many as 3 more days of cipro to take (3/7= 43% of the course) to complete their week-long regimen of therapy. Hence, I don't agree with making a final assessment of a cipro-treated patient's outcome based solely on visit 2 unless clinical symptoms were not improving or were worsening compared to baseline and warranted switching to another antimicrobial.

Superinfection:

Superinfection was defined as the growth of $\geq 10^5$ CFU/ml of urine of a pathogen other than the baseline pathogen during the course of active therapy. By definition, this outcome could only occur for patients in the ciprofloxacin group as the fosfomycin group was treated with only a single dose of therapy. Thus, for ciprofloxacin-treated patients, if during Study Days 1-6, a pathogen not found at baseline at a level $\geq 10^5$ CFU/ml was found at a level $\geq 10^5$ CFU/ml, the patient was considered to have a superinfection.

Recurrence:

A patient was considered to have a recurrent infection if the following criteria were satisfied:

1. A culture was taken within the appropriate time window [visit 3 (study days 12-18) or visit 4 (4-6 weeks posttherapy) for fosfomycin; visit 4 (4-6 weeks posttherapy) for cipro
2. The patient had a documented bacteriological cure in the Primary Evaluation Window

Applicant's Bacteriologic Efficacy Definitions (continued)

Recurrence: (continued)

3. One or more of the cultures evaluated after [redacted]entation of a cure showed that the original pathogen, which was at a level $\geq 10^5$ CFU/ml at baseline, was at a level $\geq 10^5$ CFU/ml.

MO Comment: I defined the time frame for bacteriologic recurrence as anytime after documented eradication at the 5-11 day post-treatment window, up to and including the 4-6 week post-therapy visit. I considered a positive culture $\geq 10^4$ cfu/ml of the original uropathogen.

New Infection:

A patient was considered to have a new infection if the following criteria were satisfied:

1. A culture was taken within and/or after the appropriate time window
2. A pathogen, other than the species found at baseline at a level $\geq 10^5$ CFU/ml, was present at a level $\geq 10^5$ CFU/ml.

MO Comment: New infections can be documented in scheduled visits ("appropriate time window") as well as unscheduled visits prompted by a symptomatic patient. I defined the time frame for new infections as anytime after treatment finished.

Applicant's Clinical Efficacy Definitions[1]

The investigator provided an overall clinical evaluation of the patient's response of uncomplicated UTI made within the same time windows as bacteriological evaluation (Visits 2 and 3). Parameters assessed included flank tenderness, suprapubic tenderness, frequency, dysuria, burning and urgency. Symptoms were graded on a scale of 0-3 (0=absent, 1=mild, 2=moderate, 3=severe). The possible clinical outcomes were cure, improvement, failure, and not assessable

Cure:
All pre-therapy signs and symptoms had subsided in a reasonable period of time with no evidence of their resurgence at the follow-up visit 5-11 days after the first/last dose of fosfomycin, or 5-11 days after the last dose of ciprofloxacin.

Improvement:
Most, but not all, pre-therapy signs and symptoms had subsided in a reasonab period of time but without complete resolution at the follow-up visit 5-11 days after the rst/last dose of fosfomycin or 5-11 days after the last dose of ciprofloxacin.

Failure:
This was defined as no apparent response to therapy. This included persistence of all pre-therapy signs and symptoms at the follow-up visit 5-11 days after the first/last dose of fosfomycin and 5-11 days after the last dose of ciprofloxacin.

MO Comment: In the applicant's electronic files submitted for review, only clinical "cure", clinical "failure", or "no evaluation" appeared as outcomes. The applicant lumped clinical improvements and failures in the electronic database and considered a patient with one or more symptoms present at the follow-up visit [5-11 days after the first/last dose of fosfomycin, or 5-11 days after the last dose of ciprofloxacin], as a clinical failure. I also used only cure or failure clinical assessments, but defined clinical failure as the presence of two or more UTI symptoms of any severity (or one symptom of moderate to severe degree) at the 5-11 day post-treatment window. In my opinion, a patient with a single, mild UTI-type symptom may be reasonably assessed as a cure, whereas a patient with 2 or more on-going UTI symptoms 5-11 days after treatment will likely warrant further investigation and/or treatment, and is therefore reasonably assessed as a clinical failure.

Not Assessable
A clinical judgment of cure, improvement, or failure could r ' be made due to various reasons, i.e., improper dose or length of therapy, concomitant antimicrobial therapy, no pathogen isolated, therapy discontinued due to adverse events, inadequate colony count, susceptibility test not done, or lack of follow-up cultures. The investigator was required to state the circumstances which caused the case to be rated as not assessable. ***MO Comment:*** *Lack of susceptibility testing did not render a patient clinically unassessable in my analysis. Furthermore, no fosfomycin patient had an improper dose or length of therapy (all had 1 sachet administered in the investigator's office).*

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[1] *MO Comment: I will note in comments any differences in definitions of clinical outcome assessments between the applicant and me*

Safety Evaluation

Safety analyses (adverse events, laboratory evaluations, changes in physical examination and body weight, and changes in vital sign measurements) were performed on data from all patients randomized and enrolled into the clinical study who received at least one dose of study medication.

Safety assessments were made at all follow-up visits. Data were windowed to the following visits depending on the day of study as outlined below:

TABLE: Window of Days for Visits - Safety Evaluations
(STUDY MON-US-01)

Visit	Day*
2	5-11
3	12-18
4	> 18

* Day 0 is the first day of dosing.

Adverse Events

Patients were observed and questioned at each clinic visit regarding any somatic complaints they may have experienced throughout the double-blind treatment period. The true nature and severity of the adverse event, as well as the relationship of adverse events to study drug administration, were determined by the investigator after thorough consideration of all available facts.

Investigators graded adverse events on a three point scale, i.e., mild (discomfort without disruption of daily activity), moderate (discomfort sufficient to reduce or affect normal daily activity), or severe (incapacitating with inability to work or perform normal daily activity). The investigators were requested to judge whether the adverse event was related to study medication. The following definitions were used.

Definitely related: Relationship has been confirmed by discontinuation and rechallenge; remission and recurrence follow a reasonable temporal sequence.

Probably related:	Strong suspicion of drug association when type, time course, and relationship to dosing and/or dechallenge are considered.
Possibly related:	As suggested by type, time, course, relationship to taking of medication and external events; may follow a known response pattern to suspected drug but could have been produced by patient's clinical state and/or other therapy.
Unlikely:	Drug relationship very unlikely; no clear external cause; does not follow a known response pattern to drug.
Not related:	Clearly pre-existing or caused by a specific extraneous event; not worsened by the study treatment; not a known response pattern.

Clinical Laboratory Tests

The following laboratory tests were performed within 48 hours prior to the start of therapy, and were repeated at Visit 2 and Visit 3 (excluding pregnancy tests).

- Complete Blood Count
  [Included hemoglobin, hematocrit, red blood cell count, white blood cell count (total and differential), and quantitative platelet count]
- BUN and creatinine
- SGOT, SGPT, alkaline phosphatase, and serum bilirubin
- Sodium, potassium, chloride, and bicarbonate
- Uric acid
- Cholesterol
- Urinalysis (Included both biochemical and microscopic analysis)
- Serum pregnancy test and First Response® pregnancy test
  (Performed on all females of childbearing potential)
  MO Comment: Blood glucose was not monitored in this trial.

Additionally, the urinalysis was repeated at 4-6 weeks post-therapy.

All patients who were terminated from the study prematurely underwent appropriate laboratory evaluations. Unexplained abnormal laboratory tests were repeated and patients were followed until abnormal laboratory values returned to the normal range and/or an adequate explanation of the abnormality was found.

A central laboratory was used to perform all of the laboratory tests except the urinalysis and the urine culture that were performed by the local laboratory of the clinical site. The local clinical laboratories were either licensed or accredited.

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[a] Sites are not consecutively numbered
[b] Sites were shipped drug but did not enter patients

Medical Officer's Comment: The applicant did not consecutively number sites in this trial.

Patient Enrollment by Center

Thirty-two centers throughout the United States enrolled a total of 877 patients. The table below summarizes, by center, the number of patients enrolled, the number of patients in the *applicant's modified Intent-to-Treat (ITT)* analysis, in the *applicant's evaluable (EVAL) analysis*, and in the *Medical Officer's evaluable (MO)* patient population.

TABLE: **Distribution of Patients by Center - ALL Enrolled Patients Receiving Study Medication, Number of Patients per Treatment Group (STUDY MON-US-01)**

	FT	CIPRO
Center Number	**ALL Enrolled** *(ITT/EVAL SP/ MO)*	**ALL Enrolled** *(ITT/EVAL SP/ MO)*
1	3 (1/1/1)	5 (3/3/3)
2	5 (2/2/2)	6 (6/3/6)
3	0 (0)	2 (0)
4	35 (24/22/22)	35 (22/21/19)
5	19 (11/8/10)	19 (9/8/9)
6	6 (5/5/5)	8 (4/4/4)
7	7 (4/1/4)	8 (1/0/1)
8	1 (0/0/0)	2 (1/1/1)
9	10 (2/2/2)	10 (6/4/6)
10	4 (2/2/2)	5 (2/0/2)
11	28 (19/15/19)	30 (21/18/15)
12	5 (3/0/3)	5 (2/0/1)
13	1 (0/0/0)	1 (0/0/0)
14	16 (6/3/5)	17 (5/3/5)
15	25 (15/14/13)	26 (14/12/10)
16	7 (4/3/4)	6 (3/3/3)
17	28 (14/13/13)	28 (14/12/12)
18	23 (14/7/11)	22 (9/4/8)
19	7 (7/7/7)	7 (5/4/4)
41	11 (9/6/7)	10 (8/6/5)
42	36 (27/22/25)	38 (19/17/17)
43	10 (7/7/7)	10 (9/9/8)
44	26 (26/22/23)	26 (25/21/21)
45	13 (11/9/11)	13 (12/8/10)
46	29 (19/17/18)	23 (17/14/14)
47	26 (19/16/19)	25 (17/14/14)
48	12 (6/4/4)	11 (4/4/2)
49	2 (0/0/0)	3 (1/1/1)
50	22 (15/13/12)	22 (15/11/10)
51	10 (8/7/8)	11 (10/7/10)
52	0 (0/0/0)	1 (1/0/1)
56	5 (3/3/3)	5 (0/0)
Total 32	432 (283/231/260)	445 (265/212/222)

In summary, the table below presents patient numbers and percentages of population total, by treatment group, for each of the populations analyzed.

TABLE: **Applicant's** Distribution of Patients (STUDY MON-US-01)

Analysis Group (Population Identifier)	FT N (% of Pop.)	CIPRO N (% of Pop.)	TOTAL N (% of Pop.)
Patients Randomized, Enrolled and Treated, Valid for Safety Analysis (ALL)	432 (49)	445 (51)	877 (100)
Patients in the Intent-to-Treat Group- Valid for Efficacy Analysis (ITT)	283 (52)*	265 (48)*	548 (100)
Patients in the Sponsor's Evaluable Group- Valid for Efficacy Analysis (SP EVAL)	231 (52)	212 (48)	443 (100)

% of Pop. = Percentage of Population; N = Number of patients

**MO Comment: The applicant calculated the percentages in the above table incorrectly. The figures should be based on the number of patients randomized to each arm:*

283/432 (66%) 265/445 (60%)

Applicant's Exclusions from the Modified ITT and Evaluable Patient Populations

Thirty-four percent (34%) of the patients randomized and enrolled into the FT group (149/432) and 40% of patients randomized and enrolled into the CIPRO group (180/445) were screening failures (i.e., results of a urine culture performed within two days of study start did not document growth of a known uropathogen at $\geq 10^5$ CFU/mL). The screen failure rate was greater in the CIPRO group than in the FT group (p=0.07). However, both populations were subjected to the same criteria for defining screen failure, criteria that were determined prior to breaking the blind. The difference in screen failure rate was, therefore, not considered to have compromised the analyses of the modified ITT and EVALUABLE populations.

The 283 FT patients and 265 CIPRO patients who were not screening failures were evaluated as the modified ITT population. Of those, 82% (231/283) of the FT patients and 80% (212/265) of the CIPRO patients were deemed evaluable for efficacy analysis by the applicant and identified as the EVALUABLE population.

Not all patients classified as EVALUABLE population met all protocol-defined entrance criteria. The EVALUABLE subpopulation was comprised of those ITT patients who, in the opinion of the medical monitor, had uncomplicated UTI based on medical and surgical history, and for whom the initially susceptible, UTI-defining uropathogen was found to be susceptible to both fosfomycin and ciprofloxacin. In addition, EVALUABLE patients were

required to have taken at least 10 of 14 study medication tablets

Of the 105 patients who were excluded from the evaluable population compared to the modified ITT, 52 were in the FT group and 53 in the CIPRO group. Most patients were excluded because susceptibility of the infecting uropathogen to both drugs was not established. Thirty-seven patients in the fosfomycin group and 41 in the ciprofloxacin group had pathogens that were not susceptible to both study drugs. Of the remaining patients (potentially EVALUABLE), ten ITT patients (seven FT, three CIPRO) were excluded from the EVALUABLE population, prior to breaking the blind and after review of each patient by the medical monitor, for baseline deviations of protocol entrance requirements. Finally, of those still remaining, seventeen ITT patients (eight FT, nine CIPRO) were excluded from the EVALUABLE population because they were not compliant with study medication (took <10 tablets). There was no statistically significant, between-group difference in the number of patients considered evaluable for efficacy analysis (p=0.67).

Medical Officer's Comment *My analysis differed from the applicant's and resulted in larger numbers in my evaluable pool of patients for several reasons:*

1. I examined the case record forms, in a blinded fashion, of patients excluded from the evaluable pool by the medical monitor. If the investigator documented that the patient met all inclusion and exclusion criteria, and there was no history recorded to indicate that the patient was predisposed to a complicated UTI (stones, strictures, polycystic kidneys, neurogenic bladder), then I included such a patient in my evaluable pool.

2. If a fosfomycin-treated patient did not take the entire course of "dummy" ciprofloxacin tablets, I considered such a patient appropriate in the evaluable population in order to capture information on the efficacy of fosfomycin.

3. I did not exclude patients because sensitivity to both drugs was not measured or an isolate was "resistant" or "intermediate" in susceptibility to study drug(s).

a- Many investigators followed patients with "resistant" isolates until the end of the study. By the time culture and sensitivity results were available, patients were already several days beyond single-dose treatment or several days into a 10-day treatment regimen. Their clinical course guided the investigator at that point, not the susceptibility results.

b- Resistance is usually defined relative to serum, not urine levels.

c- The NCCLS has found problems with the breakpoints for fosfomycin. The applicant presented clinical and microbiologic data to the NCCLS, and due to the committee's lack of confidence in the results of the quality control strains for in-vitro testing, the NCCLS committee could reach no conclusions regarding the breakpoints. The applicant was advised to find a solution to their in-vitro testing problems.

Medical Officer's Exclusions from the Evaluable Population

Reason	Fosfomycin	Ciprofloxacin
Protocol violation	3	5
Lost to follow-up	12	12
Adverse Event	1	4
Concomitant Antimicrobials/other	.	7
Intercurrent Illness	1	3
Missing or late 5-11 day posttherapy visit	5	12
Screening failures	149	180
Total Unevaluable	172	223
Total Evaluable	260	222
Total Enrolled	432	445

Demographic and Baseline Characteristics

A total of 877 female patients were enrolled into the MON-US-01 clinical study across 32 centers. Four-hundred thirty-two patients (49%) were randomized to the fosfomycin (FT) treatment group and 445 patients (51%) were randomized to ciprofloxacin (CIPRO).

Patient race and age were recorded as basic demographic data. These parameters and other baseline characteristics (height, weight, birth control method, UTI history, and urogenital surgical history) were evaluated to determine the similarities and differences between treatment groups.

TABLE: **Demographic Summary (Race and Age) - *ALL Enrolled Patients* (MON-US-01)**

	FT [N=432] No. Pts. (%)	CIPRO [N=445] No. Pts. (%)	Test Group Comparison [p-value]
Race			
Caucasian	374 (87)	398 (89)	0.27
Black	41 (9)	28 (6)	
Hispanic	13 (3)	11 (2)	
Asian	2 (<1)	6 (1)	
Other	2 (<1)	2 (<1)	
Age Range (Years)			
	204 (47)	205 (46)	0.59
	153 (35)	171 (38)	
	40 (9)	49 (11)	
	35 (8)	20 (4)	
Age (Years)			
Median	32.0	33.0	
Mean	36.0	35.5	0.61
Standard Deviation	15.8	14.5	
Minimum			
Maximum			
Number	432	445	

TABLE Demographic Summary (Height and Weight) - ALL Enrolled (MON-US-01)

	FT [N=432]	CIPRO [N=445]	Test Group Comparison [p-value]
Height (Inches)			
Median	65.0	64.0	
Mean	64.6	64.4	0.32
Standard Deviation	2.6	2.8	
Minimum			
Maximum			
Number	427	443	
Weight (Pounds)			
Median	137.0	136.0	
Mean	146.0	144.6	0.57
Standard Deviation	33.9	34.2	
Minimum			
Maximum			
Number	431	443	

Medical Officer's Comment: *For all patients enrolled, the two treatment arms were balanced with regard to age, race, weight and sex. There were no appreciable changes in any parameter (race, age, or weight) in the derived populations (applicant's intent-to-treat, applicant's evaluable population, or the medical officer's evaluable population). For the sake of brevity, I will not reproduce those tables here.*

Methods of birth control utilized by patients entering the trial also characterized the populations. No statistically significant differences were noted in between treatment group comparisons of birth control practices.

TABLE: **Birth Control Methodology**[a]
Number of Patients Using Each Method - ALL Enrolled Patients
(STUDY MON-US-01)

Birth Control Methods	ALL Enrolled		
	FT [N=432] No. (%)	CIPRO [N=445] No. (%)	Treatment Group Comparison [p-value]
Oral contraceptive	142 (33)	137 (31)	0.52
Intrauterine device	2 (<1)	1 (<1)	0.62
Diaphragm	9 (2)	20 (4)	0.06
Condom	105 (24)	114 (26)	0.70
Spermicide	81 (19)	92 (21)	0.50
Sponge	11 (3)	11 (2)	1.00
Abstinence	5 (1)	11 (2)	0.21
Surgically Sterilized	118 (27)	115 (26)	0.65
Other[b]	59 (14)	58 (13)	0.84

[a] Note that patients may have utilized more than one method of birth control.

[b] Other methods included: jelly, condoms/foam, contraceptive foam, and partner sterilized

Medical Officer's Comment: *Twice the number of cipro-treated patients used diaphragms as a method of birth control. This difference did not achieve statistical significance. It is of interest that Fihn et al. were able to define use of a diaphragm, together with a history of recurrent UTI and high colony count in the urine (> 10^5 cfu/mL), as risk factors that predisposed for failure with single-dose treatment in a study of trimethoprim/sulfamethoxazole, single dose versus 10-day treatment (Ann Intern Med 1988;108:350-7).*

TABLE: UTI and Urogenital Surgical History - ALL Enrolled Patients (STUDY MON-US-01)

	FT [N=432]	CIPRO [N=445]	Test Group Comparison [p-value]
Number of Days Symptomatic[a]			
0	65 (15)	71 (16)	0.57
1	170 (39)	164 (37)	
2	126 (29)	146 (33)	
≥3	71 (16)	64 (14)	
UTIs in Previous 12 Months[b]			
0	298 (69)	308 (69)	0.33
1	86 (20)	102 (23)	
2	37 (9)	28 (6)	
≥3	11 (3)	7 (2)	
Previous Surgery			
None recorded	382 (88)	395 (89)	0.61
1 year prior	7 (2)	3 (<1)	
2 years prior	3 (<1)	3 (<1)	
2+ years prior	40 (9)	44 (10)	

( ) Percentage
[a]Dose date minus symptom onset date.
[b]Not including current UTI.

Medical Officer's Comment: *For all enrolled, the treatment arms are balanced with respect to duration of UTI symptoms prior to enrollment, number of UTIs in the previous 12 months, and prior urogenital surgery. For the derived patient populations (modified Intent-to-Treat and Evaluable), the treatment arms are also balanced with regard to UTI and urogenital surgical history. The overwhelming majority (90%) of patients in each arm had 1 or no urinary tract infections in the 12 months prior to study entry.*

Microbiologic Efficacy

Applicant's Analysis: Bacteriological Evaluation 5-11 Days Post-Treatment

Among patients in the modified ITT population, 83% (225/270) of FT patients and 99% (231/233) of CIPRO patients[3] were determined to have a bacteriological cure within the Primary Evaluation Window. The ninety-five percent one-sided confidence interval for the upper bound on the difference in the cure rates was 19.7%. Seventeen percent (45/270) of FT patients and 1% (2/233) of CIPRO patients in the ITT population were determined to have a bacteriological failure of therapy ($p<0.01$).

The table below presents the number and percentage of patients in each treatment group who were determined to be bacteriological failures or cures and the number of patients for whom bacteriological evaluation was not possible.

TABLE **Applicant's** Bacteriological Evaluation in the Primary Assessment Window - Modified ITT Population (MON-US-01)

	FT N (%)	CIPRO N (%)	Test Group Comparison [p-value]
CURE[a]	225[c] (83)	231 (99)	
FAILURE	45 (17)	2 (1)	< 0.01
NO EVALUATION	13[b]	32[b]	

[a] 95% one-sided confidence interval for the upper bound on the difference in the cure rates: 19.7%
[b] Not included in Total or Percentage calculation
[c] Inclusive of four patients with *E. coli* type different from that at baseline

Medical Officer's Comment: *In a intent-to-treat type of analysis, a "no evaluation" category seems odd. I reviewed the cases of the 13 FT-treated patients and 32 cipro-treated patients with "no evaluation". Of the 13 fosfomycin patients, two were clinical failures with bacteriologic persistence presenting outside the 5-11 day window. Of the 32 cipro patients, one was a clinical failure with bacteriologic persistence presenting outside the 5-11 day window. There are more cipro patients (15/32, all cures) in the "no evaluation" category simply because their follow-up (after a 7-day course of therapy) more often fell outside the 5-11 day post-therapy time frame.*

The correct 95% confidence interval is the <u>two-sided</u> calculation (-0.21, -0.11), showing inferiority.

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[3] Note that for 13 FT patients and 32 CIPRO patients, according to the applicant, bacteriological evaluation was not available and these patients were excluded from this analysis.

Applicant's Analysis: Bacteriological Evaluation 5-11 Days Post-Treatment (cont.)

Among EVALUABLE patients, 84% (189/224) of FT patients and 99% (187/188) of CIPRO patients[4] were determined to have a bacteriological cure within the Primary Evaluation Window. The ninety-five percent one-sided confidence interval for the upper bound on the difference in the cure rates was 19.2%.

Sixteen percent (35/224) of FT patients and 1% (1/188) of CIPRO patients in the EVALUABLE population were determined to have a bacteriological failure of therapy ($p<0.01$).

The table below presents the number and percentage of patients in each treatment group who were determined to be bacteriological failures or cures and the number of patients for whom bacteriological evaluation was not possible.

TABLE: **Applicant's Bacteriological Evaluation in the Primary Assessment Window -EVALUABLE Population** (STUDY MON-US-01)

	FT N(%)	CIPRO N(%)	Test Group Comparison [p-value]
CURE[a]	189[c] (84)	187 (99)	
FAILURE	35 (16)	1 (1)	< 0.01
NO EVALUATION	7[b]	24[b]	

[a] 95% one-sided confidence interval for the upper bound on the difference in the cure rates: 19.2%

[b] Not included in Total or Percentage calculation

[c] Inclusive of four patients with *E. coli* type different from that at baseline

Medical Officer's Comment: *It is not clear why the applicant defined evaluability in such a way that patients with "no evaluation" are in the evaluable pool. Based on the MO examination of all the patients in this "no evaluation" group, 3 of the 7 FT patients were investigator-assessed failures (two with bacteriologic persistence), while only 1 of the 24 cipro "no evaluation" patients was a failure (clinical failure with bacteriologic eradication). The reason for more cipro-treated patients in the "no evaluation" category is due to more cipro patients outside the 5-11 day post-treatment window and more cipro patients with intercurrent illnesses.*

Footnote "a" in the table gives a <u>one-sided</u> 95% confidence interval. The correct calculation to use is the <u>two-sided</u> 95% confidence interval (-0.21, -0.10), showing inferiority.

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[4] Note that for 7 FT patients and 24 CIPRO patients, according to the applicant, bacteriological evaluation was not available and these patients were excluded from this analysis

MO Results **5-11 DAY POST-TREATMENT**

Outcome	Fosfomycin N (%)	Cipro N (%)
Eradication	196 (75)	218 (98)
Persistence	54 (21)[5]	2 (1)
Presumed Persistence[6]	3 (1)	1 (< 1)
New infection	7 (3)	1 (< 1)
Total	260	222

MO "Collapsed" Efficacy 5-11 Days After Therapy

Outcome	Fosfomycin	Cipro
Eradication	203 (78)	219 (98)
Persistence	57 (22)	3 (2)

CI_{95} is (-0.26, -0.14), showing inferiority.

Medical Officer's Comment: *Specific examples of why I found more failures:*

Patient *treated with fosfomycin, had UTI symptoms and a positive urine culture (>100,000 cfu/mL of the original pathogen, K. pneumoniae) 12 days post-treatment. The original pathogen was sensitive to fosfomycin (18mm), resistant to cipro (18mm). Discontinuation reason noted by investigator is "treatment failure". The medical monitor called this patient unevaluable ("no sample, no evaluation"). I classified the patient as a bacteriologic persistence with clinical failure.*

Patient *treated with fosfomycin, had UTI symptoms and positive culture (>100,000 cfu/mL of the original pathogen, K. pneumoniae) 6 days after treatment. Disk sensitivity to both drugs was not performed according to the applicant, so the patient was dropped from the EVAL population. Investigator's discontinuation reason was "treatment failure". In fact, sensitivities were reported to both FT (21mm) and cipro (as an MIC, 0.25). Hence, the isolate was sensitive to both drugs, and I included the patient in the evaluable pool as a bacteriologic persistence, clinical failure.*

Patient *FT-treated patient was a bacteriologic failure at 5-11 day post-treatment visit with continued microscopic pyuria. Pt was not a part of sponsor's evaluable group since all dummy cipro tablets were not taken.*

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[5] Includes 3 patients with resistant isolates (zone size < 16mm) at entry: /S. saprophyticus, /S. saprophyticus, and /Proteus mirabilis

[6] Includes patients whose clinical symptoms had not cleared in the early posttherapy period but for whom a urine culture was not taken at the same time. Of the 3 fosfomycin-treated patients in this category, 2 received additional antimicrobials for cystitis, the third refused further participation in the study. The one cipro-treated patient also received additional antimicrobial treatment.

Medical Officer's Comment: *Given the double-blinded nature of the trial design, patients returning for the 5-11 day post-treatment assessment were represented by visit 2 for fosfomycin patients and visit 3 for cipro patients. Visit 3 (roughly 2 weeks after the initiation of treatment) permitted an assessment of imminent recurrences in the fosfomycin group. It is of interest to note that the IDSA Guidelines for Urinary Tract Infections (CID 1992;15 December) recommends, "When short courses of therapy are compared with longer courses, follow-up for both courses should be done 5-9 days after completion of the longer course." These data are tabulated below:*

MO Results **Day 12-18 of Study (5-9 days after completion of longer course)**

Outcome	Fosfomycin N (%)	Cipro N (%)
Eradication	187 (72)	218 (98)
Early Recurrence[7]	9 (3)	--
Persistence	54 (21)[8]	2 (1)
Presumed Persistence[9]	3 (1)	1 (< 1)
New infection	7 (3)	1 (< 1)
Total	260	222

MO "Collapsed" Efficacy Day 12-18 of Study (5-9 days after completion of longer course)

Outcome	Fosfomycin	Cipro
Eradication	194 (75)	219 (98)
Persistence	66 (25)	3 (2)

CI_{95} is (-0.29, -0.17), showing inferiority.

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[7] All 9 fosfomycin-treated patients with early bacteriologic recurrence had original uropathogens sensitive to fosfomycin (8 E. coli and 1 Proteus mirabilis)

[8] Includes 3 patients with resistant isolates (zone size < 16mm) at entry (/S. saprophyticus, /S. saprophyticus, and Proteus mirabilis)

[9] Includes patients whose clinical symptoms had not cleared in the early posttherapy period but for whom a urine culture was not taken at the same time. Of the 3 fosfomycin-treated patients in this category, 2 received additional antimicrobials for cystitis, the third refused further participation in the study. The one cipro-treated patient also received additional antimicrobial treatment

Late Follow Up: 4-6 Weeks Post-Therapy

Applicant's Analysis for the ITT Population

The sponsor presented long-term bacteriological outcomes by treatment group below.

TABLE: Sponsor's Bacteriological Evaluations of Superinfection, Recurrence and New Infection - ITT Population (STUDY MON-US-01)

	FT N(%) [N=283]	CIPRO N(%) [N=265]	Test Group Comparison [p-value]
Superinfection			
NO	N/A[b]	100 (100)	
YES	N/A	0 (0)	
NO SAMPLE/NOT EVALUABLE[a]	283	165	
Recurrence			
NO	183 (86)	210 (96)	< 0.01
YES	30[c](14)	8[d](4)	
NO SAMPLE/NOT EVALUABLE[a]	70[e]	47[f]	
New Infection			
NO	255 (91)	249 (96)	0.02
YES	25 (9)	10 (4)	
NO SAMPLE/NOT EVALUABLE[a]	3	6	

[a] See APPENDIX 10 for list of patients for whom bacteriological evaluation could not be made. **MO Comment**: *Appendix 10 is simply a list of patient ID numbers. No reason is given by the applicant.*
[b] FT patients received only a single dose of active therapy; therefore, no FT patients could meet the definition of superinfection.
[c] Eight (8) of these patients had *E. coli* type different from that at baseline.
[d] Three (3) of these patients had *E. coli* type different from that at baseline.
[e] Inclusive of 12 FT patients who were bacteriological cures, but had no final bacteriological outcome; therefore, recurrence could not be assessed.
[f] Inclusive of 13 CIPRO patients who were bacteriological cures, but had no final bacteriological outcome; therefore, recurrence could not be assessed.

***Medical Officer's Comment**. It does not appear in the applicant's table above that bacteriologic failures are carried over from the 5-11 day post-treatment assessment. The applicant doesn't state why the 165 cipro patients could not be assessed for superinfection. Presumably, some of these cipro patients had visit 2 (study day range 5-11) on day 8, 9, 10, or 11, which was off-therapy.*

Late Follow Up: 4-6 Weeks Post-Therapy (continued)

Applicant's Analysis for the EVALUABLE Population

TABLE: **Bacteriological Evaluations of Superinfection, Recurrence and New Infection** - EVALUABLE Population (STUDY MON-US-01)

	FT N(%) [N=231]	CIPRO N(%) [N=212]	Test Group Comparison [p-value]
Superinfection			
NO	N/A[b]	80 (100)	
YES	N/A	0 (0)	
NO SAMPLE/NOT EVALUABLE[a]	231	132	
Recurrence			
NO	153 (85)	173 (96)	< 0.01
YES	28[c](15)	7[d](4)	
NO SAMPLE/NOT EVALUABLE[a]	50[e]	32[f]	
New Infection			
NO	209 (92)	196 (97)	0.06
YES	18 (8)	7 (3)	
NO SAMPLE/NOT EVALUABLE[a]	4	9	

[a] See APPENDIX 11 for list of patients for whom bacteriological evaluation could not be made.
[b] FT patients received only a single dose of active therapy; therefore, no FT patients could meet the definition of superinfection.
[c] Seven (7) of these patients had *E. coli* type different from that at baseline.
[d] Three (3) of these patients had *E. coli* type different from that at baseline.
[e] Inclusive of 8 FT patients who were bacteriological cures, but had no final bacteriological outcome; therefore, recurrence could not be assessed.
[f] Inclusive of 7 CIPRO patients who were bacteriological cures, but had no final bacteriological outcome; therefore, recurrence could not be assessed.

Late Follow Up: 4-6 Weeks Post-Therapy (continued)

MO Results

Outcome	Fosfomycin N (%)	Cipro N (%)
Eradication	148 (57)	192 (87)
Late Recurrence	19 (7)	11 (5)
Late New Infection	10 (4)	5 (2)
Late Presumed Recurrence[10]	2 (1)	6 (3)
Clinical Failures at the 5-11 day post-therapy visit[11]	8 (3)	4 (2)
Sub-total	187	218
Early Recurrence	9 (3)	0
Persistence	54 (21)[13]	2 (1)
Presumed Persistence[14]	3 (1)	1 (< 1)
New infection	7 (3)	1 (< 1)
Total	260	222

MO Comment: If one combines all patients with "eradication", "new infections", and "clinical failures with documented bacteriologic eradication", the data can be collapsed as indicated below.

MO "Collapsed" Efficacy at the 4-6 Week Follow-Up

Outcome	Fosfomycin	Cipro
Eradication	173 (67)	202 (91)
Persistence	87 (33)	20 (9)

CI_{95} is (-0.31, -0.17), showing inferiority.

[10] These patients with "late presumed recurrence" had clinical symptoms of cystitis which reappeared at the 4-6 week follow-up, but for whom a urine culture was not done

[11] These patients were clinical failures/bacteriologic eradication at the early follow-up (5-11 days post-therapy) who received another course of antimicrobial therapy based on their clinical presentation. Therefore, a late bacteriologic assessment could not be made

The table below presents the applicant's bacteriological cure rates at end of treatment, by isolated baseline pathogen, for the modified ITT population.

TABLE **Applicant's Bacteriological Cure Rate in the Primary Assessment Window by Pathogen - ITT Population** (STUDY MON-US-01)

Pathogens	FT No. Cures/Total(%)	CIPRO No. Cures/Total(%)
Enterobacter	0/0 (-)	1/1 (100)
Enterobacter aerogenes	2/3 (67)	3/3 (100)
Enterobacter agglomerans	0/0 (-)	1/1 (100)
Enterobacter cloacae	1/1 (100)	5/5 (100)
Enterococcus	3/4 (75)	2/2 (100)
Enterococcus faecalis	5/5 (100)	0/0 (-)
Escherichia coli	201/232 (87)	194/196 (99)
Klebsiella	2/3 (67)	2/2 (100)
Klebsiella ozaenae	0/0 (-)	0/0 (-)
Klebsiella pneumoniae	10/13 (77)	6/6 (100)
Proteus	0/1 (0)	0/0 (-)
Proteus mirabilis	6/9 (67)	7/7 (100)
Providencia	1/1 (100)	0/0 (-)
Pseudomonas	0/0 (-)	0/0 (-)
Staphylococcus saprophyticus	5/9 (56)	12/12 (100)
Streptococcus Group D	1/1 (100)	0/0 (-)
Streptococcus faecalis	0/0 (-)	1/1 (100)
TOTAL ISOLATES	**237/282 (84%)**	**234/236 (99%)**

MO Comment: 95% CI on all isolates is (-0.20, -0.10), showing inferiority.
N/N = Number of patients with cure/total number of patients with pathogen
Note: More than one pathogen may have been isolated from one patient. Therefore, the number of pathogens may exceed the number of patients.

Susceptibility testing on *S. saprophyticus* showed three of the four isolates tested out of nine isolates available from FT-treated patients were resistant to FT, while only one of the 13 tested out of 14 total isolates in the CIPRO-treated patients was resistant to CIPRO.

Applicant's Bacteriologic Cure Rate by Pathogen - EVALUABLE Population

The most prevalent pathogen in the evaluable patients was *E. coli*. In the fosfomycin patients, there was a total of 204 patients with an infection caused by *E. coli* of which 87% (177/204) were classified as a bacteriological cure. Among the 171 ciprofloxacin-treated patients in whom *E. coli* was isolated, the bacteriological cure rate was 99% (170/171). There were fewer than ten evaluable patients with any one other pathogen in either treatment group.

TABLE 4.39. Bacteriological Cure Rate in the Primary Assessment Window by Pathogen - EVALUABLE Population (STUDY MON-US-01)

Pathogens	FT No. Cures/Total(%)	CIPRO No. Cures/Total(%)
Enterobacter	0/0 (-)	1/1 (100)
Enterobacter aerogenes	1/2 (50)	0/0 (-)
Enterobacter agglomerans	0/0 (-)	0/0 (-)
Enterobacter cloacae	1/1 (100)	3/3 (100)
Enterococcus	2/2 (100)	1/1 (100)
Enterococcus faecalis	2/2 (100)	0/0 (-)
Escherichia coli	177/204 (87)	170/171 (99)
Klebsiella	2/3 (67)	1/1 (100)
Klebsiella pneumoniae	5/7 (71)	3/3 (100)
Proteus	0/1 (0)	0/0 (-)
Proteus mirabilis	5/7 (71)	5/5 (100)
Providencia	1/1 (100)	0/0 (-)
Staphylococcus saprophyticus	3/4 (75)	6/6 (100)
Streptococcus Group D	1/1 (100)	0/0 (-)

N/N = Number of patients with cure/total number of patients with pathogen
Cross-Reference: APPENDIX 24
Note: More than one pathogen may have been isolated from one patient. Therefore, the number of pathogens may exceed the number of patients.

TABLE **Medical Officer's** Bacteriological Eradication Rate at the 5-11 Day Post-Therapy Window by Pathogen - (MON-US-01)

Pathogens	FT No. Eradicated/Total(%)	CIPRO No. Eradicated/Total(%)
Enterobacter	0/0 (-)	1/1 (100)
Enterobacter aerogenes	2/3 (67)	3/3 (100)
Enterobacter agglomerans	0/0 (-)	0/0 (-)
Enterobacter cloacae	1/1 (100)	5/5 (100)
Enterococcus	3/4 (75)	1/1 (100)
Enterococcus faecalis	5/5 (100)	0/0 (-)
Escherichia coli	175/216 (81)	184/187 (98)
Klebsiella	2/3 (67)	2/2 (100)
Klebsiella pneumoniae	7/11 (64)	4/4 (100)
Proteus	0/1 (0)	0/0 (-)
Proteus mirabilis	6/9 (67)	7/7 (100)
Providencia	1/1 (100)	0/0 (-)
Staphylococcus saprophyticus	4/9 (44)	12/12 (100)
Streptococcus Group D	1/1 (100)	0/0 (-)
TOTAL ISOLATES	**207/264 (78%)**	**219/222 (98%)**

95% CI on all isolates is (-0.26, -0.14), showing inferiority.

Note: More than one pathogen may have been isolated from one patient. Therefore, the number of pathogens may exceed the number of patients.

***Medical Officer's Comment**: The overwhelming majority of patients in both treatment arms had E. coli isolated as the uropathogen. No other isolate, with the exception of K. pneumoniae for fosfomycin-treated patients and S. saprophyticus for cipro patients, numbered greater than 10 per treatment arm.*

TABLE **Medical Officer's Bacteriological Eradication Rate at Study Day 12-18** (5-11 days after completion of the longer course/cipro) (MON-US-01)

Pathogens	FT No. Eradicated/Total(%)	CIPRO No. Eradicated/Total(%)
Enterobacter	0/0 (-)	1/1 (100)
Enterobacter aerogenes	2/3 (67)	3/3 (100)
Enterobacter agglomerans	0/0 (-)	0/0 (-)
Enterobacter cloacae	1/1 (100)	5/5 (100)
Enterococcus	3/4 (75)	1/1 (100)
Enterococcus faecalis	5/5 (100)	0/0 (-)
Escherichia coli	167/216 (77)	**184/187 (98)**
Klebsiella	2/3 (67)	2/2 (100)
Klebsiella pneumoniae	7/11 (64)	4/4 (100)
Proteus	0/1 (0)	0/0 (-)
Proteus mirabilis	5/9 (56)	7/7 (100)
Providencia	1/1 (100)	0/0 (-)
Staphylococcus saprophyticus	4/9 (44)	12/12 (100)
Streptococcus Group D	1/1 (100)	0/0 (-)
TOTAL ISOLATES	**198/264 (75%)**	**219/222 (99%)**

95% CI on total isolates is (-0.30, -0.18), showing inferiority.

Note: More than one pathogen may have been isolated from one patient. Therefore, the number of pathogens may exceed the number of patients.

TABLE **Medical Officer's Bacteriological Eradication Rate 4-6 Weeks Post-Therapy** (STUDY MON-US-01)

Pathogens	FT No. Eradicated/Total(%)	CIPRO No. Eradicated/Total(%)
Enterobacter	0/0 (-)	0/1 (0)
Enterobacter aerogenes	2/3 (67)	3/3 (100)
Enterobacter agglomerans	0/0 (-)	0/0 (-)
Enterobacter cloacae	1/1 (100)	5/5 (100)
Enterococcus	3/4 (75)	1/1 (100)
Enterococcus faecalis	5/5 (100)	0/0 (-)
Escherichia coli	149/216 (69)	168/187 (90)
Klebsiella	2/3 (67)	2/2 (100)
Klebsiella pneumoniae	6/11 (55)	4/4 (100)
Proteus	0/1 (0)	0/0 (-)
Proteus mirabilis	4/9 (44)	7/7 (100)
Providencia	1/1 (100)	0/0 (-)
Staphylococcus saprophyticus	4/9 (44)	12/12 (100)
Streptococcus Group D	1 1 (100)	0/0 (-)
TOTAL ISOLATES	**178/264 (67%)**	**202/222 (91%)**

95% CI on all isolates is (0.31, -0.17), showing inferiority.

Note: More than one pathogen may have been isolated from one patient. Therefore, the number of pathogens may exceed the number of patients.

Clinical Efficacy

The applicant made the following clinical assessments 5-11days posttherapy:

TABLE: **Applicant's** Clinical Evaluation in Primary Assessment Window - Modified ITT Population (STUDY MON-US-01)

Clinical Outcome	FT N(%)	CIPRO N(%)	Test Group Comparison [p-value]
Cure[a]	207(81)	217(94)	<0.01
Improvement	40(16)	13(6)	
Failure	9(4)	0(-)	
No Evaluation[b]	27	35	

[a] 95% one-sided confidence interval for the upper bound on the difference in the cure rates: 18.2%
[b] See APPENDIX 12 for a list of patients for whom a clinical evaluation could not be made

Cross-Referer APPENDIX 24 and Raw Data Listing 9.

TABLE: Clinical Evaluation in Primary Assessment Window - EVALUABLE Population (STUDY MON-US-01)

	FT N(%)	CIPRO N(%)	Test Group Comparison [p-value]
Cure[a]	177 (83)	178 (95)	<0.01
Failure	37(17)	10(5)	
No Evaluation[b]	17	24	

[a] 95% one-sided confidence interval for the upper bound on the difference in the cure rates: 17.0%
[b] See APPENDIX 13 for a list of patients for whom a clinical evaluation could not be made.

Note that patients in the EVALUABLE population who were clinically "improved" were considered to be clinical failures in this analysis.

Medical Officer's Comment: *The applicant's analysis with a "no evaluation" category requires comment. In order to be considered evaluable in the company's "EVAL" population, a patient needed to have a uropathogen at 10^5 cfu/mL, no protocol violations, organism with susceptibility to both drugs, and medical compliance. In addition, patients were required to fall within the 5-11 day post-treatment window for follow-up, whether they were cures or failures. I have listed the 17-FT patients and 24-cipro patients below, with the applicant's clinical assessment, mo's clinical assessment, mo evaluability, and mo comments with investigators' assessments. Of the applicant's 17 "no evaluation" patients treated with fosfomycin, 11 were clinical failures according to the investigator and medical officer. Of the 24 cipro patients with "no evaluation", 3 were clinical failures according to the investigator and medical officer. The applicant's analysis underestimates the number of patient's with clinical failure, more in the fosfomycin arm than the cipro arm.*

Listing of Patients with "No Evaluation" in Applicant's Clinical Efficacy Table(5-11 Days Post-Treatment)

Pt No.	Treat	Ap Clin	Mo Clin	Mo Eval	Mo Comments
	Cipro			No	Concom Antimicrobial/Other
	Cipro	No Eval	Cure	No	Toc Beyond 5-11days/Cure
	Cipro	No Eval	Cure	No	Toc Beyond 5-11days/Cure
	Cipro	No Eval		No	Concom Antimicrobial/Other
	Cipro			No	Concom Antimicrobial/Other
	Cipro	No Eval	Cure	No	Toc Beyond 5-11days/Cure
	Cipro	No Eval	Cure	Yes	Toc Study Day 18
	Cipro	No Eval	Cure	No	Toc Beyond 5-11days/Cure
	Cipro	No Eval	Fail	Yes	Investigator: "Clinical Recurrence"
	Cipro	No Eval	Cure	No	Toc Beyond 5-11days/Cure
	Cipro	No Eval	Fail	Yes	Investigator: "Treatment Failure"
	Cipro			No	Concom Antimicrobial/Other
	Cipro	No Eval	Cure	No	Lost to Follow-Up
	Cipro	No Eval	Fail	Yes	Investigator: "Treatment Failure"
	Cipro	No Eval	Cure	Yes	Toc Study Day 18
	Cipro	No Eval	Cure	No	Toc Beyond 5-11days/Cure
	Cipro	No Eval	Cure	No	Toc Beyond 5-11days/Cure
	Cipro	No Eval	Cure	Yes	Toc Study Day 18
	Cipro	No Eval		No	Lost to Follow-Up
	Cipro	No Eval		No	Concom Antimicrobial/Other
	Cipro	No Eval		No	Lost to Follow-Up
	Cipro		Cure	No	Intercurrent Medical Illn
	Cipro		Cure	No	Protocol Viol
	Cipro			No	Intercurrent Medical Illn
	Ft	No Eval	Cure	Yes	Toc Beyond 5-11days/Cure
	Ft	No Eval	Fail	Yes	Investigator: "Treatment Failure"
	Ft	No Eval	Fail	Yes	Investigator: "Treatment Failure"
	Ft	No Eval	Fail	Yes	Investigator: "Treatment Failure"
	Ft	No Eval		No	No Toc
	Ft	No Eval	Cure	No	No Toc
	Ft	No Eval	Fail	Yes	Investigator: "Treatment Failure"
	Ft	No Eval	Fail	Yes	Investigator: "Treatment Failure"
	Ft	No Eval	Fail	Yes	Investigator: "Treatment Failure"
	Ft	No Eval	Fail	Yes	Investigator: "Treatment Failure"
	Ft		Fail	Yes	Investigator: "Treatment Failure"
	Ft	No Eval	Cure	No	Toc Beyond 5-11days/Cure
	Ft		Fail	Yes	Investigator: "Treatment Failure"
	Ft	No Eval	Fail	Yes	Investigator: "Treatment Failure"
	Ft	No Eval		No	No Toc
	Ft	No Eval	Fail	Yes	Investigator: "Treatment Failure"
	Ft	No Eval	Cure	Yes	Investigator: "Completed Study"/Cure

Clinical Efficacy (continued)

MO Results *5-11 Days Post-Treatment*

Outcome	Fosfomycin N (%)	Cipro N(%)	
Cure	199 (77)	213 (96)	CI_{95} (-0.25, -0.13), showing inferiority
Failure	61 (23)	9 (4)	
Total	260	222	

Day 12-18 of Study

Outcome	Fosfomycin N (%)	Cipro N (%)	
Cure	189 (73)	212 (95)	CI_{95} (-0.29, -0.16), showing inferiority
Early Relapse	10 (4)	1 (<1)	
Failure (carried)	61 (23)	9 (4)	
Total	260	222	

4-6 Weeks Post-Treatment

Outcome	Fosfomycin N (%)	Ciprofloxacin N(%)	
Cure	153 (59)	196 (88)	CI_{95} (-0.37, -0.22), showing inferiority
Relapse	16 (6)	14 (6)	
Unassessable[12]	20 (8)	2 (1)	
Sub-total	189	212	
Early Relapse(carried)	10 (4)	1 (<1)	
Failure (carried)	61 (23)	9 (4)	

[12]Assessment at the 5-11 day window was clinical cure/bacteriologic persistence, and patient was re-treated with antibiotics. Thus, a late clinical assessment is not possible

SAFETY EVALUATION

All patients randomized to receive study drug were included in the safety assessment: 432 patients treated with fosfomycin and 445 patients treated with ciprofloxacin. Those assessments included: incidence and severity of adverse events, discontinuations from study due to adverse event and intercurrent illness, and changes in clinical laboratory findings (serum and urine).

Adverse Events (AEs):

Deaths: There were no deaths in this study.

Discontinuation due to AEs:

Six patients in each of the treatment groups (1% of each group) were discontinued from the study due to adverse events. The adverse events requiring discontinuation from study for fosfomycin-treated patients were: diarrhea in one patient, diarrhea, abdominal cramps and vertigo in one patient, hives in one patient, herpetic vulvovaginitis requiring hospitalization in one patient, transient elevations in serum enzymes in one patient, and stomach pains/gas in one patient. Among ciprofloxacin-treated patients who discontinued from the study due to adverse events, the following were reasons given: rash in two patients, tachycardia in one patient, nausea and headache in one patient, nausea, headache and dizziness in one patient, and dizziness in one patient.

MO Comment: According to the investigators' assessments, 11/432 (3%) FT-treated patients and 13/445 (3%) cipro-treated patients discontinued due to adverse events. It is not clear how long "continuous" symptoms lasted, since the patient was dropped from the study and no further information was provided on the case report form:

Patient	Rx	Adverse Event (AE)	1st Dose	AE Start	AE Stop
	Ft	Mild Diarrhea	5/22/91	5/22/91	5/25/91
	Ft	Mod Hives/Urticaria	2/26/91	2/27/91	3/1/91
	Ft	Mild Abdom Cramps	8/6/91	8/6/91	continuous
	Ft	Severe Diarrhea	8/6/91	8/6/91	continuous
	Ft	Mild vertigo	8/6/91	8/6/91	continuous
	Ft	Severe Herpetic Vulvovaginitis	10/27/92	11/9/92	11/16/92
	Ft	Mod Hiatal Hernia	10/27/92	11/9/92	continuous
	Ft	Mild Yeast Infection	10/27/92	11/1/92	11/7/92
	Ft	Severe Abnormal Labs	4/24/92	5/8/92	7/23/92
	Ft	Moderate Gas	2/17/93	2/17/93	2/25/93
	Ft	Moderate Stomach Pains	2/17/93	2/17/93	2/25/93
	Cipro	Mild Rash	5/10/91	5/11/91	5/13/91
	Cipro	Mild Rash	7/26/91	7/28/91	7/30/91
	Cipro	Mod Diarrhea	7/23/92	7/24/92	7/24/92
	Cipro	Mod Irreg Heartbeat	7/23/92	7/28/92	7/29/92
	Cipro	Mod Ortho Dizziness	7/23/92	7/25/92	7/30/92
	Cipro	Mod Queasy Stomach	7/23/92	7/25/92	7/30/92
	Cipro	Severe Diarrhea	6/12/92	6/15/92	6/16/92
	Cipro	Severe Headache	6/12/92	6/14/92	6/16/92
	Cipro	Moderate Nausea	6/12/92	6/12/92	6/16/92
	Cipro	Moderate Dizziness	7/22/92	7/22/92	continuous
	Cipro	Moderate Headache C 7/22/92	7/22/92		
	Cipro	Mild Nausea C /22/92	7/22/92		
	Cipro	Moderate Dizzy	1/28/93	1/29/93	1/30/93

Twelve patients (5/432 FT, 7/445 CIPRO) were discontinued from the study due to intercurrent illness. The illnesses requiring discontinuation from study for FT patients were: urethral irritation with white vaginal discharge in one patient, pleurisy, bronchitis and congestion in one patient, vaginal infection in one patient, upper respiratory tract infection in one patient and sinusitis in one patient. Among CIPRO patients who discontinued the study due to intercurrent illness, the following reasons were given: breast infection in one patient, bronchitis in two patients, bronchial upper respiratory infection in one patient, acute vaginitis in one patient, probable gastroenteritis in one patient and diverticulitis with a Mallory-Weiss tear in one patient.

Serious Adverse Events:

Two patients were hospitalized during the course of the study. One patient (ciprofloxacin group) was diagnosed as having diverticulitis and diverticular abscess. Endoscopy revealed a Mallory-Weiss tear. The second patient (fosfomycin group) had urinary retention secondary to severe herpetic vulvovaginitis caused by herpes. Both adverse events met the definition of a serious event but neither were considered to be study drug related. In addition, one CIPRO patient was seen in a hospital emergency room for tachycardia and another was treated as an outpatient for a broken hand.

Summary of All Adverse Events

In this clinical study, 199 of 432 (46%) FT patients and 193 of 445 (43%) CIPRO patients reported at least one adverse event during the study period. A total of 383 adverse events were reported by FT patients and 348 events were reported by CIPRO patients. The majority of these adverse events were considered to be mild to moderate in severity. The only statistically significant difference between the treatment groups was in the metabolic and nutritional body system. This difference is largely due to a greater incidence of blood chemistry changes in FT patients than in CIPRO patients. These laboratory changes were not considered to be clinically significant. The table below presents the body systems and the number of events reported in each.

TABLE **Occurrences of Adverse Events and Number of Patients (Safety Population) Experiencing an Adverse Reaction by Body System (STUDY MON-US-01)**

	FT (N=432)		CIPRO (N=445)		
BODY SYSTEM	Occurrences of AEs	Number of Pts	Occurrences of AEs	Number of Pts	Treatment Group Comparison (p-value)*
BODY AS A WHOLE	146	102	133	94	0.42
CARDIOVASCULAR	8	7	6	6	0.79
DIGESTIVE	78	60	64	51	0.31
HEMIC AND LYMPHATIC	3	3	3	3	1.00
METABOLIC AND NUTRITIONAL	11	9	3	2	**0.04**
MUSCULOSKELETAL	5	5	11	10	0.30
NERVOUS	18	17	16	16	0.86
RESPIRATORY	34	27	35	32	0.59
SKIN AND SKIN STRUCTURES	18	16	21	19	0.73
SPECIAL SENSES	2	2	8	7	0.18
UROGENITAL	60	53	49	43	0.24
OVERALL	383 events reported by 199 patients		348 events reported by 193 patients		

*Fisher's Exact Test

The table below presents the individual adverse events in the "metabolic and nutritional" body system.

TABLE **Occurrences of Adverse Events in the Metabolic and Nutritional Body System (STUDY MON-US-01)**

METABOLIC AND NUTRITIONAL BODY SYSTEM	FT [N=432]			CIPRO [N=445]		
	Occurrences of AEs	Number of Pts.	% of FT Pts.	Occurrences of AEs	Number of Pts.	% of CIPRO Pts
SGPT Increased	3	3	0.7	1	1	0.2
SGOT Increased	2	2	0.5	1	1	0.2
Alkaline Phosphatase Increased	0	0	0.0	1	1	0.2
Bilirubin Elevated	1	1	0.2	0	0	0.0
Cholesterol Increased	1	1	0.2	0	0	0.0
Gout	1	1	0.2	0	0	0.0
Hypoglycemia	1	1	0.2	0	0	0.0
Lab Test Abnormal	1	1	0.2	0	0	0.0
Uric Acid Elevated	1	1	0.2	0	0	0.0
TOTALS	11	9	2.1	3	2	0.4

Adverse Events Occurring in ≥ 1.0% of the Patients (Most Common Adverse Events)

TABLE Occurrences of Adverse Events ≥ 1.0%[a] of the Patients - All Body Systems
STUDY MON-US-01

BODY SYSTEM	FT [N-432] Occurrences of Adverse Events	FT [N-432] No. of Patients	FT [N-432] % FT Patients	CIPRO [N-445] Occurrences of Adverse Events	CIPRO [N-445] No. of Patients	CIPRO [N-445] % CIPRO Patients	Treatment Group Comparison (p-value)[c]
Body as a Whole[b]	**146**	**102**	—	**133**	**94**	—	
Headache	50	38	8.8	56	42	9.4	0.82
Yeast infection	13	13	3.0	22	20	4.5	0.29
Backache	16	15	3.5	12	11	2.5	0.43
Cold	11	10	2.3	9	9	2.0	0.82
Abdominal pain	9	8	1.9	2	2	0.4	0.06
Tired	6	6	1.4	2	2	0.4	0.17
Cardiovascular[b]	**8**	**7**	—	**6**	**6**	—	
Migraine	5	5	1.2	2	2	0.4	0.28
Digestive[b]	**78**	**60**	—	**64**	**51**	—	
Diarrhea	34	33	7.6	22	19	4.3	0.04
Nausea	18	18	4.2	22	21	4.7	0.75
Stomach upset	6	6	1.4	3	3	0.7	0.34
Nervous[b]	**18**	**17**	—	**16**	**16**	—	
Dizziness	9	8	1.9	10	10	2.2	0.91
Respiratory[b]	**34**	**27**	—	**35**	**32**	—	
Congestion	7	6	1.4	5	5	1.1	0.77
Cough	4	4	0.9	5	5	1.1	1.00
Sinusitis	4	4	0.9	5	5	1.1	1.00
Sore throat	2	2	0.5	6	6	1.3	0.29
Skin and Skin Structures[b]	**18**	**16**	—	**21**	**19**	—	
Rash	**10**	**10**	**2.3**	**3**	**3**	**0.7**	**0.05**
Herpes simplex	0	0	0.0	5	5	1.1	0.06
Urogenital[b]	**60**	**53**	—	**48**	**43**	—	
Vaginal itching	10	10	2.3	8	8	1.8	0.64
Vaginitis	8	7	1.6	8	8	1.8	1.00
Urinary symptoms	8	8	1.9	4	4	0.9	0.26
Menstrual cramps	7	6	1.4	3	3	0.7	0.34
Vaginal discharge	4	4	0.9	6	6	1.3	0.75

a Full listing of adverse events in APPENDIX 15
b Total number of adverse events for Body System
c Fisher's Exact Test

The table below summarizes the adverse events that were, in the opinion of the investigator, probably or definitely related to study drug administration. *MO Comment: This is a study primarily of young, healthy women (50% between 18 and 30 years of age, 80% between 18 and 50 years of age), with a long list of exclusion criteria detailed earlier in this review that selected out patients with significant medical histories. As such, I think most of the adverse events reported by patients could fit into the category of "possibly related to study drug", if not probably or definitely related*

TABLE **Adverse Events That Were Classified as Probably or Definitely Related to Study Drug**
All Body Systems (STUDY MON-US-01)

	FT [N=432]			CIPRO [N=445]		
BODY SYSTEM	Occurrences of Adverse Events	No. of Patients	% FT Patients	Occurrences of Adverse Events	No. of Patients	% CIPRO Patients
Body as a Whole (Total)	**9**	**9**	—	**9**	**6**	—
Abdominal pain	1	1	0.2	0	0	0.0
Headache	1	1	0.2	5	2	0.4
Fatigue	1	1	0.2	0	0	0.0
Yeast Infection	6	6	1.4	4	4	0.9
Cardiovascular (Total)	**1**	**1**	—	**0**	**0**	—
Heartbeat irregular	1	1	0.2	0	0	0.0
Digestive (Total)	**18**	**17**	—	**14**	**12**	—
Diarrhea	15	15	3.5	6	6	1.3
Nausea	1	1	0.2	7	7	1.6
Abnormal stools	2	2	0.5	0	0	0.0
Dry mouth	0	0	0.0	1	1	0.2
Hemic and Lymphatic (Total)	**2**	**2**	—	**1**	**1**	—
CBC Abnormal	1	1	0.2	1	1	0.2
Blood count low	1	1	0.2	0	0	0.0
Metabolic and Nutritional (Total)	**3**	**2**	—	**0**	**0**	—
SGPT Increased	2	2	0.5	0	0	0.0
SGOT Increased	1	1	0.2	0	0	0.0
Nervous (Total)	**1**	**1**	—	**0**	**0**	—
Insomnia	1	1	0.2	0	0	0.0
Skin and Skin Structure (Total)	**3**	**2**	—	**2**	**2**	—
Rash	1	1	0.2	2	2	0.4
Pruritus	1	1	0.2	0	0	0.0
Urticaria	1	1	0.2	0	0	0.0
Special Senses (Total)	**0**	**0**	—	**2**	**2**	—
Taste perversion	0	0	0.0	2	2	0.4
Urogenital System (Total)	**3**	**3**	—	**7**	**7**	—
Vaginitis	1	1	0.2	5	5	1.1
Vaginal Itching	2	2	0.5	2	2	0.4
Overall	40 events reported by 36 patients			35 events reported by 28 patients		

Markedly Abnormal Test Results

The Medical Monitor determined the markedly abnormal value for each laboratory parameter evaluated and, in general, these were considered to be three times the upper limit of normal. Post-baseline serum chemistry results and hematology results were screened for values that were considered to be markedly abnormal. TABLE 4.76 presents the incidence of post-baseline serum laboratory values considered to be markedly abnormal, for each parameter assessed.

TABLE **Incidence of Serum Laboratory Values (Post-baseline) Considered to be Markedly Abnormal** (STUDY MON-US-01)

		# PTS / # OF PTS EVALUATED (%)		# OCCURRENCES / TOTAL # OF PT VISITS (%)	
Laboratory Parameters (units)	**Markedly Abnormal Labs**	**FT**	**CIPRO**	**FT**	**CIPRO**
SGOT (U/L)	> 150	2/339 (0.6)	0/358 (0)	2/646 (0.3)	0/650 (0)
SGPT (U/L)	> 165	1/339 (0.3)	0/358 (0)	1/646 (0.2)	0/650 (0)
Alkaline Phosphatase (U/L)	> 420	0/339 (0)	0/358 (0)	0/645 (0)	0/650 (0)
Bilirubin (mg/dL)	> 3.6	0/339 (0)	0/358 (0)	0/647 (0)	0/650 (0)
Creatinine (mg/dL)	> 2.0	0/339 (0)	0/358 (0)	0/647 (0)	0/650 (0)
BUN (mg/dL)	> 45	0/339 (0)	0/358 (0)	0/647 (0)	0/650 (0)
Hematocrit (%)	< 27	0/340 (0)	1/357 (0.3)	0/628 (0)	1/643 (0.2)
Hemoglobin (g/dL)	< 9.5	0/340 (0)	2/357 (0.6)	0/628 (0)	1/643 (0.5)
Red Blood Cells ($x10^6/\mu L$)	< 2.9	0/340 (0)	0/357 (0)	0/628 (0)	0/643 (0)
White Blood Cells (x1000/μL)	< 2.0	0/340 (0)	0/357 (0)	0/628 (0)	0/643 (0)
Eosinophils (%)	>10.0	0/340 (0)	0/357 (0)	0/629 (0)	0/644 (0)
Platelets (x1000/μL)	< 90	0/340 (0)	0/357 (0)	0/628 (0)	0/643 (0)

Cross-Reference: Raw Data Listing 13.

Two of the FT patients each had an elevated SGOT value that exceeded 150 U/L.

[redacted] **(Center 46)** was a 20 year-old woman, weight 159 lbs., who presented to the study within one day of the onset of UTI symptoms. The patient's medical history was unremarkable. The patient was taking birth control medication at baseline. She entered the study with moderate frequency, dysuria, burning, and urinary urgency. The patient was randomized to the FT group and treatment was initiated at the baseline visit (Day 0). She took all medication (4/24 - 4/30/92), and completed Visits 2 and 3 without incident. A lab report from Visit 3 indicated an increase in liver enzymes: SGOT = 666, SGPT = 213 (T. Bilirubin = 0.6 and Alkaline Phosphatase = 73, both normal). These abnormalities were considered severe and, although follow up to resolution was required, the patient was dropped from the study. Liver function tests were within normal limits at the evaluation done approximately 12 weeks post dosing (7/23/92). At that time SGOT = 33, SGPT = 28 (T. Bilirubin = 0.5, Alkaline Phosphatase = 61). The investigator considered the event to have been "unlikely" related to FT.

MO Comment: No further information is provided about any other lab testing done- e.g., hepatitis serology. The investigator does not speculate what these marked abnormalities could have been attributed to.

Patient [redacted] (Center 42) was a 24 year-old white female (weight 109 lbs.) who presented to the study within one day of the onset of UTI symptoms. The patient's medical history was unremarkable. Her past surgical history included cervical cancer with cyst removal. At baseline the patient was taking fluoxetine hydrochloride (Prozac®) for anxiety and calcium carbonate for an upset stomach. She entered the study complaining of severe frequency, dysuria, burning, and urinary urgency and moderate flank tenderness and suprapubic tenderness. The patient was randomized to the FT group, and treatment was initiated at the baseline visit (Day 0, 10/27/92). It was later discovered that the baseline sample was lost and no UTI was confirmed. A follow-up phone call on Day 3 revealed no UTI signs or symptoms. ***MO Comment: On study day 9 (11/5/92), the patient was seen in follow-up, and no complaints were noted. Routine blood drawn on that day for safety evaluation revealed a tripling of SGOT and doubling of SGPT. (See table below.)*** **The patient developed herpetic vulvovaginitis on Day 13 (11/9/92) and was hospitalized for associated urinary retention.** She was discontinued from the study. Treatment included acyclovir begun on 11/9/92. In the opinion of the investigator, this serious adverse event (i.e., genital herpes) was not related to study medication. The patient recovered and was discharged from the hospital.

MO Comment: No further information is reported with regard to the patient's lab abnormalities.

LABORATORY TEST	NORMAL RANGE			UNITS	VISIT 1 10/27/92		VISIT 2 11/05/92	
HEMATOLOGY								
Basophils	0	-	2	%	0		1	
CO2	20	-	34	MEQ/L	30		30	
Eosinophils	0	-	6	%	1		0	
Hematocrit	35.0	-	46.0	%	40.9		46	
Hemoglobin	12.0	-	15.6	G/DL	14		15.5	
Lymphocytes	18	-	47	%	26		22	
Monocytes	0	-	10	%	4		2	
Neutrophils	40	-	75	%	69		75	
Platelet Count	130000	-	400000	PER CUMM	329000		362000	
RBC	3.9	-	5.2	MILL/MCL	4		4.6	
Blood Urea Nitrogen	7	-	25	MG/DL	11		12	
WBC	3.8	-	10.1	THOU/MCL	9.8		11.3	H
CLINICAL CHEMISTRY								
Alkaline Phosphatase	20	-	140	U/L	100		114	
Bilirubin	0.2	-	1.2	MG/DL	0.2		0.2	
Chloride	96	-	112	MEQ/L	99		92	L
Cholesterol	0	-	199	MG/DL	277	H	271	H
Creatinine	0.7	-	1.4	MG/DL	0.8		0.8	
Sodium	135	-	148	MEQ/L	141		141	
Potassium	3.5	-	5.3	MEQ/L	4.1		5.4	H
SGOT	0	-	50	U/L	56	H	164	H
SGPT	0	-	55	U/L	77	H	154	H
Uric Acid	2.5	-	7.5	MG/DL	3.6		5.2	

L = BELOW NORMAL RANGE H = ABOVE NORMAL RANGE

MO Comment: Two other patients with increases in liver-associated enzymes are of note-

Patient (center 19) was a 27 year-old female, weight 160 lbs., in good health and taking birth control pills only (Loestrin 21 1.5/30 (norethindrone acetate/ethinyl estradiol). She was randomized to the FT arm. Labs on study entry included SGOT 37 (0-50 normal range) and SGPT 53 (0-55 normal range). Seven days after single-dose FT, the patient returned in follow-up without complaints. Repeat safety labs showed a doubling of transaminase values (SGOT 69, SGPT 99). Repeat labs after another week (study day 14) revealed SGOT 41, SGPT 94. Three subsequent determinations over the next 3 months showed SGOT 50, 44, and 66, and SGPT 87, 104, and 97. At the last follow-up 8 months post-treatment, SGOT was 78, SGPT 165. The principal investigator considered the abnormalities in liver-associated enzymes as possibly related to fosfomycin.

Patient (center 17) was a 23 year old female, weight 125 lbs., with a prior history of cervical dysplasia treated with laser surgery and a history of manic depression treated with fluoxetine hydrochloride (Prozac®) and lithium for six months prior to study entry. Liver-associated enzymes at study entry were normal (SGOT 27 and SGPT 37). The patient took a single dose of FT and was seen on study day 7 in follow-up: repeat SGOT 147, SGPT 81. On study day 12, the values were SGOT 54, SGPT 59.

Patients in the CIPRO group had similarly low percentages of abnormal chemistry evaluations.

No markedly abnormal hematology values were noted in any of the FT patients evaluated. The incidence of markedly abnormal test results in both treatment groups was similar and in all cases less than 1%.

Medical Officer's Comment on Diarrhea as an Adverse Event:

Diarrhea was noted in 8% of fosfomycin-treated patients and 4% of ciprofloxacin-treated patients ($p = 0.04$). The majority of patients had mild to moderate symptoms. Mean duration of diarrhea was twice as long in fosfomycin patients- 2 days- compared to less than a day in patients treated with 7 days of cipro. The maximum number of days of diarrhea was 13 days for fosfomycin, 4 days for cipro. Case record forms did not document further evaluation of cases with diarrhea (e.g., assessment of possible Clostridium difficile).

NDA 50717

MEDICAL OFFICER'S SUMMARY AND CONCLUSIONS FOR STUDY MON-US-01

In this first U.S. clinical trial comparing single dose fosfomycin tromethamine to a 7-day course of ciprofloxacin in women with uncomplicated lower urinary tract infections (cystitis), efficacy results for both microbiologic and clinical outcome show single dose fosfomycin to be inferior to standard therapy. Safety overall of the two regimens appeared comparable.

The Division has previously approved two products for short course therapy of cystitis:

norfloxacin (Noroxin®)	400 mg q12h for 3 days, and
ofloxacin (Floxin®)	200 mg q12h for 3 days.

In each case, the short-term treatment was clinically and microbiologically equivalent (95% confidence interval met) to standard therapy for 7-10 days.

Potential advantages of single dose treatment are obvious: better patient compliance, possible reduced risk side effects. Whether one should accept lesser efficacy to gain these advantages remains unclear.

The Medical Officer recommended that this New Drug Application be taken to the Anti-Infective Advisory Committee for further discussion. The Committee met in an open session on July 20, 1995, and their recommendations are briefly summarized on pages 138-139 of this review.

PROTOCOL MON-US-02.....Volume 1.56-1.58

Title:

Single Dose Fosfomycin Tromethamine Versus Multiple Dose Trimethoprim/ Sulfamethoxazole for the Treatment Of Uncomplicated Urinary Tract Infections In Patients

Study Design

The study was a multi-center, randomized trial with double-blind, double-dummy design comparing the efficacy and safety of Monurol® (fosfomycin) Sachet and Trimethoprim/ Sulfamethoxazole Tablets in the treatment of adult women with acute cystitis.

Inclusion criteria, exclusion criteria, entry and evaluation procedures, evaluability criteria, microbiologic and clinical outcome definitions and safety assessment were the same in this study as in Mon-US-01.

Study Drug Regimens

The two treatment groups were:

Fosfomycin (FT):	Fosfomycin, 3 g single dose plus placebo tablets every 12 hours for 10 days
Trimethoprim/ Sulfamethoxazole (TMP/SMX):	TMP/SMX 160 mg/800 mg was administered every 12 hours for 10 days plus one placebo sachet taken on the first day of dosing

The study drugs used were the following:

Fosfomycin tromethamine, 3 g sachet (Lot Nos. 01268 and 011608)

TMP/SMX, 160 mg/800 mg tablet (Batch No. 04064C, Manufactured by

Placebo sachets (Batch No. 01495) and Placebo tablets (Batch No. 04063C).

Medical Officer's Comment: In this second pivotal U.S. study, the comparator TMP/SMX was administered for 10 days. Hence, Visit 3 (the 5-9 day post-treatment visit for TMP/SMX patients) occurred slightly later than in study MON-US-01.

Table: Schedule of Follow-up Visits (STUDY MON-US-02)

Visits	Study Day	Study Timepoint
1	0	First Day of Therapy (Prior to dosing)
1A[a]	2 - 4	48-96 hrs after first dose
2	5 - 9[b]	5-9 days after first dose
3	14-18[c]	5-9 days after last dose
4	---	4-6 weeks after last dose

[a] Optional clinic visit, all patients were either to be seen in clinic or contacted via telephone.

[b] For FT patients, the visit scheduled for Days 5-9 was the Primary Evaluation Visit.

[c] For TMP/SMX patients, the visit scheduled for Days 14-18 was the Primary Evaluation Visit.

Medical Officer's Comment: This schedule of visits gave time-frames as originally stated in the protocol. To be consistent with the applicant's extension of the "5-9 day" visit to 5-11 days post-therapy in the first study (MON-US-01), I similarly accepted patients with follow-up in the following ranges: visit 2 (5-11 days) and visit 3 (15-21 days).

STUDY RESULTS

LIST OF INVESTIGATORS AND CLINICAL SITES [a]

Study Site 21:
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Study Site 22:
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Study Site 23:
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Study Site 24:
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Study Site 26:
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Study Site 27:
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Harbor UCLA Medical Center
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Study Site 28:
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Jackson Foundation/
Physicians Plus
345 West Washington Avenue
Madison, WI 53701

Study Site 29[b,c]:
Gary E. Ruoff, M.D.
Westside Family Medical Center
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Kalamazoo, MI 49009

Study Site 30:
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3231 McMullen Booth Road
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Study Site 31:
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Harleysville, PA 19438

Study Site 32:
Anthony Lama, M.D.
1350 South Eliseo Drive
Greenbrae, CA 94904

Study Site 33:
Stephen Mintz, M.D.
1311 Milstead Avenue
Conyers, GA 30207

Study Site 34:
Jon Salisbury, M.D.
2 Kings Highway
Middletown, NJ 07748

Study Site 35:
Peter J. Costantini, D.O.
Jersey Research Foundation, Inc.
1001 North Main Street
Pleasantville, NJ 08232

[a] Sites are not consecutively numbered
[b] Sites were shipped drug but did not enter patients
[c] Mario Padilla, M.D. [1255 Hill Rise Circle, Las Cruces, NM 88001] was originally assigned site #29. Dr. Padilla did not enroll any patients and his site number was reassigned to Dr. Ruoff.

LIST OF INVESTIGATORS AND CLINICAL SITES *

Study Site 36: Murray Kornlit, M.D. 550 West Vista Way Suite 402 Vista, CA 92083	**Study Site 63:** Stanley A. Gall, M.D. University of Louisville Department of Obstetrics and Gynecology 550 South Jackson Street Louisville, KY 40292	**Study Site 71:** Richard L. Sweet, M.D. Department of Ob/Gyn Magee-Women's Hospital 300 Halket Street Pittsburgh, PA 15213
Study Site 37: Donald B. Campbell, M.D. 3100 Blue Ridge Road Suite 300 Raleigh, NC 27612	**Study Site 64:** Walter E. Stamm, M.D. University of Washington Harborview Medical Center 325 Ninth Avenue Seattle, WA 98104	**Study Site 73:** Lee A. Fisher, M.D. Medical Director Palm Beach Center for Clinical Investigation 2669 Forest Hill Boulevard Suite 100 West Palm Beach, FL 33406
Study Site 38: Timothy Bruya, M.D. Inland Empire Internal Medicine Medical Center Building South 820 McClellan Suite 306 Spokane, WA 99204	**Study Site 65:** Ira W. Klimberg, M.D. Urology Center of Florida 3201 South West 34th Street Ocala, FL 32674	**Study Site 75:** Lawrence L. Pelletier, M.D. The University of Kansas School of Medicine - Wichita 1010 North Kansas Wichita, KS 67214
Study Site 61: David A. Baker, M.D. Department OB/GYN SUNY @ Stony Brook Health Science Tower-9, Room 080 Stony Brook, NY 11794	**Study Site 69:** Eric Wall, M.D. Department of Family Medicine 3181 South West Sam Jackson Park Road Portland, OR 97201	**Study Site 76:** Abdollah Iravani, M.D. Central Florida Medical Research Center 1720 South Orange Avenue Suite 401 Orlando, FL 32806
Study Site 62: Claire Cox, M.D. Professor and Chairman Department of Urology, University of Tennessee 956 Court Avenue, Room H216 Memphis, TN 38163	**Study Site 70:** John B. Gregorio, M.D. Highland Clinic 1455 E. Bert Kouns Industrial Loop Shreveport, LA 71105	**Study Site 77:** Suzanne Weakley, M.D. BioLogica Research Group, Inc. 2700 Osler Boulevard Bryan, TX 77802

* Sites are not consecutively numbered

Patient Enrollment by Center

Thirty centers throughout the United States enrolled a total of 854 patients. The table below summarizes by center, the number of patients in the applicant's modified Intent-to-Treat analysis (MITT), the applicant's evaluable (EVAL) patient population derived from the modified ITT, and the medical officer's evaluable population.

TABLE: **Distribution of Patients by Center - ALL Enrolled Patients Receiving Study Medication, Number of Patients per Treatment Group (MON-US-02)**

		FT	TMP/SMX
	Center Number	**ALL Enrolled (MITT/EVAL/MO)**	**ALL Enrolled (MITT/EVAL/MO)**
	21	30 (25/21/24)	30 (25/18/21)
	22	28 (20/16/18)	29 (17/13/12)
	23	3 (2/2/1)	3 (1/1/1)
	24	1 (1/0/1)	2 (1/0/1)
	25	15 (8/5/8)	16 (5/5/5)
	26	14 (12/9/10)	14 (10/9/7)
	27	1 (1/0/0)	2 (2/0/0)
	28	35 (24/20/23)	34 (21/21/20)
	29	23 (9/7/7)	22 (9/6/9)
	30	37 (22/14/19)	36 (21/19/16)
	31*	38 (18/4/0)	40 (24/10/0)
	32	1 (0)	2 (0)
	33	7 (5/3/5)	8 (7/5/5)
	34	20 (10/6/10)	20 (13/10/12)
	35	30 (25/22/25)	30 (18/17/18)
	36	14 (8/5/4)	12 (9/4/3)
	37	4 (3/3/3)	4 (1/0/0)
	38	8 (6/2/6)	10 (4/1/2)
	61	9 (4/0/4)	8 (2/0/1)
	62	11 (11/9/9)	12 (12/8/8)
	63	9 (4/4/4)	9 (4/3/4)
	64	12 (8/8/8)	12 (9/8/9)
	65	17 (15/13/12)	16 (11/8/8)
	69	2 (2/1/2)	2 (2/0/2)
	70	15 (9/8/9)	16 (7/5/7)
	71	3 (2/0/2)	4 (2/0/1)
	73	4 (3/1/2)	2 (0)
	75	2 (2/2/2)	2 (1/1/0)
	76	30 (30/27/29)	29 (27/20/24)
	77	3 (2/1/2)	2 (1/1/1)
Total Number	30	426 (291/213/249)	428 (266/193/197)

***MO Comment**: On analysis of the 78 patients enrolled by Dr. David Ginsberg at Center 31, the largest enrollment by any one investigator in the study, I noted problems with both the microbiologic and clinical data recorded. The susceptibility data from this investigator's laboratory followed an unusual pattern, with most isolates recorded as "resistant" to one or both study drugs. I conferred with the reviewing microbiologist, Mr. Peter Dionne, who agreed there was a problem. The applicant was asked to explain the susceptibility data at this center and provided the following information on June 13, 1995:*

"In February of 1994 it was identified that Dr Ginsberg had a significantly higher rejection rate of patients than did the other sites. A series of investigations were undertaken... Ultimately it was determined that there was a systematic error occurring at [his] lab where the microbiologist was measuring the radius of the disk instead of the disk diameter... Appropriate measures were undertaken to prevent recurrence of the problem. At that time it was impossible to go back and retrospectively correct the microbiology in Protocol 02."

"We have examined the impact of this error on Protocol 02, with the results listed below:

	FT	TMP/SMX
Enrolled	38	40
cure rate (ITT)	16/16 (100%)	17/17 (100%)
cure rate (evaluable)	4/4 (100%)	8/8 (100%)

Thus, the impact of the error in zone size is minimal on the primary efficacy variables."

In addition, Dr. Ginsberg assessed as clinical failures 4 patients in the FT arm and 2 in the TMP/SMX arm. What became of some of these clinical failures is not always clear, as illustrated by the following examples:

Patient was treated with a single dose of fosfomycin, subsequently developed severe flank tenderness and was assessed by the investigator as a treatment failure. Yet, the investigator documents no further treatment given, no post-therapy antimicrobial medication prescribed. Likewise, patient treated with TMP/SMX, was still symptomatic with mild frequency and burning after taking a week of the drug. The investigator commented, "Patient dropped from study because symptoms worsened, organism resistant to Bactrim." There is no record of other treatment given, of post-therapy antimicrobial medication required.

Because of concerns about the validity and reliability of these data, I chose not to include Dr. Ginsberg's patients in my analysis.

The table below summarizes patient numbers and percentages of population total, by treatment group, for each of the populations analyzed

TABLE Distribution of Patients (STUDY MON-US-02)

Analysis Group (Population Identifier)	FT N (% of Pop.)	TMP/SMX N (% of Pop.)	TOTAL N (% of Pop.)
Patients Randomized, Enrolled and Treated, Valid for Safety Analysis (ALL)	426 (50)	428 (50)	854 (100)
Applicant's Intent-to-Treat Group- Valid for Efficacy Analysis (ITT)	291 (52)*	266 (48)*	557 (100)
Applicant's Evaluable Group- Valid for Efficacy Analysis (EVAL)	213 (52)	193 (48)	406 (100)
Medical Officer's Evaluable Population (MO)	249 (58)	197 (46)	

% of Pop = Percentage of Population N = Number of patients

** Medical Officer's Comment: The applicant calculated the percentages above incorrectly. Figures should be based on the total number of patients randomized to each arm:*

291/426 (68%) 266/428 (62%)

213/426 (50%) 193/428 (45%)

Applicant's Exclusion's from the Modified ITT and Evaluable Patient Populations

Thirty-two percent (32%) of the patients randomized and enrolled into the FT group (135/426) and 38% of patients randomized and enrolled into the TMP/SMX group (162/428) were screening failures (i.e., results of a urine culture performed within two days of study start did not document growth of a known uropathogen at $\geq 10^5$ cfu/ml). The screen failure rate tended to be greater in the TMP/SMX group than in the FT group ($p=0.06$). However, both populations were subjected to the same criteria for defining the screen failure, criteria that were determined prior to breaking the blind. The difference in screen failure rate was, therefore, not considered to have compromised the analyses of the ITT and EVALUABLE populations.

The 291 FT patients and 266 TMP/SMX patients who were not screening failures were evaluated as the ITT population. Of those, 73% (213/291) of the FT patients and 73% (193/266) of the TMP/SMX patients were deemed evaluable for efficacy analysis and identified as the EVALUABLE population.

Not all patients analyzed in the EVALUABLE population met all protocol-defined entrance criteria. The EVALUABLE subpopulation was comprised of those ITT patients who, in the

opinion of the medical monitor, had uncomplicated UTI based on medical and surgical history, and for whom the initially susceptible, UTI-defining uropathogen was found to be susceptible to both fosfomycin and TMP/SMX. In addition, EVALUABLE patients were required to have taken at least 14 of 20 study medication tablets.

Of the 151 patients who were excluded from the evaluable population, 78 were in the FT group and 73 in the TMP/SMX group. Most patients were excluded because susceptibility of the infecting uropathogen to both drugs was not established. Fifty-seven patients in the FT group and 51 in the TMP/SMX group had pathogens that were not susceptible to both study drugs.

Of the remaining patients (potentially EVALUABLE), 17 ITT patients (9 FT, 8 TMP/SMX) were excluded from the EVALUABLE population, prior to breaking the blind and after review of each patient by the medical monitor, for baseline deviations of protocol entrance requirements. Finally, of those still remaining, 26 ITT patients (12 FT, 14 TMP/SMX) were excluded from the EVALUABLE population because they were not compliant with study medication (took < 14 tablets). There was no statistically significant, between-group difference in the number of patients considered EVALUABLE for efficacy analysis ($p = 0.87$).

Medical Officer's Comment. My analysis differed from the applicant's and resulted in larger numbers in my evaluable pool of patients for several reasons:

1. I examined the case record forms, in a blinded fashion, of patients excluded from the evaluable pool by the medical monitor. If the investigator documented that the patient met all inclusion and exclusion criteria, and there was no recent history recorded to indicate that the patient was predisposed to a complicated UTI (stones, strictures, polycystic kidneys, neurogenic bladder), then I included such a patient in my evaluable pool.

2. If a fosfomycin-treated patient did not take the entire course of "dummy" TMP/SMX tablets, I considered such a patient appropriate in the evaluable population in order to capture information on the efficacy of fosfomycin.

3. I did not exclude patients because sensitivity to both drugs was not measured or an isolate was "resistant" or "intermediate" in susceptibility to study drug(s).

a- Many investigators followed patients with "resistant" isolates until the end of the study. By the time culture and sensitivity results were available, patients were already several days beyond single-dose treatment or several days into a 10-day treatment regimen.

b- Resistance is usually defined relative to serum, not urine levels. So even levels of 16, 32, 64, etc, are within the urine drug level possibilities.

c- The NCCLS has found problems with the breakpoints for fosfomycin. The applicant presented clinical and microbiologic data to the NCCLS, and due to the committee's lack of confidence in the results of the quality control strains for in-vitro testing, the NCCLS committee could reach no conclusions regarding the breakpoints. The applicant was advised to find a solution to their in-vitro testing problems.

Medical Officer's Exclusions from the Evaluable Population

Reason	Fosfomycin	TMP/SMX
Protocol violation	4	6
Lost to follow-up	11	8
Adverse Event	3	7
Concomitant Antimicrobials/other	1	2
Intercurrent Illness	3	4
Missing or late 5-11 day posttherapy visit	1	11
Dropped due to resistance	1	5
Patient withdrew consent	0	2
Screening failures	115	146
Dr. Ginsberg/Center 31[1]		
-Screening Failures	20	16
-Patients with $\geq 10^5$ cfu/ml	18	24
Total Unevaluable	177	231
Total Evaluable	249	197
Total Enrolled	426	428

[1]Dr Ginsberg's entire center is excluded, with the number of patients who had negative cultures or positive cultures at entry specified in the table

Demographic and Baseline Characteristics

A total of A total of 854 female patients were enrolled into the MON-US-02 clinical study across 30 centers Four-hundred twenty-six patients (50%) were randomized to the fosfomycin (FT) treatment group and 428 patients (50%) were randomized to the trimethoprim/sulfamethoxazole (TMP/SMX) treatment group

Patient race and age were recorded as basic demographic data. These parameters and other baseline characteristics (height, weight, birth control method, UTI history, and urogenital surgical history) were evaluated to determine the similarities and differences between treatment groups

TABLE **Demographic Summary (Race and Age) - *ALL Enrolled Patients* (MON-US-02)**

	FT [N=426] No Pts (%)	**TMP/SMX** [N=428] No Pts. (%)	Treatment Group Comparison [p-value]
Race			
Caucasian	361 (85)	369 (86)	0.07
Black	46 (11)	36 (8)	
Hispanic	15 (4)	9 (2)	
Asian	2 (< 1)	10 (2)	
Other	2 (< 1)	4 (1)	
Age Range (Years)			
	198 (46)	204 (48)	0.45
	151 (35)	136 (32)	
	48 (11)	54 (13)	
	29 (7)	34 (8)	
Age (Years)			
Median	32 0	31.5	
Mean	36 1	36 7	0 59
Standard Deviation	15 4	16 4	
Minimum			
Maximum			

TABLE **Demographic Summary (Height and Weight) - *ALL Enrolled* (MON-US-02)**

	FT (N=426)	TMP/SMX (N=428)	Treatment Group Comparison (p-value)
Height (Inches)			
Median	64.0	64.5	
Mean	64.4	64.5	0.53
Standard Deviation	2.7	2.7	
Minimum			
Maximum			
Number	421	425	
Weight (Pounds)			
Median	139.0	138.0	
Mean	146.1	145.1	0.66
Standard Deviation	35.0	33.7	
Minimum			
Maximum			
Number	424	423	

***Medical Officer's Comment**: For all patients enrolled, the two treatment arms were balanced with regard to age, race and weight. For the derived populations, there are minor imbalances noted below, but I do not think the differences have any major impact on study results.*

For the applicant's modified ITT population, the two ITT treatment groups were statistically different (p=0.03) only with respect to patient race. The largest difference was in blacks (FT=11%, TMP/SMX=8%). In both groups, the majority of patients were Caucasian (84% and 86% in the FT and TMP/SMX groups, respectively). With respect to patient age and weight, the two ITT treatment groups were similar.

For the applicant's EVALUABLE population, the two treatment groups were statistically different (p=0.02) only with respect to patient race. The largest differences were in Caucasians (FT=83%, TMP/SMX=88%) and blacks (FT=11%, TMP/SMX=6%). With respect to patient age and weight, the two EVAL treatment groups were similar. The tables are reproduced below.

TABLE: **Demographic Summary (Race and Age) - *ITT Population* (MON-US-02)**

	FT [N=291] N (%)	TMP/SMX [N=266] N (%)	Treatment Group Comparison [p-value]
Race			
Caucasian	244 (84)	228 (86)	0.03[a]
Black	31 (11)	20 (8)	
Hispanic	13 (4)	8 (3)	
Asian	1 (0.3)	9 (3)	
Other	2 (1)	1 (0.4)	
Age Range (Years)			
	140 (48)	132 (50)	0.73[b]
	93 (32)	77 (29)	
	58 (20)	57 (21)	
Age (Years)			
Median	31.0	31.0	
Mean	36.1	36.4	0.83[c]
Standard Deviation	16.2	16.5	
Minimum			
Maximum			
Number	291	266	

[a] Fisher's exact test
[b] Chi-square analysis
[c] t-test

TABLE: **Demographic Summary (Race and Age) - *APPLICANT'S EVALUABLE Population* (STUDY MON-US-02)**

	FT [N = 213] N (%)	TMP/SMX [N = 193] N (%)	Treatment Group Comparison [p-value]
Race			
Caucasian	177 (83)	170 (88)	0.02[a]
Black	24 (11)	12 (6)	
Hispanic	9 (4)	3 (2)	
Asian	1 (< 1)	7 (4)	
Other	2 (1)	1 (< 1)	
Age Range (Years)			
	101 (47)	98 (51)	0.72[b]
	66 (31)	53 (27)	
	46 (22)	42 (22)	
Age (Years)			
Median	32.0	30.0	
Mean	36.5	36.2	0.85[c]
Standard Deviation	16.4	16.8	
Minimum			
Maximum			
Number	213	193	

[a] Fisher's exact test
[b] Chi-square analysis
[c] t-test

No statistically significant differences were noted in between treatment group comparisons of birth control practices

TABLE **Birth Control Methodology - *ALL Enrolled* (MON-US-02)**

Birth Control Methods*	ALL Enrolled*		
	FT [N=426]	TMP/SMX [N=428]	Treatment Group Comparison [p-value]
Oral contraceptive	108 (25)	127 (30)	0.17
Intrauterine device	3 (<1)	2 (<1)	0.69
Diaphragm	15 (4)	14 (3)	0.85
Condom	139 (33)	129 (30)	0.46
Spermicide	101 (24)	86 (20)	0.22
Sponge	7 (2)	5 (1)	0.58
Abstinence	7 (2)	12 (3)	0.35
Surgically Sterilized	116 (27)	120 (28)	0.82
Other*	66 (15)	60 (14)	0.56

* Note that patients may have utilized more than one method of birth control.
* Other methods included: jelly, condoms/foam, contraceptive foam, and partner sterilized.

***Medical Officer's Comment**: For the derived populations (modified ITT and evaluable), both treatment groups were similar with respect to birth control practices.*

The majority of patients in both treatment groups were enrolled within two days of the onset of symptoms of UTI. For the majority of patients in both treatment groups, the current UTI was the first UTI within the twelve month period prior to the study, and there was no history of previous urogenital surgery.

TABLE **UTI and Urogenital Surgical History - *ALL Enrolled* (MON-US-02)**

	FT [N=426] N (%)	TMP/SMX [N=428] N (%)	Treatment Group Comparison [p-value]
Number of Days Symptomatic[a]			
0	57 (13)	61 (14)	0.71
1	172 (40)	156 (36)	
2	131 (31)	140 (33)	
≥3	66 (15)	71 (17)	
UTIs in Previous 12 Months[b]			
0	298 (70)	291 (68)	0.81
1	76 (18)	79 (18)	
2	44 (10)	46 (11)	
≥3	8 (2)	12 (3)	
Previous Surgery			
None or Missing	381 (89)	376 (88)	0.35
1 year prior	2 (<1)	5 (1)	
2 years prior	2 (<1)	6 (1)	
>2 years prior	41 (10)	41 (10)	

( ) Percentage
Cross-Reference: Raw Data Listings 1 and 3.
[a]Dose date minus symptom onset date.
[b]Not including current UTI.

***Medical Officer's Comment**: The treatment arms are balanced for all patients enrolled with respect to UTI symptom duration, number of UTIs in the preceding year, and prior urogenital surgery. This holds true for the derived patient populations (modified ITT and evaluable) as well.*

Microbiologic Efficacy Results

Time Frame: *5-11 Days Post-therapy*
Analysis: *Applicant's Modified Intent-to-Treat*

Among patients in the ITT population, 89% (246/276) of FT patients and 98% (207/211) of TMP/SMX patients[2] were determined to have a bacteriological cure within the Primary Evaluation Window. The ninety-five percent one-sided confidence interval for the difference in the cure rates was 12.4%. Eleven percent (30/276) of FT patients and 2% (4/211) of TMP/SMX patients in the ITT population were determined to have a bacteriological failure of therapy ($p<0.01$).

TABLE: **Applicant's** Bacteriological Evaluation in the Primary Assessment Window - ITT Population (STUDY MON-US-02)

	FT N(%)	TMP/SMX N(%)	Treatment Group Comparison [p-value]
CURE[a]	246[b] (89)	207 (98)	
FAILURE	30 (11)	4 (2)	< 0.01
NO EVALUATION	15[c]	55[c]	

See APPENDIX 10 for the list of patients for whom bacteriological evaluation could not be made. ***MO Comment**: This is simply a list of patient numbers without reasons for "no evaluation".*

[a] 95% one-sided confidence interval for the upper bound on difference in cure rates: 12.4%.
[b] Inclusive of one patient with *E. coli* type different from that at baseline.
[c] Not included in Total or Percentage calculation.

***Medical Officer's Comment**: The confidence interval calculation done by the applicant above should be two-sided, not one. For the figures given by the applicant, the two-sided 95% confidence interval is (-0.14, -0.044).*

In the applicant's modified intent-to-treat analysis (which already excludes patients without a positive urine culture of 10^5 cfu/mL), there should not be a "no evaluation" category. It appears the applicant assessed patients with "no evaluation" if patients were not seen in the "primary assessment window", day 5-11 post-therapy for each drug (visit 2 for FT, visit 3 for TMP-SMX, respectively). As one would expect, patients who are failures, experience adverse events, get an intercurrent illness, etc, often present at unscheduled visits. Of the 15 "no evaluation" FT-treated patients, 8 were assessed by investigators as having failed fosfomycin therapy and were given additional antimicrobials. They failed prior to or just after the 5-11 day "primary assessment window". Of the 8 failures, 4 had proven bacteriologic persistence, 1 patient started herself on another antibiotic before a urine culture could be taken (presumed persistence), 1 patient's culture was discarded in error (presumed persistence), and 2 patients had new infections. If one counts the 6 patients with bacteriologic persistence to the 30 failures above, the 95% confidence interval is (-0.16, -0.06), showing inferiority.

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[2] For 15 FT patients and 55 TMP/SMX patients, according to the applicant, bacteriological evaluation was not available, and these patients were excluded from this analysis.

Of the 55 TMP/SMX patients, 9 were assessed by investigators as treatment failures based on clinical symptoms and re-treated with antibiotics. Of these 9 patients, all had negative urine cultures at the time of clinical failure. I have listed all the applicant's "no evaluation" patients below, with comments and need for additional antimicrobials.

No evaluation" FT patients in applicant's modified ITT analysis above, with investigators' and MO comments

FT-Patients	Investigator's Comments	Additional Antibiotics	MO Evaluation/Comments
	discontinued/intercurrent illness	N	no/intercurrent illness
	lost to f/u until day 27; recurrence	Y	no/new infection
	treatment failure	Y	yes/bact persist/clin fail
	recurrence; adverse experience	Y	yes/new infection/clin fail
	non-compliance	N	no/lost to f/u
	lost to f'u	N	lost to f'u
	adverse experience/rash	N	no/patient not followed
	treatment failure	?	yes/bact erad/clin fail
	treatment failure/no culture done	Y	yes/bact ppersist/clin fail
	treatment failure/no culture done	Y	yes/bact ppersist/clin fail
	severe frequency/dysuria/burning	Y	yes/bact persist/clin fail
	adverse experience/vomiting	N	no/adverse experience
	treatment failure	Y	yes/bact persist/clin fail
	treatment failure	Y	yes/bact persist/clin fail
	adverse event	N	no/adverse experience
TMP-SMX Patients			
	Lost to follow-up	N	no/lost to f/u
	dropped study day 7 due to resistance	N	no/sterile culture, no symptoms on study day 7
	Tmp/smx shows resistance	Y	no/dropped study day 2 due to resistance
	adverse event/possible allergy	Y	no/sterile culture, no uti symptoms on study day 4
	(none)	N	yes/bact eradication, clinical cure
	removed from study early due to resistance	Y	no/dropped study day 4 due to resistance
	withdrew consent	N	no/sterile culture study day 9
	(none)	Y	yes/bact erad study day 13, new infection study day 25
	(none)	N	yes/bact eradication with clinical relapse study day 41
	(none)	N	no/outside 5-11 day window/bacteriologic eradication/cure
	(none)	N	no/outside 5-11 day window/bacteriologic eradication/cure
	(none)	N	no/outside 5-11 day window/bacteriologic eradication/cure
	Adverse experience	N	no/sterile culture, no uti symptoms study day 5
	Removed from study	N	no/misread entry urine culture as screen failure/dropped
	Removed from study	N	no/misread entry urine culture as screen failure/dropped
	(none)	N	yes/bact erad/clin cure study day 11
	(none)	N	no/no test of cure culture
	(none)	N	no/outside 5-11 day window/bacteriologic eradication/cure
	Lost to follow-up	N	no/lost to f/u
	(none)	N	no/outside 5-11 day window/bacteriologic eradication/cure
	(none)	N	no/outside 5-11 day window/bacteriologic eradication/cure
	(none)	N	no/outside 5-11 day window/bacteriologic eradication/cure

TMP-SMX Patients (cont)	Investigator's Comments	Additional Antibiotics	MO Evaluation/Comments
	Treatment failure	Y	yes/bact erad study day 22 with recurrence study day 29
	Treatment failure	?	yes/bact erad, clinical failure
	adverse experience	N	no/bact eradication, no uti symptoms study day 6
	non-compliance with scheduled visits	N	no/lost to follow-up
	lost to f/u	N	no/lost to f/u
	Treatment failure	Y	yes/bact erad, clinical failure
	Lost to follow-up	N	no/lost to f/u
	lab error	N	no/5-11 day post therapy culture not done/clin cure
	non-compliance with scheduled visits	N	no/missed 5-11 day post therapy visit
	Treatment failure	Y	yes/bact erad, clin failure
	(none)	N	yes/bact erad/clin cure study day 11
	Treatment failure	Y	yes/bact erad/clin cure 12 days post therapy/later clin
	Treatment failure	N	yes/bact eradication, clin failure
	lost to f/u	N	no/lost to follow-up
	Adverse experience	N	no/sterile culture, no uti symptoms when discontinued
	Resistant organism	Y	no/ bact erad study day 4/dropped due to resistance
	(none)	N	no/outside 5-11 day window/bacteriologic eradication/cure
	Patient organism resistant	N	no/sterile culture, no uti symptoms/dropped due to
	Non-compliance after 3 days	N	no/sterile culture study day 6
	treatment failure	Y	no/pt removed from study at her request on study day 2
	Intercurrent medical illness	N	no/intercurrent medical illness
	(none)	N	no/test of cure culture not done/clin cure
	Adverse experience	Y	no/adverse event study day 2
	Adverse experience	Y	no/adverse event study day 3
	Adverse experience	N	no/adverse event study day 3
	Treatment failure	Y	yes/bact eradication/clin failure 3 days post therapy
	adverse experience	Y	no/adverse event
	lost to follow-up	N	no/lost to f/u
	Treatment failure	Y	yes/bact erad/clin cure study day 12 with clin relapse sd34
	(none)	N	no/no test of cure urine culture
	Adverse experience	N	no/adverse event
	Lost to follow-up	N	lost to f/u
	Intercurrent medical illness	N	intercurrent medical illness

Microbiologic Efficacy Results (continued)

Time Frame: *5-11 Days Post-therapy*
Analysis: *Applicant's Evaluable Population*

TABLE: *Applicant's* Bacteriological Evaluation in the Primary Assessment Window - Evaluable Population (STUDY MON-US-02)

	FT N(%)	TMP/SMX N(%)	Treatment Group Comparison [p-value]
CURE[a]	187[b] (90)	166 (98)	
FAILURE	21 (10)	3 (2)	<0.01
NO EVALUATION	5[c]	24[c]	

See APPENDIX 10 for the list of patients for whom the bacteriological evaluation could not be made

[a] 95% one-sided confidence interval for the upper bound on the difference in the cure rates: 12.2%.

[b] Inclusive of one patient with *E. coli* type different from that at baseline.

[c] Not included in Total or Percentage calculation.

Cross-Reference: APPENDICES 11 and 24.

MO Comment: *The "no evaluation" patients above are a subset of those in the previously described modified ITT analysis. For fosfomycin, the patient numbers are*
Two of the 5 FT-treated patients in the "no evaluation" category were investigator- and MO -assessed clinical failures with bacteriologic persistence. Of the 24 excluded TMP-SMX patients, 3 were investigator- and MO-assessed clinical failures , all with bacteriologic eradication. The two-sided 95% confidence interval based on the difference in successful outcome is (-0.143, -0.037), showing inferiority.

Microbiologic Efficacy Results (continued)

Time Frame: *5-11 Days Post-therapy*
Analysis: ***Medical Officer's Evaluable Population***

Outcome	Fosfomycin N (%)	TMP-SMX N (%)
Eradication[3]	204 (82)	190 (96)
Persistence[4]	37[5] (15)	3 (2)
New infection	8 (3)	4 (2)
Total	249	197

MO "Collapsed" Efficacy ***5-11 Days Post-Therapy***

Outcome	Fosfomycin	TMP-SMX	
Eradication	212 (85)	194 (98)	CI_{95} (-0.18, -0.08), showing inferiority.
Persistence	37 (15)	3 (2)	

[3] Includes 5 FT-patients with isolates resistant to FT (zone diameter <16 mm) and 9 FT-patients with sensitivity not tested. In the TMP-SMX-arm, 7 patients had isolates resistant to TMP-SMX; 6 patients, not measured.

[4] Includes 4 FT-patients with isolates of intermediate susceptibility (zone size 12-15 mm), 1 FT-patient with a resistant isolate (zone diameter < 12), and 1 FT-patient with sensitivity not tested. In the TMP-SMX arm, 1 patient had an isolate resistant to TMP-SMX.

[5] Includes 2 out of 37 FT-patients with presumed persistence (i.e., clinical failures at end of therapy, but the required urine culture was not performed).

Microbiologic Efficacy Results (continued)

MO Comment: Given the double-blinded nature of the trial design, patients returning for the 5-9 post-treatment assessment were represented by visit 2 for fosfomycin patients and visit 3 for TMP-SMX patients. Visit 3 (study days 15-21, i.e. 5-11 days after the longer course, TMP/SMX) permitted an assessment of imminent recurrences in the fosfomycin group. It is of interest to note that the IDSA Guidelines for Urinary Tract Infections (CID 1992;15 December) recommends, "When short courses of therapy are compared with longer courses, follow-up for both courses should be done 5-9 days after completion of the longer course." These data are tabulated below:

Time Frame: ***5-11 Days after the Longer Course***
Analysis: ***Medical Officer's Evaluable Population***

Outcome	Fosfomycin N (%)	TMP-SMX N (%)
Eradication	190 (76)	190 (96)
Early Recurrence[6]	11 (4)	--
New infection	3 (1)	--
Persistence (carried for FT)	37 (15)	3 (2)
New infection (carried for FT)	8 (3)	4 (2)
Total	249	197

MO "Collapsed" Efficacy ***5-11 Days after the Longer Course***

Outcome	Fosfomycin	TMP-SMX	
Eradication	201 (81)	194 (98)	Cl_{95} (-0.23, -0.11), showing inferiority
Persistence	48 (19)	3 (2)	

[6] All 11 fosfomycin-treated patients with early bacteriologic recurrence had original uropathogens sensitive to fosfomycin (10 *E. coli* and 1 *Proteus mirabilis*)

Time Frame: *4-6 Weeks Post-therapy*
Analysis: *Medical Officer's Evaluable Population*

Outcome	Fosfomycin N (%)	TMP-SMX N (%)
Eradication	159 (64)	165 (84)
Late Recurrence	27 (11)	14 (7)
New infection	2 (1)	7 (4)
Clin Failures End of Therapy	2 (1)	4 (2)
Early Recurrence (carried forward)	11 (4)	--
Persistence (carried forward)	37 (15)	3 (<2)
New infection (carried forward)	11 (4)	4 (2)
Total	249	197

MO "Collapsed" Efficacy **4-6 Weeks Post-therapy**

Outcome	Fosfomycin	TMP-SMX	
Eradication[1]	174 (70)	180 (91)	CI_{95} (-0.28, -0.14), showing inferiority
Persistence	75 (30)	17 (9)	

[1]Includes all patients for whom the original pathogen was eradicated

Microbiologic Efficacy Results (continued)

Time Frame: *4-6 Weeks Post-therapy*
Analysis: *Applicant's Modified Intent-to-Treat Population*

TABLE 4.40: Bacteriological Evaluations of Superinfection, Recurrence and New Infection - ITT Population (STUDY MON-US-02)

	FT N(%) [N=291]	TMP/SMX N(%) [N=266]	Treatment Group Comparison [p-value]
Superinfection			
NO	N/A[b]	238 (99.6)	
YES	N/A	1 (0.4)	
NO SAMPLE/NOT EVALUABLE[a]	291	27	
Recurrence			
NO	209 (89)	190 (94)	0.09
YES	25[c] (11)	12[d] (6)	
NO SAMPLE/NOT EVALUABLE[a]	57[e]	64[f]	
New Infection			
NO	267 (93)	233 (95)	0.47
YES	20 (7)	13 (5)	
NO SAMPLE/NOT EVALUABLE[a]	4	20	

[a] See APPENDIX 10 for list of patients for whom bacteriological evaluation could not be made.
[b] Patients in the FT group received only a single dose of active therapy; therefore, no FT patients could meet the definition of superinfection.
[c] Four (4) of these patients had *E. coli* type different from that at baseline.
[d] Three (3) of these patients had *E. coli* type different from that at baseline.
[e] Inclusive of 12 FT patients who were bacteriological cures, but had no final bacteriological outcome; therefore, recurrence could not be assessed.
[f] Inclusive of five TMP/SMX patients who were bacteriological cures, but had no final bacteriological outcome; therefore, recurrence could not be assessed.
N/A: Not Applicable

Medical Officer's Comment: Failures at the early follow-up are not carried forward. In the applicant's modified intent-to-treat type of analysis above, a "no sample/not evaluable" category is odd. Appendix 10 simply lists patient ID numbers, not specific reasons why these patients are in a "no sample/no evaluation" category. In my review of the data, this "no sample" group includes patients who presented outside proscribed follow-up windows (such as investigator-assessed failures or recurrences, patients with adverse events or intercurrent illnesses, etc.) as well as patients who were lost to follow-up. When patients were treatment failures or recurrences, I have brought them back into my analysis. If patients dropped out of the study early for reasons other than treatment failure (adverse event, patient request, lost to follow-up, etc.) then I did not include such patients in my analysis.

Microbiologic Efficacy Results (continued)

Time Frame: *4-6 Weeks Post-therapy*
Analysis: *Applicant's Evaluable Population*

TABLE: Bacteriological Evaluations of Superinfection, Recurrence and New Infection - EVALUABLE Population (STUDY MON-US-02)

	FT N(%) [N=213]	TMP/SMX N(%) [N=193]	Treatment Group Comparison [p-value]
Superinfection			
NO	N/A[b]	182 (99.5)	
YES	N/A	1 (0.5)	
NO SAMPLE/NOT EVALUABLE[a]	213	10	
Recurrence			
NO	164 (90)	155 (94)	0.24
YES	18[c] (10)	10[d] (6)	
NO SAMPLE/NOT EVALUABLE[a]	31[e]	28[f]	
New Infection			
NO	194 (93)	177 (94)	1.00
YES	14 (7)	12 (6)	
NO SAMPLE/NOT EVALUABLE[a]	5	4	

[a] See APPENDIX 11 for list of patients for whom bacteriological evaluation could not be made.
[b] Patients in the FT group received only a single dose of active therapy; therefore, no FT patients could meet the definition of superinfection.
[c] Four of these patients had *E. coli* different from that at baseline.
[d] Three of these patients had *E. coli* different from that at baseline.
[e] Inclusive of five FT patients who were bacteriological cures, but had no final bacteriological outcome; therefore, recurrence could not be assessed.
[f] Inclusive of one TMP/SMX patient who was a bacteriological cure, but had no final bacteriological outcome; therefore, recurrence could not be assessed.

The table below presents the applicant's bacteriological cure rates at end of treatment (5-11 days post-therapy), by isolated baseline pathogen, for the modified ITT population.

TABLE: ***Applicant's*** Bacteriological Cure Rate in the Primary Assessment Window by Pathogen - ITT Population (STUDY MON-US-02)

Pathogens	FT No. Cures/Total (%)	TMP/SMX No. Cures/Total (%)
Enterobacter	1/1 (100)	2/2 (100)
Enterobacter aerogenes	2/3 (67)	2/2 (100)
Enterobacter cloacae	2/2 (100)	1/1 (100)
Enterococcus	5/6 (83)	1/2 (50)
Enterococcus faecalis	3/3 (100)	2/2 (100)
Escherichia coli	211/234 (90)	183/187 (98)
Klebsiella	1/3 (33)	1/1 (100)
Klebsiella pneumoniae	7/10 (70)	5/5 (100)
Proteus mirabilis	13/13 (100)	7/7 (100)
Pseudomonas	0/0 (-)	1/1 (100)
Pseudomonas aeruginosa	0/0 (-)	1/1 (100)
Staphylococcus saprophyticus	3/4 (75)	6/6 (100)
Streptococcus Group D	2/2 (100)	2/2 (100)

N/N = Number of patients with cure/total number of patients with pathogen
Cross-Reference: APPENDIX 24.
Note: More than one pathogen may have been isolated from one patient. Therefore, the number of pathogens may exceed the number of patients.

The table below presents the applicant's bacteriological cure rates at end of treatment (5-11 days post-therapy), by isolated baseline pathogen, for the applicant's evaluable population.

TABLE *Applicant's* Bacteriological Cure Rate in the Primary Assessment Window by Pathogen - EVALUABLE Population - (STUDY MON-US-02)

Pathogens	FT No Cures/Total (%)	TMP/SMX No Cures/Total (%)
Enterobacter	0/0 (-)	1/1 (100)
Enterobacter aerogenes	0/0 (-)	1/1 (100)
Enterobacter cloacae	2/2 (100)	0/0 (-)
Enterococcus	4/4 (100)	0/1 (0)
Enterococcus faecalis	2/2 (100)	2/2 (100)
Escherichia coli	163/182 (90)	156/159 (98)
Klebsiella	0/1 (0)	1/1 (100)
Klebsiella pneumoniae	6/7 (86)	3/3 (100)
Proteus mirabilis	9/9 (100)	3/3 (100)
Pseudomonas aeruginosa	0/0 (-)	1/1 (100)
Staphylococcus saprophyticus	2/3 (67)	3/3 (100)
Streptococcus Group D	1/1 (100)	2/2 (100)

N/N=Number of patients with cure/total number of patients with pathogen
Cross-Reference APPENDIX 24
Note More than one pathogen may have been isolated from one patient. Therefore, the number of pathogens may exceed the number of patients.

TABLE *Medical Officer's* Bacteriologic Eradication Rate at 5-11 day Post Treatment Window by Pathogen (STUDY MON-US-02)

Pathogens	FT No. Eradicated/Total (%)	TMP/SMX No. Eradicated/Total (%)
Enterobacter	0/0 (-)	2/2 (100)
Enterobacter aerogenes	2/3 (67)	2/2 (100)
Enterobacter cloacae	2/2 (100)	0/0 (-)
Enterococcus	5/6 (83)	2/2 (100)
Enterococcus faecalis	4/4 (100)	4/4 (100)
Escherichia coli	179/207 (86)	171/174 (98)
Klebsiella	1/3 (33)	1/1 (100)
Klebsiella pneumoniae	5/8 (63)	5/5 (100)
Proteus mirabilis	12/12 (100)	8/8 (100)
Pseudomonas aeruginosa	0/0 (-)	1/1
Staphylococcus saprophyticus	3/6 (50)	8/8 (100)
Streptococcus Group D	2/2 (100)	1/1 (100)
Total isolates	**215/253 (85)**	**205/208 (99)**
CL_{95} (-0.19, -0.09) showing inferiority		

***Medical Officer's Comment**: The overwhelming majority of patients in both treatment arms had E. coli isolated as the uropathogen. The 95% confidence interval between the difference in successful outcomes overall is (-0.19, -0.09).*

TABLE *Medical Officer's* Bacteriologic Eradication Rate at **Study Day 15-21** - (5-11 days after the longer course, TMP-SMX) by Pathogen - (MON-US-02)

Pathogens	FT No. Eradicated/Total (%)	TMP/SMX No. Eradicated/Total (%)
Enterobacter	0/0 (-)	2/2 (100)
Enterobacter aerogenes	2/3 (67)	2/2 (100)
Enterobacter cloacae	2/2 (100)	0/0 (-)
Enterococcus	5/6 (83)	2/2 (100)
Enterococcus faecalis	4/4 (100)	4/4 (100)
Escherichia coli	169/207 (82)	171/174 (98)
Klebsiella	1/3 (33)	1/1 (100)
Klebsiella pneumoniae	5/8 (63)	5/5 (100)
Proteus mirabilis	11/12 (92)	8/8 (100)
Pseudomonas aeruginosa	0/0 (-)	1/1
Staphylococcus saprophyticus	3/6 (50)	8/8 (100)
Streptococcus Group D	2/2 (100)	1/1 (100)
Total isolates	**204/253 (80)**	**205/208 (99)**

CI_{95} (-0.25, -0.14), showing inferiority

TABLE ***Medical Officer's*** Bacteriologic Eradication Rate at 4-6 Weeks Post-Treatment by Pathogen - (STUDY MON-US-02)

Pathogens	**FT** No. Eradicated/Total (%)	**TMP/SMX** No. Eradicated/Total (%)
Enterobacter	0/0 (-)	2/2 (100)
Enterobacter aerogenes	2/3 (67)	2/2 (100)
Enterobacter cloacae	2/2 (100)	0/0 (-)
Enterococcus	4/6 (67)	2/2 (100)
Enterococcus faecalis	4/4 (100)	4/4 (100)
Escherichia coli	145/207 (70)	157/174 (90)
Klebsiella	1/3 (33)	1/1 (100)
Klebsiella pneumoniae	4/8 (50)	5/5 (100)
Proteus mirabilis	11/12 (92)	8/8 (100)
Pseudomonas aeruginosa	0/0 (-)	1/1
Staphylococcus saprophyticus	3/6 (50)	8/8 (100)
Streptococcus Group D	2/2 (100)	1/1 (100)
Total isolates	**178/253 (70%)**	**190/208 (91%)**

CI_{95} (-0.28, -0.14), showing inferiority

Clinical Efficacy Results

Time Frame: *5-11 Days Post-Therapy*
Analysis: ***Applicant's Intent-to-Treat Population***

TABLE: ***Applicant's*** Clinical Evaluation in Primary Assessment Windows - ITT Population (STUDY MON-US-02)

Clinical Outcome	FT N(%)	TMP/SMX N(%)	Treatment Group Comparison [p-value]
Cure[a]	205 (77)	195 (93)	<0.01
Improvement	57 (22)	14 (7)	
Failure	3 (1)	0 (-)	
No Evaluation[b]	26	57	

[a] 95% one-sided confidence interval for the upper bound on the difference in the cure rates: 21.0%

[b] See APPENDIX 12 for a list of patients for whom a clinical evaluation could not be made.

Medical Officer's Comment: The 26 "no evaluation" patients treated with FT were actually investigator-assessed clinical failures in 13/26 (50%) of cases by the 5-11 day post-therapy window. Of the 57 TMP/SMX patients without evaluation, 9/57 (16%) were investigator assessed clinical failures by the 5-11 day post-therapy window. I have listed below investigator assessments for these applicant "no evaluation" patients:

Rx	Investigator's Assessment	Patient Count
Ft	Adverse Experience	4
Ft	Intercurrent Medical Illn	2
Ft	Lost to Follow-Up	2
Ft	Non-Compliance	1
Ft	Other,adverse Experience: Can't Keep Med	1
Ft	Other: Removed from Study	1
Ft	Other: Resistant Organism	1
Ft	Other: Resistant to Monuril	1
Ft	Treatment Failure	13
Tmp/Smx	[f/u visit fell outside 5-11 days post-Rx, all cures]	16
Tmp/Smx	Adverse Experience	9
Tmp/Smx	Intercurrent Medical Illn	2
Tmp/Smx	Intercurrent Medical Illn	1
Tmp/Smx	Lost to Follow-Up	7
Tmp/Smx	Non-Compliance	3
Tmp/Smx	Other: Pt.org res Bactrim	1
Tmp/Smx	Other: Removed from Study	2
Tmp/Smx	Other: Resistant Organism	1
Tmp/Smx	Other: See Comment	1
Tmp/Smx	Other: Withdrew Consent	1
Tmp/Smx	Screening Failure	1
Tmp/Smx	Treatment Failure	9

Clinical Efficacy Results (continued)

Time Frame: ***5-11 Days Post-Therapy***
Analysis: ***Applicant's Evaluable Population***

TABLE: ***Applicant's*** Clinical Evaluation in Primary Assessment Window - EVALUABLE Population (STUDY MON-US-02)

	FT N(%)	TMP/SMX N(%)	Treatment Group Comparison [p-value]
Cure[a]	156 (76)	158 (93)	<0.01
Failure	48 (24)	11 (7)	
No Evaluation[b]	9	24	

[a] 95% one-sided confidence interval for the upper bound on the difference in the cure rates: 22.9%
[b] See APPENDIX 13 for a list of patients for whom a clinical evaluation could not be made.
Note that patients in the EVALUABLE population who were clinically "improved" were considered to be clinical failures in this analysis.

Medical Officer's Comment: *I have listed below investigator assessments at 5-11 days post-therapy for the applicant's "no evaluation" patients. For the 9 FT patients with "no evaluation", 6/9 (67%) were treatment failures. For TMP-SMX, 2/24 (8%) were treatment failures.*

Rx	Investigator's Assessment	Patient Count
Ft	Lost to Follow-Up	2
Ft	Non-Compliance	1
Ft	Treatment Failure	6
Tmp/Smx	[f/u visit outside 5-11 days post-Rx; all cases]	16
Tmp/Smx	Intercurrent Medical Illn	1
Tmp/Smx	Lost to Follow-Up	1
Tmp/Smx	Non-Compliance	1
Tmp/Smx	Other: Withdrew Consent	1
Tmp/Smx	Treatment Failure	2

Clinical Efficacy Results (continued)

Time Frame: ***5-11 Days Post-Therapy***
Analysis: ***Medical Officer's Evaluable Population***

Outcome	Fosfomycin N (%)	TMP-SMX N(%)	
Cure	199 (80)	186 (94)	CI_{95} (-0.20, -0.08) showing inferiority
Failure	50 (20)	11 (6)	
Total	249	197	

Day 15-21 of Study (5-11 Days after the Longer Course, TMP-SMX)

Outcome	Fosfomycin N (%)	TMP-SMX N (%)	
Cure	189 (76)	186 (94)	CI_{95} (-0.25, -0.11) showing inferiority
Early Relapse	10 (4)	--	
Failure (carried for FT)	50 (20)	11 (6)	
Total	249	197	

4-6 Weeks Post-Treatment

Outcome	Fosfomycin N (%)	TMP-SMX N(%)
Cure	164 (66)	173 (88)
Relapse	16 (6)	11 (6)
Unassessable[1]	9 (4)	2 (1)
Sub-total	189	186
Early Relapse (carried forward)	10 (4)	--
Failure (carried forward)	50 (20)	11 (6)
Total	249	197

[1]Assessment at the 5-11 day window was clinical cure/bacteriologic persistence, and patient was re-treated with antibiotics. Thus, a late clinical assessment is not possible

SAFETY EVALUATION

All patients randomized to receive study drug were included in the safety assessment: 426 patients treated with fosfomycin and 428 patients treated with TMP-SMX. Those assessments included: incidence and severity of adverse events, discontinuations from study due to adverse event and intercurrent illness, and changes in clinical laboratory findings (serum and urine).

Adverse Events (AEs):

Deaths: There were no deaths in this study.

Discontinuation due to AEs:

Twenty-five patients (seven FT, 18 TMP/SMX patients) were discontinued from the study due to an adverse event. The table below outlines the specific reasons for discontinuation of each of these patients

TABLE List of Patients Who Were Discontinued from the Study Due to an Adverse Event (STUDY MON-US-02)

Center/Patient	Description of adverse event
FT Treatment Group	
26	Diarrhea, intestinal cramping, mouth sores; last dose of medication Day 0
30	Pruritus and erythema (neck and arm); last dose of medication Day 3
35	Vomiting; last dose of medication Day 0.
36	Rash and nausea; last dose of medication Day 1 (Screen Failure).
36	Vomiting; last dose of medication Day 3.
37	Patient missed period, was confirmed to be pregnant, was withdrawn from study; last dose of medication Day 9
73	Very dry mouth; last dose of medication Day 1
TMP/SMX Treatment Group	
21	Nausea, vomiting and flank pain; last dose of medication Day 1.
21	Lymph node, hives, eye swelling; last dose of medication Day 9.
21	Rash; last dose of medication Day 8.
25	Angioedema and urticaria; last dose of medication Day 0.
26	Nausea and vomiting; last dose of medication Day 1.
30	Pruritus and rash; last dose of medication Day 6.
31	Urticaria; last dose of medication Day 0.
31	Itchy hives, rechallenged and hives returned; last dose of medication Day 4.
35	Rash; last dose of medication Day 6.
36	Urticaria; last dose of medication Day 6.
62	Rash and pruritus; last dose of medication Day 2.
62	Itchy, generalized rash; last dose of medication Day 0
62	Nausea; last dose of medication Day 1.
65	Headache, nausea, redness and swelling of face; last dose of medication: Unknown.
65	Nausea, vomiting, headache, and dizziness; last dose of medication Day 4.
70	Nausea; last dose of medication Day 4
76	Facial swelling and red face, itchy arms and body, bodily warmth; last dose of medication Day 0
76	Rash, headache, nausea and vomiting; last dose of medication Day 5.

Serious or Potentially Serious Adverse Events

Seven patients (two FT, five TMP/SMX) had serious adverse events; six of these patients (one FT, five TMP/SMX) were hospitalized due to the adverse event. These events met the definition of a serious adverse event, but were not considered to be study drug-related (see table below).

TABLE: Summary of Serious or Potentially Serious Adverse Events (MON-US-02)

Center/Patient	Description of Adverse Event
FT Treatment Group	
30	Automobile accident; hospitalized; all study medication was taken.
61.	Optic neuritis; all study medication was taken.
TMP/SMX	
31	*Cerebrovascular accident; hospitalized; all study medication was taken.
33	Acute UTI; hospitalized; all study medication was taken.
36	Broken ankle; hospitalized; all study medication was taken.
38.	Acute pyelonephritis; hospitalized; last dose of medication Day 9.
62.	Anemia; hospitalized; last dose of study medication Day 2.

Summary of All Adverse Events

In this clinical study, 176 of 426 (41%) FT patients and 212 of 428 (50%) TMP/SMX patients reported at least one adverse event during the study period. A total of 363 adverse events were reported by FT patients and 439 events were reported by TMP/SMX patients. The majority of these adverse events were considered to be mild to moderate in severity. Statistically significant differences between treatment groups were seen in the nervous body system ($p<0.01$) and in the skin and skin structures body system ($p<0.01$). Within the nervous body system, the difference is largely due to the greater incidence of dizziness noted in TMP/SMX patients than in FT patients. Within the skin and skin structures body system, the difference is largely due to the greater incidence of allergic-type skin reactions (i.e., rash, hives, itching, and urticaria) in TMP/SMX patients than in FT patients. The table below presents the body systems and the number of events reported in each.

TABLE Occurrences of Adverse Events and Number of Patients (Safety Population) Experiencing an Adverse Reaction by Body System (STUDY MON-US-02)

	FT (N=426)		TMP/SMX (N=428)		
BODY SYSTEM	Occurrences of AEs	Number of Pts	Occurrences of AEs	Number of Pts.	Treatment Group Comparison (p-value)*
BODY AS A WHOLE	130	93	154	102	0.52
CARDIOVASCULAR	1	1	2	2	1.00
DIGESTIVE	95	76	102	80	0.79
ENDOCRINE	1	1	0	0	0.50
HEMIC AND LYMPHATIC	5	5	6	6	1.00
METABOLIC AND NUTRITIONAL	6	3	5	5	0.73
MUSCULOSKELETAL	15	15	11	11	0.43
NERVOUS	14	12	35	30	< 0.01
RESPIRATORY	29	20	27	22	0.88
SKIN AND SKIN STRUCTURES	12	12	52	41	< 0.01
SPECIAL SENSES	7	7	8	8	1.00
UROGENITAL	48	39	37	34	0.54
OVERALL	363 events reported by 176 patients		439 events reported by 212 patients		

* Fisher's exact test

TABLE Occurrences of **Adverse Events in the Nervous Body System**
(STUDY MON-US-02)

	FT (N=426)			TMP/SMX (N=428)		
NERVOUS BODY SYSTEM	Occurrences of AEs	Number of Pts	% of FT Pts	Occurrences of AEs	Number of Pts	% of TMP/SMX Pts
Depression	2	2	0.5	1	1	0.2
Drowsiness	1	1	0.2	2	2	0.5
Lightheadedness	1	1	0.2	2	2	0.5
Paresthesia	1	1	0.2	1	1	0.2
Shakey	0	0	0.0	2	2	0.5
Sleepy	2	1	0.2	0	0	0.0
Tingling Inside Mouth	0	0	0.0	2	2	0.5
Anxiety Attack	0	0	0.0	1	1	0.2
Cerebrovascular Accident	0	0	0.0	1	1	0.2
Concussion	1	1	0.2	0	0	0.0
Euphoria	0	0	0.0	1	1	0.2
Optic Neuritis	1	1	0.2	0	0	0.0
Tingling in Toes	0	0	0.0	1	1	0.2
Vasovagel	0	0	0.0	1	1	0.2
Dizziness	5	5	1.2	15	15	3.5
Insomnia	0	0	0.0	5	5	1.2
TOTALS	14	12	2.8	30	30	7.0

TABLE Occurrences of **Adverse Events in the Skin and Skin Structures Body System** (STUDY MON-US-02)

SKIN AND SKIN STRUCTURES BODY SYSTEM	FT [N=426] Occurrences of AE's	FT [N=426] Number of Pts	FT [N=426] % of FT Pts	TMP/SMX [N=428] Occurrences of AEs	TMP/SMX [N=428] Number of Pts	TMP/SMX [N=428] % of TMP/SMX Pts
Rash	3	3	0 7	22	22	5 1
Hives	1	1	0.2	7	6	1 4
Itching	1	1	0.2	6	6	1 4
Urticaria	0	0	0 0	5	5	1 2
Acne	1	1	0 2	2	2	0 5
Itchy Arms	1	1	0.2	2	2	0 5
Pruritus	1	1	0 2	2	2	0 5
Sweating	0	0	0 0	2	2	0 5
Blisters-Wrist	1	1	0.2	0	0	0 0
Herpes Simplex	0	0	0 0	1	1	0 2
Hair Loss	1	1	0 2	0	0	0 0
Itchy Eyes	1	1	0.2	0	0	0 0
Maculopapular Rash	0	0	0 0	1	1	0 2
Ringworm	0	0	0 0	1	1	0.2
Skin Disorder	1	1	0.2	0	0	0 0
Skin Cut	0	0	0.0	1	1	0.2
TOTALS	12	12	2.8	52	41	9 6

TABLE **Occurrences of Adverse Events ≥ 1.0%[a] of the Patients - All Body Systems**
(STUDY MON-US-02)

BODY SYSTEM	FT [N=426] Occurrences of Adverse Events	FT [N=426] Number of Patients	FT [N=426] % of FT Patients	TMP/SMX [N=428] Occurrences of Adverse Events	TMP/SMX [N=428] Number of Patients	TMP/SMX [N=428] % of TMP/SMX Patients	Treatment Group Comparison [p-value][c]
Body as a Whole	**130**	**93**	—	**154**	**102**	—	
Headache	58	48	11.3	54	46	10.7	0.83
Yeast infection	9	8	1.9	9	9	2.1	1.00
Cold	9	9	2.1	7	7	1.6	0.63
Backache	10	8	1.9	5	5	1.2	0.42
Fatigue	4	4	0.9	7	7	1.6	0.55
Flu syndrome	5	5	1.2	5	5	1.2	1.00
Chills	1	1	0.2	7	6	1.4	0.12
Fever	4	4	0.9	4	4	0.9	1.00
Malaise	1	1	0.2	6	6	1.4	0.12
Digestive[b]	**95**	**76**	—	**102**	**80**	—	
Nausea	22	21	4.9	44	43	10.0	<0.01
Diarrhea	44	40	9.4	11	11	2.6	<0.01
Vomiting	6	6	1.4	12	12	2.8	0.23
Constipation	0	0	0.0	8	8	1.9	<0.01
Gastritis	2	2	0.5	5	5	1.2	0.45
Abnormal stools	5	5	1.2	0	0	0.0	0.03
Nervous[b]	**14**	**12**	—	**35**	**30**	—	
Dizziness	5	5	1.2	15	15	3.5	0.04
Insomnia	0	0	0.0	5	5	1.2	0.06
Respiratory[b]	**29**	**20**	—	**27**	**22**	—	
Congestion	5	5	1.2	4	4	0.9	0.75
Sore throat	3	3	0.7	6	6	1.4	0.51
Sinusitis	3	3	0.7	5	5	1.2	0.73
Skin and Skin Structures[b]	**12**	**12**	—	**52**	**41**	—	
Rash	3	3	0.7	22	22	5.1	<0.01
Hives	1	1	0.2	7	6	1.4	0.12
Itching	1	1	0.2	6	6	1.4	0.12
Urticaria	0	0	0.0	5	5	1.2	0.06
Urogenital[b]	**48**	**39**	—	**37**	**34**	—	
Vaginitis	10	10	2.3	6	6	1.4	0.33
Vaginal discharge	7	6	1.4	7	7	1.6	1.00

[a] Full listing of adverse events in APPENDIX 15
[b] Total number of adverse events for Body System
[c] Based on Fisher's exact test

The table below summarizes the adverse events that were, in the opinion of the investigator, probably or definitely related to study drug administration

TABLE **Adverse Events* That Were Classified as Probably or Definitely Related to Study Drug** (Both Treatment Groups) - All Body Systems (STUDY MON-US-02)

BODY SYSTEM	FT [N = 426] Occurrences of Adverse Events	FT [N = 426] Number of Patients	FT [N = 426] % of FT Patients	TMP/SMX [N = 428] Occurrences of Adverse Events	TMP/SMX [N = 428] Number of Patients	TMP/SMX [N = 428] % of TMP/SMX Patients
Body as a Whole (Total)	2	2	—	13	11	—
Headache	0	0	0.0	4	4	0.9
Yeast infection	2	2	0.5	2	2	0.5
Flushed	0	0	0.0	2	2	0.5
Edema	0	0	0.0	1	1	0.2
Fatigue	0	0	0.0	1	1	0.2
Hot	0	0	0.0	1	1	0.2
Pain	0	0	0.0	1	1	0.2
Swelling	0	0	0.0	1	1	0.2
Digestive (Total)	13	11	—	14	11	—
Nausea	4	4	0.9	7	7	1.6
Diarrhea	4	4	0.9	1	1	0.2
Vomiting	1	1	0.2	3	3	0.7
Stomach upset	1	1	0.2	2	2	0.5
Appetite (Decreased)	2	2	0.5	0	0	0.0
Abnormal Stools	1	1	0.2	0	0	0.0
Gastritis	0	0	0.0	1	1	0.2
Heroic and Lymphatic (Total)	1	1	—	2	2	—
WBC Low	0	0	0.0	2	2	0.5
High platelet count	1	1	0.2	0	0	0.0
Metabolic and Nutritional (Total)	3	1	—	1	1	—
SGOT increased	1	1	0.2	1	1	0.2
Phosphatase alkaline	1	1	0.2	0	0	0.0
SGPT increased	1	1	0.2	0	0	0.0
Nervous (Total)	0	0	—	2	2	—
Dizziness	0	0	0.0	1	1	0.2
Tingling inside mouth	0	0	0.0	1	1	0.2
Skin and Skin Structure (Total)	2	2	—	21	16	—
Rash	1	1	0.2	10	10	2.3
Hives	1	1	0.2	2	1	0.5
Itching	0	0	0.0	3	3	0.7
Urticaria	0	0	0.0	3	3	0.7
Itchy arms	0	0	0.0	1	1	0.2
Maculopapular rash	0	0	0.0	1	1	0.2
Pruritus	0	0	0.0	1	1	0.2
Urogenital System (Total)	10	8	—	2	2	—
Vaginitis	5	5	1.2	0	0	0.0
Vaginal itching	2	2	0.5	1	1	0.2
WBC in urinalysis	1	1	0.2	1	1	0.2
Urethral syndrome	1	1	0.2	0	0	0.0
Vaginal discharge	1	1	0.2	0	0	0.0
Overall	31 events reported by 25 patients			55 events reported by 45 patients		

Markedly Abnormal Lab Results

The medical monitor determined the markedly abnormal value for each laboratory parameter evaluated and, in general, these were considered to be three times the upper limit of normal. Post-baseline serum chemistry results and hematology results were screened for values that were considered to be markedly abnormal. The table below presents the incidence of post-baseline serum laboratory values considered to be markedly abnormal for each parameter assessed.

TABLE: Incidence of Serum Laboratory Values (Post-baseline) Considered to be Markedly Abnormal (STUDY MON-US-02)

		# PTS/ # OF PTS EVALUATED (%)		# OCCURRENCES/ TOTAL # OF PT VISITS (%)	
Laboratory Parameters (units)	Markedly Abnormal Values	FT	TMP/SMX	FT	TMP/SMX
SGOT (U/L)	> 150	1/338 (0.3)	2/327 (0.6)	1/634 (0.2)	3/604 (0.5)
SGPT (U/L)	> 165	1/338 (0.3)	2/327 (0.6)	1/634 (0.2)	4/604 (0.7)
Alkaline Phosphatase (U/L)	> 420	0/338 (0)	1/327 (0.3)	0/634 (0)	1/603 (0.2)
Bilirubin (mg/dL)	> 3.6	0/338 (0)	0/327 (0)	0/634 (0)	0/604 (0)
Creatinine (mg/dL)	> 2.0	0/338 (0)	2/327 (0.6)	0/634 (0)	3/604 (0.5)
BUN (mg/dL)	> 45	0/338 (0)	0/327 (0)	0/635 (0)	0/605 (0)
Hematocrit (%)	< 27	0/338 (0)	0/323 (0)	0/629 (0)	0/596 (0)
Hemoglobin (g/dL)	< 9.5	0/338 (0)	2/323 (0.6)	0/629 (0)	3/596 (0.5)
Red Blood Cells (x10⁶/μL)	< 2.9	0/338 (0)	0/323 (0)	0/629 (0)	0/596 (0)
White Blood Cells (x1000/μL)	< 2.0	0/338 (0)	0/323 (0)	0/629 (0)	0/596 (0)
Eosinophils (%)	> 10.0	1/338 (0.3)	0/325 (0)	1/628 (0.2)	0/596 (0)
Platelets (x1000/μL)	< 90	0/338 (0)	0/323 (0)	0/629 (0)	0/596 (0)

Cross-Reference: Raw Data Listing 13.

One FT patient Center 38) had an elevated SGOT value that exceeded 150 U/L (169 U/L at Visit 3) and an elevated SGPT value that exceeded 165 U/L (175 U/L at Visit 3). Baseline SGOT and SGPT values for patient were 110 and 129 U/L, respectively. One FT patient Center 25) had an eosinophil evaluation that exceeded 10.0% (14% at Visit 3). Visit 1 (baseline) and Visit 2 eosinophil counts were both 3% for patient None of the marked elevations was considered to be clinically significant.

Patients in the TMP/SMX group also had few markedly abnormal chemistry and hematology evaluations. The incidence of markedly abnormal test results in both treatment groups was less than 1% for all chemistry and hematology parameters assessed.

MEDICAL OFFICER'S SUMMARY AND CONCLUSIONS FOR MON-US-02

In this second U.S. clinical trial comparing single dose fosfomycin tromethamine to a 10-day course of trimethoprim/sulfamethoxazole (TMP/SMX) in women with uncomplicated lower urinary tract infections (cystitis), efficacy results for both microbiologic and clinical outcome show single dose fosfomycin to be inferior to standard therapy. Safety overall of the two regimens appeared comparable (more diarrhea with fosfomycin, more nausea, rashes and hives with TMP/SMX). These findings of lesser efficacy and similar safety corroborate those found in the first study.

At the time fosfomycin was filed as an IND to the Agency (1990), no short-term therapy for cystitis was approved. Since 1990, the Division has approved two products for short course therapy of cystitis:

norfloxacin (Noroxin®)	400 mg q12h for 3 days, and
ofloxacin (Floxin®)	200 mg q12h for 3 days.

In each case, the short-term treatment was clinically and microbiologically equivalent (95% confidence interval met) to standard therapy for 7-10 days.

Potential advantages of single dose treatment are clear: better patient compliance, possible reduced risk of side effects. Whether one should accept lesser efficacy to gain these advantages remains unclear.

The Medical Officer recommended that this New Drug Application be taken to the Anti-Infective Advisory Committee for further discussion. The committee met in an open session on July 20, 1995.

ADVISORY COMMITTEE MEETING SUMMARY

During the July 20 open session the Committee reviewed NDA 50-717, fosfomycin tromethamine (Monurol), Forest Laboratories, Inc /Zambon Corporation, for short-term treatment (3 g single dose oral therapy) of uncomplicated lower urinary tract infection (UTI) in women.

Traditional antibacterial therapy for uncomplicated UTI is a 7-10 day course of treatment. Currently in the US, there is no approved *single dose* short-term treatment for UTI, although norfloxacin (Noroxin) and ofloxacin (Floxin), as noted above, are approved for a 3-day course of therapy.

The following questions were posed to the Committee:

1 Should short course therapy (single dose or 3 days) for the treatment of cystitis in women be held to the same standard as traditional courses of 7-10 days?

COMMITTEE VOTE: 5 = No
3 = Yes
2 = Abstain

2 If no, what is the minimum efficacy acceptable for approval of short-term therapy?

The Committee declined to answer this question.

3 Based on the efficacy and safety data you have seen presented today, would you recommend that fosfomycin be approved as a single dose therapy for cystitis in women?

COMMITTEE VOTE 8 = No
2 = Yes

The majority of Committee members concluded that efficacy for single dose fosfomycin was relatively low, in the 70-80% range, while comparators (ciprofloxacin and trimethoprim/sulfamethoxazole, given for 7 and 10 days, respectively) were in the 90-99% range. Some expressed concern that the pharmacokinetic (pK) profile of the drug had not been adequately studied, with 40% of a 3 g oral fosfomycin dose not accounted for in clinical pK trials. Finally, there was a consensus that the safety profile of fosfomycin as a single dose did not balance the lesser efficacy of the drug, particularly with regard to diarrhea.

MEDICAL OFFICER'S OVERALL SUMMARY FOR PIVOTAL US TRIALS

STUDY MON-US-01/EFFICACY:

BACTERIOLOGICAL OUTCOME BY PATIENT

Evaluation Period	Fosfomycin n/N (%)	Ciprofloxacin n/N (%)	95% C.I.
@ 5-11 days after last dose of drug	203/260 (78%)	219/222 (98%)	(-26%, -14%)
@ 12-18 days of the study	194/260 (75%)	219/222 (98%)	(-29%, -17%)
@ 4-6 weeks after last dose of drug	173/260 (67%)	202/222 (91%)	(-31%, -17%)

n = number of patients whose isolates were eradicated
N = number of patients evaluable

BACTERIOLOGICAL OUTCOME FOR SELECTED PATHOGENS
at Days 12-18 of Study

Pathogens Evaluated	Fosfomycin n/N (%)	Ciprofloxacin n/N (%)	95% C.I.
All Pathogens	198/264 (75%)	219/222 (99%)	(-30%, -18%)
Escherichia coli	167/216 (77%)	184/187 (98%)	
Klebsiella pneumoniae	7/11 (64%)	4/4	
Proteus mirabilis	5/9 (56%)	7/7	
Enterobacter aerogenes	2/3	3/3	
Enterobacter cloacae	1/1	5/5	

CLINICAL OUTCOME BY PATIENT

Evaluation Period	Fosfomycin n/N (%)	Ciprofloxacin n/N (%)	95% C.I.
@ 5-11 days after last dose of drug	199/260 (77%)	213/222 (96%)	(-25%, -13%)
@ 12-18 days of the study	189/260 (75%)	212/222 (95%)	(-29%, -16%)
@ 4-6 weeks after last dose of drug	153/260 (59%)	196/222 (88%)	(-37%, -22%)

n = number of patients whose were cured of acute cystitis
N = number of patients evaluable

STUDY MON-US-01/SAFETY:

Adverse Events Occurring in ≥ 1.0% of the Patients (Most Common Adverse Events)

TABLE: **Occurrences of Adverse Events ≥ 1.0%[a] of the Patients - All Body Systems (STUDY MON-US-01)**

BODY SYSTEM	FT [N-432] Occurrences of Adverse Events	FT [N-432] No. of Patients	FT [N-432] % FT Patients	CIPRO [N-445] Occurrences of Adverse Events	CIPRO [N-445] No. of Patients	CIPRO [N-445] % CIPRO Patients	Treatment Group Comparison [p-value][c]
Body as a Whole[b]	146	102	—	133	94	—	
Headache	50	38	8.8	56	42	9.4	0.82
Yeast infection	13	13	3.0	22	20	4.5	0.29
Backache	16	15	3.5	12	11	2.5	0.43
Cold	11	10	2.3	9	9	2.0	0.82
Abdominal pain	9	8	1.9	2	2	0.4	0.06
Tired	6	6	1.4	2	2	0.4	0.17
Cardiovascular[b]	8	7	—	6	6	—	
Migraine	5	5	1.2	2	2	0.4	0.28
Digestive[b]	78	60	—	64	51	—	
Diarrhea	34	33	7.6	22	19	4.3	0.04
Nausea	18	18	4.2	22	21	4.7	0.75
Stomach upset	6	6	1.4	3	3	0.7	0.34
Nervous[b]	18	17	—	16	16	—	
Dizziness	9	8	1.9	10	10	2.2	0.81
Respiratory[b]	34	27	—	35	32	—	
Congestion	7	6	1.4	5	5	1.1	0.77
Cough	4	4	0.9	5	5	1.1	1.00
Sinusitis	4	4	0.9	5	5	1.1	1.00
Sore throat	2	2	0.5	6	6	1.3	0.29
Skin and Skin Structures[b]	18	16	—	21	19	—	
Rash	10	10	2.3	3	3	0.7	0.05
Herpes simplex	0	0	0.0	5	5	1.1	0.06
Urogenital[b]	60	53	—	48	43	—	
Vaginal itching	10	10	2.3	8	8	1.8	0.64
Vaginitis	8	7	1.6	8	8	1.8	1.00
Urinary symptoms	8	8	1.9	4	4	0.9	0.26
Menstrual cramps	7	6	1.4	3	3	0.7	0.34
Vaginal discharge	4	4	0.9	6	6	1.3	0.75

[a] Full listing of adverse events in APPENDIX 15
[b] Total number of adverse events for Body System
[c] Fisher's Exact Test

STUDYMON-US-02/EFFICACY:

BACTERIOLOGICAL OUTCOME BY PATIENT

Evaluation Period	Fosfomycin n/N (%)	TMP/SMX n/N (%)	95% C.I.
@ 5-11 days after last dose of drug	212/249 (85%)	194/197 (98%)	(-18%, -8%)
@ 15-21 days of the study	201/249 (81%)	194/197 (98%)	(-23%, -11%)
@ 4-6 weeks after last dose of drug	174/249 (70%)	180/197 (91%)	(-28%, -14%)

n = number of patients whose isolates were eradicated
N = number of patients evaluable

BACTERIOLOGICAL OUTCOME FOR SELECTED PATHOGENS
at Days 15-21 of Study

Pathogens Evaluated	Fosfomycin n/N (%)	TMP/SMX n/N (%)	95% C.I.
All Pathogens	204/253 (80%)	205/208 (99%)	(-25%, -14%)
Escherichia coli	169/207 (82%)	171/174 (98%)	
Klebsiella pneumoniae	5/8 (63%)	5/5	
Proteus mirabilis	11/12 (92%)	8/8	
Enterobacter aerogenes	2/3	2/2	
Enterobacter cloacae	2/2	-	

CLINICAL OUTCOME BY PATIENT

Evaluation Period	Fosfomycin n/N (%)	TMP/SMX n/N (%)	95% C.I.
@ 5-11 days after last dose of drug	199/249 (80%)	186/197 (94%)	(-20%, -8%)
@ 15-21 days of the study	189/249 (76%)	186/197 (94%)	(-25%, -11%)
@ 4-6 weeks after last dose of drug	164/249 (66%)	173/197 (88%)	(-30%, -14%)

n = number of patients whose were cured of acute cystitis
N = number of patients evaluable

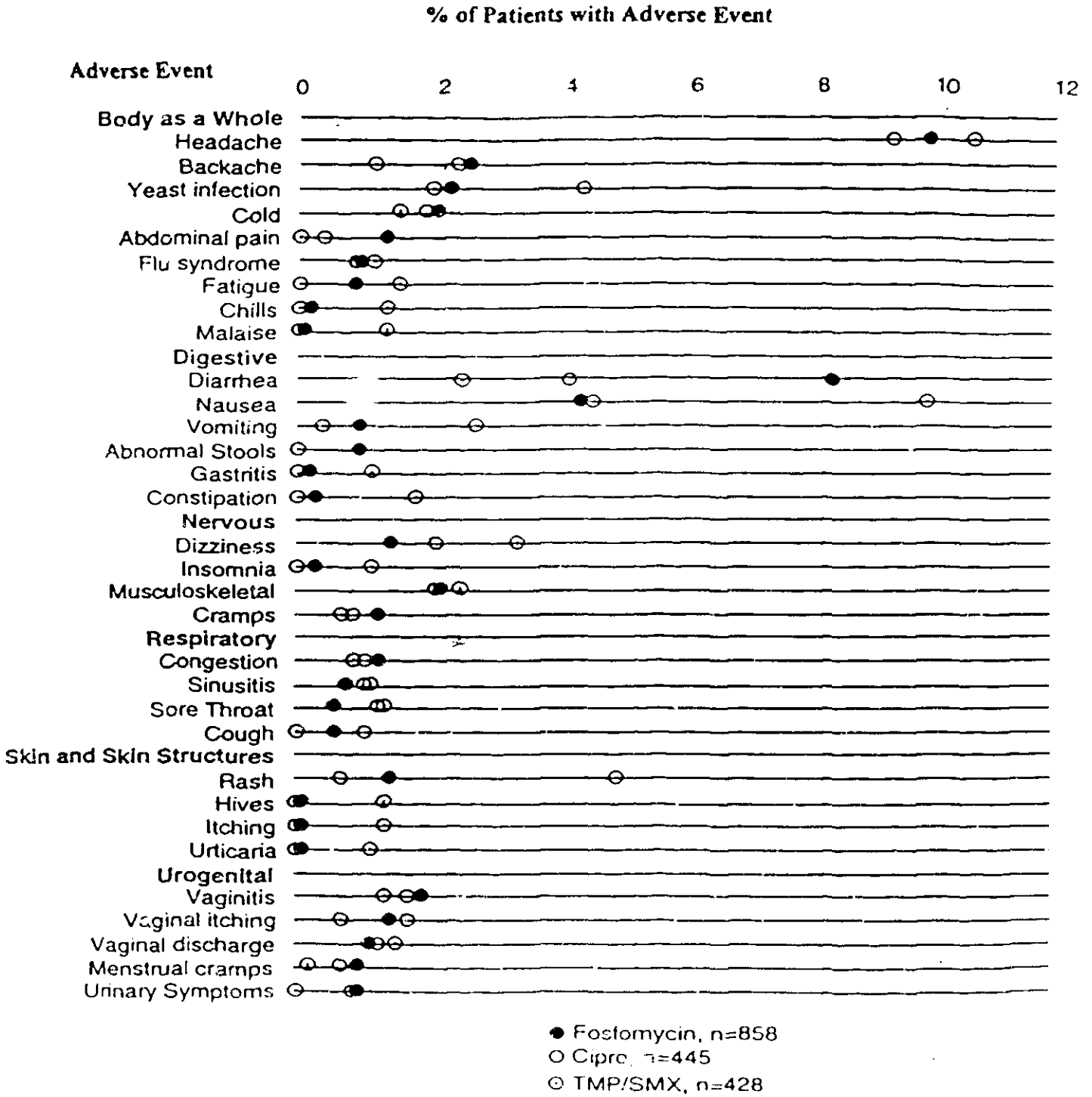
STUDY MON-US-02/SAFETY:

TABLE Occurrences of Adverse Events ≥ 1.0%[a] of the Patients - All Body Systems (STUDY MON-US-02)

BODY SYSTEM	FT [N=426] Occurrences of Adverse Events	FT [N=426] Number of Patients	FT [N=426] % of FT Patients	TMP/SMX [N=428] Occurrences of Adverse Events	TMP/SMX [N=428] Number of Patients	TMP/SMX [N=428] % of TMP/SMX Patients	Treatment Group Comparison [p-value][c]
Body as a Whole	**130**	**93**	—	**154**	**102**	—	
Headache	58	48	11.3	54	46	10.7	0.83
Yeast infection	9	8	1.9	9	9	2.1	1.00
Cold	9	9	2.1	7	7	1.6	0.63
Backache	10	8	1.9	5	5	1.2	0.42
Fatigue	4	4	0.9	7	7	1.6	0.55
Flu syndrome	5	5	1.2	5	5	1.2	1.00
Chills	1	1	0.2	7	6	1.4	0.12
Fever	4	4	0.9	4	4	0.9	1.00
Malaise	1	1	0.2	6	6	1.4	0.12
Digestive[b]	**95**	**76**	—	**102**	**80**	—	
Nausea	22	21	4.9	44	43	10.0	<0.01
Diarrhea	44	40	9.4	11	11	2.6	<0.01
Vomiting	6	6	1.4	12	12	2.8	0.23
Constipation	0	0	0.0	8	8	1.9	<0.01
Gastritis	2	2	0.5	5	5	1.2	0.45
Abnormal stools	5	5	1.2	0	0	0.0	0.03
Nervous[b]	**14**	**12**	—	**35**	**30**	—	
Dizziness	5	5	1.2	15	15	3.5	0.04
Insomnia	0	0	0.0	5	5	1.2	0.06
Respiratory[b]	**29**	**20**	—	**27**	**22**	—	
Congestion	5	5	1.2	4	4	0.9	0.75
Sore throat	3	3	0.7	6	6	1.4	0.51
Sinusitis	3	3	0.7	5	5	1.2	0.73
Skin and Skin Structures[b]	**12**	**12**	—	**52**	**41**	—	
Rash	3	3	0.7	22	22	5.1	<0.01
Hives	1	1	0.2	7	6	1.4	0.12
Itching	1	1	0.2	6	6	1.4	0.12
Urticaria	0	0	0.0	5	5	1.2	0.06
Urogenital[b]	**48**	**39**	—	**37**	**34**	—	
Vaginitis	10	10	2.3	6	6	1.4	0.33
Vaginal discharge	7	6	1.4	7	7	1.6	1.00

[a] Full listing of adverse events in APPENDIX 15
[b] Total number of adverse events for Body System
[c] Based on Fisher's exact test

SAFETY SUMMARY FOR PIVOTAL U.S TRIALS (MON-US-01 and MON-US-02)

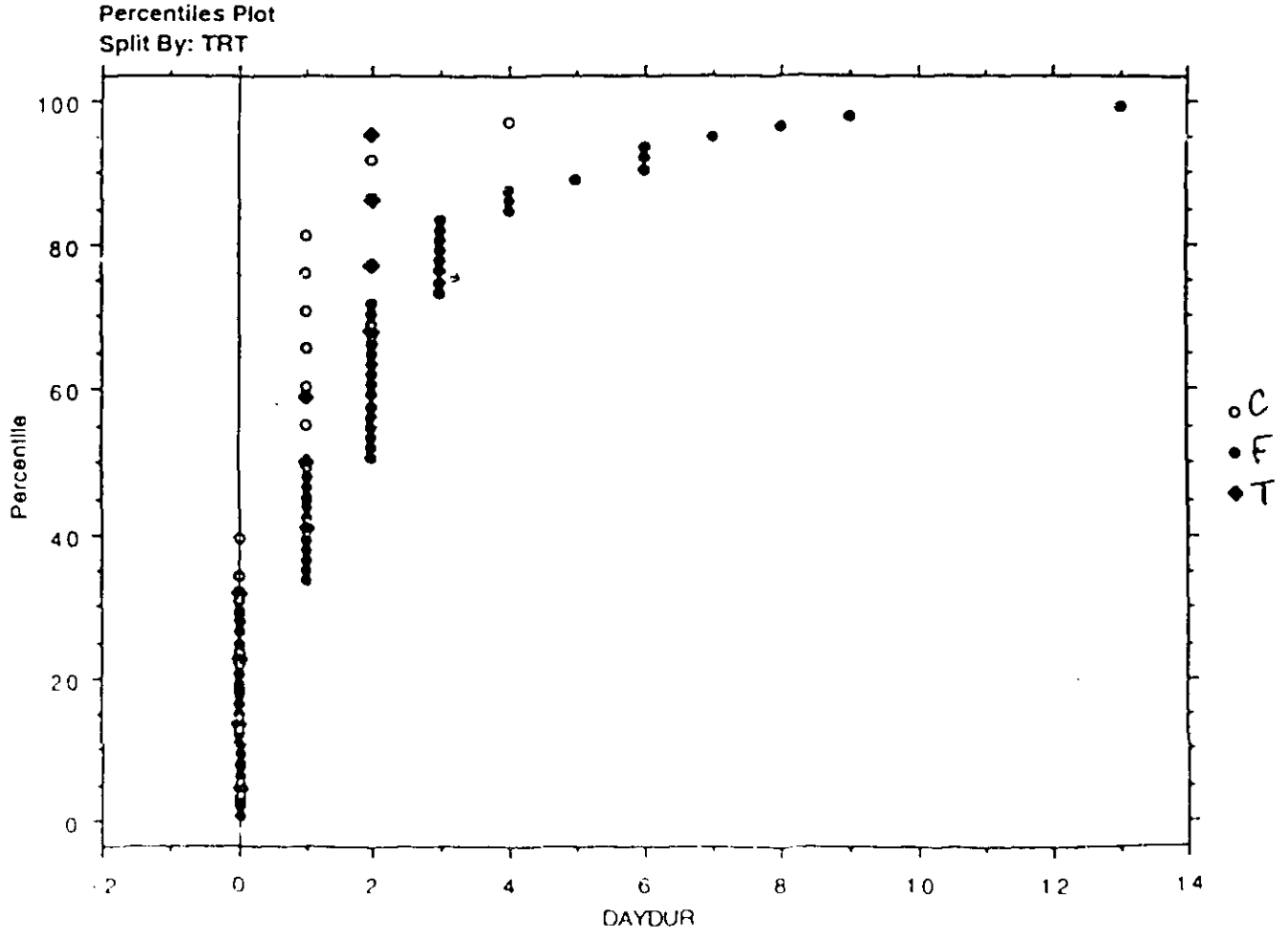


Incidence and Duration of Diarrhea, by Treatment
From U.S. Clinical Studies (#1 and #2)

Parameter	Fosfomycin	Ciprofloxacin	TMP/SMX
No. (%) of Cases	70/858 (8%)	19/445 (4%)	11/428 (3%)
Mean Duration (days)	2.0	0.8	1.0
Duration Range (days)			

As seen in the table above, the incidence of diarrhea in patients on single-dose fosfomycin was higher than in either of the other treatment arms. Furthermore, the average duration of diarrhea was twice as long (2 days) when compared to ciprofloxacin or TMP/SMX.

A graphical presentation of the cumulative incidence over time is provided below.



MEDICAL OFFICER'S RECOMMENDATION

Based on her review of the data and the Advisory Committee discussion and vote, the Medical Officer recommends not approving fosfomycin tromethamine (Monurol®) as a single dose treatment for uncomplicated urinary tract infections (cystitis) in women

8/8/95

Janice Soreth, M.D.
Medical Officer

Concurrence only
HFD-500/Act DepDir ODE II/Feigal 9-19-95
HFD-520/DivDir/Fanning
cc
Orig. NDA
HFD-340
HFD-520/DepDir/Gavrilovich 8/9/95
HFD-520/SMO/Albrecht 8/31/95
HFD-520/Chem/Timper 8/12/95
HFD-520/Micro-Dionne
HFD-520/Pharm-Buko
HFD-520/Stat-Turney
HFD-520/Project Mgt-Dillon-Parker