

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 050762

**Trade Name: TROVAN/ZITHROMAX COMPLIANCE
PAK (100 MG TROVAN TABLET AND 1 GM
ZITHROMAX SINGLE DOSE PACKET)**

**Generic Name: TROVAFLOXACIN MESYLATE/
AZITHROMYCIN FOR ORAL SUSPENSION**

Sponsor: PFIZER, INC.

Approval Date: 12/28/98

**Indication(s): TREATMENT OF SEXUALLY TRANSMITTED
DISEASES**

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 050762

APPROVAL LETTER



NDA 50-762

Food and Drug Administration
Rockville MD 20857

Pfizer Inc.
Attention: Malvina Laudicina
Director, Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

DEC 18 1998

Dear Ms. Laudicina:

Please refer to your new drug application (NDA) dated December 17, 1997, received December 19, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the TROVAN/ZITHROMAX Compliance Pak (trovafloxacin mesylate/azithromycin for oral suspension) containing a 100 mg TROVAN Tablet and 1 gram ZITHROMAX Single-Dose Packet.

We acknowledge receipt of your submissions dated January 21, February 2, 6 and 27, March 17 and 19, April 14, June 15 and December 2, 3, 8 and 16, 1998.

This new drug application provides for the use of the TROVAN/ZITHROMAX Compliance Pak (trovafloxacin mesylate/azithromycin for oral suspension) 100 mg TROVAN Tablet and 1 gram ZITHROMAX Single-Dose Packet for two Sexually Transmitted Diseases (STDs).

We have completed the review of this application, as amended, 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 agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling submitted December 16, 1998 and the patient package insert submitted December 16, 1998. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 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 "FPL for approved NDA 50-762." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials 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 this Division and two copies of both the promotional materials and the package insert directly to:

NDA 50-762

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

Please submit one market package of the drug product 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, contact Robin Anderson, Project Manager, at (301) 827-2127.

Sincerely,

/s/

Mark J. Goldberger, M.D., M.P.H.

Director

Division of Special Pathogen and Immunologic Drug
Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050762

FINAL PRINTED LABELING

12-16-1998 Pfizer Version

TROVAN[®] /ZITHROMAX[®] Compliance Pak (trovafloxacin mesylate/azithromycin for oral suspension)

The TROVAN[®]/ZITHROMAX[®] Compliance Pak provides a single dose treatment for two separate Sexually Transmitted Diseases. (See **INDICATIONS AND USAGE** section.) The Compliance Pak contains a single 100-mg TROVAN (trovafloxacin mesylate) tablet and one ZITHROMAX (azithromycin for oral suspension) Single-Dose Packet, 1 gram.

The TROVAN/ZITHROMAX Compliance Pak refers to a specific dual treatment for uncomplicated urethral gonorrhea in males and endocervical and rectal gonorrhea in females caused by *Neisseria gonorrhoeae* and non-gonococcal urethritis/cervicitis caused by *Chlamydia trachomatis*.

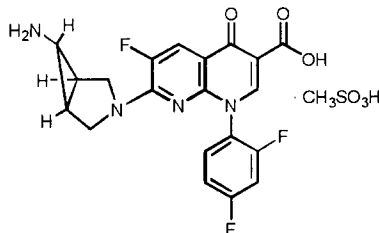
The data provided in this prescribing information is specific **only** to these two indications. TROVAN and ZITHROMAX are each indicated for additional infections due to other susceptible microorganisms as individually administered products. For complete information on other available forms of TROVAN and ZITHROMAX as well as their uses, please consult the relevant product prescribing information.

DESCRIPTION

TROVAN TABLETS

TROVAN Tablets contain trovafloxacin mesylate, a synthetic broad-spectrum antibacterial agent for oral administration. Chemically, trovafloxacin mesylate, a fluoronaphthyridone related to the fluoroquinolone antibacterials, is (1 α , 5 α , 6 α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate. Trovafloxacin mesylate differs from other quinolone derivatives by having a 1,8-naphthyridine nucleus.

The chemical structure is:



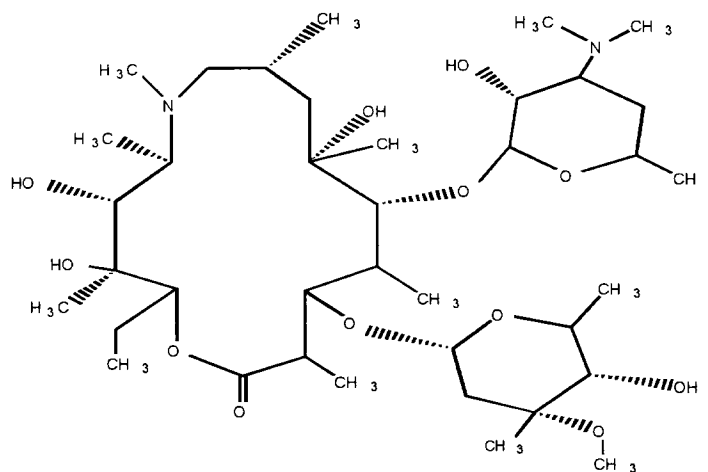
Its empirical formula is $C_{20}H_{15}F_3N_4O_3 \cdot CH_3SO_3H$ and its molecular weight is 512.46.

Trovafloxacin mesylate is a white to off-white powder.

This Compliance Pak contains a single 100 mg (trovafloxacin equivalent) blue, film-coated TROVAN tablet. TROVAN Tablets contain microcrystalline cellulose, crosslinked sodium carboxymethyl cellulose, and magnesium stearate. The tablet coating is a mixture of hydroxypropyl cellulose, hydroxypropylmethyl cellulose, titanium dioxide, polyethylene glycol, and FD&C blue #2 aluminum lake.

ZITHROMAX SINGLE DOSE PACKET

ZITHROMAX SINGLE DOSE PACKET contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -*L*-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[[3,4,6-trideoxy-3-(dimethylamino)- β -*D*-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.0. Azithromycin has the following structural formula:



Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12} \times 2H_2O$ and a molecular weight of 785.0.

This Compliance Pak also contains one ZITHROMAX[®] Single Dose Packet consisting of azithromycin dihydrate equivalent to 1 g azithromycin. The Single Dose Packet also contains the following inactive ingredients: colloidal silicon dioxide, sodium phosphate tribasic, anhydrous; spray dried artificial banana flavor, spray dried artificial cherry flavor, and sucrose.

CLINICAL PHARMACOLOGY

TROVAFLOXACIN

Absorption

Trovafloxacin is well-absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 88%.

Pharmacokinetics

The mean pharmacokinetic parameters ($\pm$ SD) of trovafloxacin after a 100-mg oral dose appear in the table below.

TROVAFLOXACIN PHARMACOKINETIC PARAMETERS – 100-mg SINGLE ORAL DOSE			
$C_{\max}$ ($\mu\text{g/mL}$)	$T_{\max}$ (hrs)	$\text{AUC}^{(0-\infty)}$ ($\mu\text{g}\cdot\text{h/mL}$)	$T_{1/2}$ (hrs)
1.0 $\pm$ 0.3	0.9 $\pm$ 0.4	11.2 $\pm$ 2.2	9.1

$C_{\max}$ = Maximum serum concentration; $T_{\max}$ =Time to $C_{\max}$; $\text{AUC}^{(0-\infty)}$ =Area under concentration vs. time curve to infinite time; $T_{1/2}$ =serum half-life

Oral absorption of trovafloxacin is not altered by concomitant food intake; therefore, it can be administered without regard to food.

The systemic exposure to trovafloxacin ($\text{AUC}_{0-\infty}$) administered as crushed tablets via nasogastric tube into the stomach was identical to that of orally administered intact tablets. Administration of concurrent enteral feeding solutions had no effect on the absorption of trovafloxacin given via nasogastric tube into the stomach. When trovafloxacin was administered as crushed tablets into the duodenum via nasogastric tube, the $\text{AUC}_{0-\infty}$ and peak serum concentration ($C_{\max}$) were reduced by 30% relative to the orally administered intact tablets. Time to peak serum level ($T_{\max}$) was also decreased from 1.7 hrs to 1.1 hrs.

Distribution

The mean plasma protein bound fraction is approximately 76%, and is concentration-independent. Trovafloxacin is widely distributed throughout the body. Rapid distribution of trovafloxacin into tissues results in significantly higher trovafloxacin concentrations in most target tissues than in plasma or serum.

Reproductive Fluid or Tissue	Tissue-Fluid/Serum Ratio* (Range)
prostatic tissue	1.0 (0.5-1.6)
cervix (multiple dose)	0.6 (0.5-0.7)
ovary	1.6 (0.3-2.2)
fallopian tube	0.7 (0.2-1.1)
myometrium (multiple dose)	0.6 (0.4-0.8)
uterus	0.6 (0.3-0.8)
vaginal fluid (multiple dose)	4.7 (0.8-20.8)

* Mean values in adults over 2-29 hours following single 200-mg tablet administration (multiple 200-mg doses where noted).

Presence in Human Milk

Trovafloxacin has been detected in the human milk of lactating subjects. (See

PRECAUTIONS: Nursing Mothers)

Metabolism

Trovafloxacin is metabolized by conjugation (the role of cytochrome P₄₅₀ oxidative metabolism of trovafloxacin is minimal). Thirteen percent of the administered dose appears in the urine in the form of the ester glucuronide, and 9% appears in the feces as the N-acetyl metabolite. (2.5% of the dose is found in the serum as the active N-acetyl metabolite.) Other minor metabolites (diacid, sulfamate, hydroxycarboxylic acid) have been identified in both urine and feces in small amounts (<4% of the administered dose).

Excretion

Approximately 50% of an oral dose is excreted unchanged (43% in the feces and 6% in the urine).

After multiple 200-mg doses, to healthy subjects, mean ($\pm$ SD) cumulative urinary trovafloxacin concentrations were 12.1 ± 3.4 μ g/mL. With these levels of trovafloxacin in urine, crystals of trovafloxacin have not been observed in the urine of human subjects.

Special Populations

Geriatric

The pharmacokinetics of trovafloxacin are not affected by age (range 19-78 years).

Pediatric

The pharmacokinetics of trovafloxacin have not been fully characterized in pediatric populations less than 18 years of age.

Gender

There are no significant differences in trovafloxacin pharmacokinetics between males and females when differences in body weight are taken into account. After single 200-mg doses, trovafloxacin C_{max} and AUC(0-∞) were 60% and 32% higher, respectively, in healthy females compared to healthy males. The clinical importance of the increases in serum levels of trovafloxacin in females has not been established. (See **PRECAUTIONS: Information for Patients.**)

Chronic Hepatic Disease

No dosage adjustment is recommended in patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) cirrhosis receiving a 100-mg oral dose. There are no data in patients with severe cirrhosis (Child-Pugh Class C). (See **DOSAGE AND ADMINISTRATION.**)

Renal Insufficiency

The pharmacokinetics of trovafloxacin are not affected by renal impairment. Trovafloxacin serum concentrations are not significantly altered in subjects with severe renal insufficiency (creatinine clearance < 20 mL/min), including patients on hemodialysis.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 48 healthy volunteers (12 per group), the minimum erythematous dose (MED) was measured for ciprofloxacin, lomefloxacin, trovafloxacin, and placebo before and after drug administration for 5 days. In this study, trovafloxacin (200 mg q.d.) was shown to have a lower potential for producing delayed photosensitivity skin reactions than ciprofloxacin (500 mg b.i.d.) or lomefloxacin (400 mg q.d.), although greater than placebo. (See **PRECAUTIONS: Information for Patients.**)

Drug-drug Interactions

The systemic availability of trovafloxacin following oral tablet administration is significantly reduced by the concomitant administration of antacids containing aluminum and magnesium salts, sucralfate, vitamins or minerals containing iron, and concomitant intravenous morphine administration.

Administration of trovafloxacin (300 mg p.o.) 30 minutes after administration of an antacid containing magnesium hydroxide and aluminum hydroxide resulted in reductions in systemic exposure to trovafloxacin (AUC) of 66% and peak serum concentration (C_{max}) of 60%. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION.**)

Concomitant sucralfate administration (1g) with trovafloxacin 200 mg p.o. resulted in a 70% decrease in trovafloxacin systemic exposure (AUC) and a 77% reduction in peak serum concentration (C_{max}). (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION.**)

Concomitant administration of ferrous sulfate (120 mg elemental iron) with trovafloxacin 200 mg p.o. resulted in a 40% reduction in trovafloxacin systemic exposure (AUC) and a 48% decrease in trovafloxacin C_{max}. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION.**)

Concomitant administration of intravenous morphine (0.15 mg/kg) with oral trovafloxacin (200 mg) resulted in a 36% reduction in trovafloxacin AUC and a 46% decrease in trovafloxacin C_{max}. Trovafloxacin administration had no effect on the pharmacokinetics of morphine or its pharmacologically active metabolite, morphine-6-β-glucuronide. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION.**)

Minor pharmacokinetic interactions that are most likely without clinical significance include calcium carbonate, omeprazole, and caffeine.

Concomitant administration of calcium carbonate (1000 mg) with trovafloxacin 200 mg p.o. resulted in a 20% reduction in trovafloxacin AUC and a 17% reduction in peak serum trovafloxacin concentration (C_{max}).

A 40-mg dose of omeprazole given 2 hours prior to trovafloxacin (300 mg p.o.) resulted in a 17% reduction in trovafloxacin AUC and a 17% reduction in trovafloxacin peak serum concentration (C_{max}).

Administration of trovafloxacin (200 mg) concomitantly with caffeine (200 mg) resulted in a 17% increase in caffeine AUC and a 15% increase in caffeine C_{max}. These changes in caffeine exposure are not considered clinically significant.

No significant pharmacokinetic interactions include cimetidine, theophylline, digoxin, warfarin, and cyclosporine.

Cimetidine co-administration (400 mg twice daily for 5 days) with trovafloxacin (200 mg p.o. daily for 3 days) resulted in changes in trovafloxacin AUC and C_{max} of less than 5%.

Trovafloxacin (200 mg p.o. daily for 7 days) co-administration with theophylline (300 mg twice daily for 14 days) resulted in no change in theophylline AUC and C_{max}.

Trovafloxacin (200 mg p.o. daily for 10 days) co-administration with digoxin (0.25 mg daily for 20 days) did not significantly alter systemic exposure (AUC) to digoxin or the renal clearance of digoxin.

Trovafloxacin (200 mg p.o. daily for 7 days) does not interfere with the pharmacokinetics nor the pharmacodynamics of warfarin (daily for 21 days). Concomitant oral administration of trovafloxacin did not affect the systemic exposure (AUC) or peak plasma concentrations (C_{max}) of the S or R isomers of warfarin, nor did it influence prothrombin time.

Trovafloxacin (200 mg p.o. daily for 7 days) co-administration with cyclosporine (daily doses from 150-450 mg for 7 days) resulted in decreases of 10% or less in systemic exposure to cyclosporine (AUC) and in the peak blood concentrations of cyclosporine.

AZITHROMYCIN

Pharmacokinetics: Following oral administration, azithromycin is rapidly absorbed and widely distributed throughout the body. Rapid distribution of azithromycin into tissues and high concentration within cells result in significantly higher azithromycin concentrations in tissues than in plasma or serum. The 1-g single-dose packet is bioequivalent to four 250 mg capsules.

The mean pharmacokinetic parameters ($\pm$ SD) of azithromycin after the 1 g single dose packet appear in the table below.

AZITHROMYCIN PHARMACOKINETIC PARAMETERS – 1-g SINGLE-DOSE PACKET IN FASTED STATE		
C _{max} (μ g/mL)	T _{max} (hrs)	AUC(0-72) (μ g•hr/mL)
0.75 $\pm$ 0.42	1.5 $\pm$ 0.7	6.49 $\pm$ 1.54

C_{max}= Maximum serum concentration; T_{max}=Time to C_{max}; AUC(0-72) = Area under concentration vs. time curve to 72 hr postdose

When the oral suspension of azithromycin was administered with food, the C_{max} increased by 46% and the AUC by 14%.

The AUC of azithromycin was unaffected by coadministration of an antacid containing aluminum and magnesium hydroxide with ZITHROMAX[®] capsules (azithromycin); however, the C_{max} was reduced by 24%. Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

When studied in healthy elderly subjects from age 65 to 85 years, the pharmacokinetic parameters of azithromycin (500 mg Day 1, 250 mg Days 2-5) in elderly men were similar to those in young adults; however, in elderly women, although higher peak

concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred.

The high values in adults for apparent steady-state volume of distribution (31.1 L/kg) and plasma clearance (630 mL/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues. Cervical tissue concentration and tissue to serum concentration ratio are shown in the following table:

TIME AFTER DOSE (h)	AZITHROMYCIN CERVICAL TISSUE CONCENTRATION (mg/g) ¹	CORRESPONDING SERUM LEVEL (µg/mL)	TISSUE TO SERUM RATIO ¹
19*	2.8	0.04	70

¹High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of azithromycin is pH related. Azithromycin is concentrated in cell lysosomes which have a low intraorganelle pH, at which the drug's activity is reduced. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

*Sample was obtained 19 hours after a single 500-mg (two 250 mg) capsule dose in adults.

The extensive tissue distribution was confirmed by examination of additional tissues and fluids (e.g., ejaculum, prostate, ovary, uterus, salpinx). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg/mL to 7% at 2 µg/mL. Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

There are no pharmacokinetic data available from studies in hepatically- or renally-impaired individuals.

The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses adequate to reach therapeutic steady-state plasma levels is not known. (See PRECAUTIONS.)

Trovafloracin-Azithromycin

Coadministration of the 1-gram azithromycin Single Dose Packet did not affect the bioavailability of a 100 mg tablet of trovafloracin in healthy volunteers.

Coadministration with a 100-mg tablet of trovafloracin produced serum azithromycin concentrations at 1.5 hr post-dose similar to those observed in previous studies with the 1-gram azithromycin Single Dose Packet.

Microbiology

Mechanism of Action: Trovafloracin

Trovafloracin is a fluoronaphthyridone related to the fluoroquinolones with *in vitro* activity against a wide range of gram-negative and gram-positive aerobic and anaerobic microorganisms. The bactericidal action of trovafloracin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. Mechanism of action of fluoroquinolones including trovafloracin is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, fluoroquinolones may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between trovafloracin and the mentioned classes of antibiotics. The overall results obtained from *in vitro* synergy studies, testing combinations of trovafloracin with beta-lactams and aminoglycosides, indicate that synergy is strain specific and not commonly encountered. This agrees with results obtained previously with other fluoroquinolones. Resistance to trovafloracin *in vitro* develops slowly via multiple-step mutation in a manner similar to other fluoroquinolones. Resistance to trovafloracin *in vitro* occurs at a general frequency of between 1×10^{-7} to 10^{-10} . Although cross-resistance has been observed between trovafloracin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to trovafloracin.

Mechanism of Action: Azithromycin

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was > 30 after one hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Trovafloxacin and azithromycin have both 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:

Aerobic gram-negative microorganisms

Neisseria gonorrhoeae

“Other” Microorganisms

Chlamydia trachomatis

Information on the *in vitro* activity of either trovafloxacin or azithromycin may be found in the respective prescribing information of these products.

Susceptibility Tests:

Trovafloxacin

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods¹ (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trovafloxacin mesylate powder. The MIC values should be interpreted according to the following criteria:

For testing *Neisseria gonorrhoeae*^a:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 0.125	Susceptible (S)
0.25	Intermediate (I)
≥ 0.5	Resistant (R)

^a These interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement¹.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard trovafloxacin mesylate powder should provide the following MIC values:

<u>Microorganism</u>	<u>MIC Range (µg/mL)</u>
<i>Neisseria gonorrhoeae</i> ^b ATCC 49226	0.004-0.016

- ^b This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement¹.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with trovafloxacin mesylate equivalent to 10 µg trovafloxacin to test the susceptibility of microorganisms to trovafloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a trovafloxacin mesylate disk (equivalent to 10 µg trovafloxacin) should be interpreted according to the following criteria:

The following zone diameter interpretive criteria should be used for testing *Neisseria gonorrhoeae*^c:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 37	Susceptible (S)
34-36	Intermediate (I)
≤ 33	Resistant (R)

- ^c These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement² incubated in 5% CO₂.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for trovafloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the trovafloxacin mesylate equivalent to 10-µg trovafloxacin disk should provide the following zone diameters in this laboratory quality control strain:

<u>Microorganism</u>	<u>Zone Diameter Range (mm)</u>
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^d This quality control range is only applicable to tests performed by disk diffusion using GC agar base and 1% defined growth supplement².

No testing method or interpretive criteria have been established for trovafloxacin against *Chlamydia trachomatis*.

Azithromycin

No interpretive criteria have been established for testing azithromycin against *Neisseria gonorrhoeae*. This species is usually not tested against azithromycin.

No testing method or interpretive criteria have been established for azithromycin against *Chlamydia trachomatis*.

INDICATIONS AND USAGE

The TROVAN/ZITHROMAX Compliance Pak is indicated for single-dose treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Uncomplicated urethral gonorrhea in males and endocervical and rectal gonorrhea in females caused by *Neisseria gonorrhoeae*.

Non-gonococcal urethritis and cervicitis due to *Chlamydia trachomatis*.

CONTRAINDICATIONS

TROVAN is contraindicated in persons with a history of hypersensitivity to trovafloxacin, alatrofloxacin, quinolone antimicrobial agents, or any other components of these products.

ZITHROMAX is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide antibiotic.

WARNINGS

TROVAFLOXACIN

THE SAFETY AND EFFECTIVENESS OF TROVAFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS LESS THAN 18 YEARS OF AGE, PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Mothers subsections.)

As with other members of the quinolone class, trovafloxacin has caused arthropathy and/or chondrodysplasia in immature rats and dogs. The significance of these findings to humans is unknown. (See **ANIMAL PHARMACOLOGY**.)

Convulsions, increased intracranial pressure and psychosis have been reported in patients receiving quinolones. Quinolones may also cause central nervous system stimulation which may lead to tremors, restlessness, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, and insomnia. These reactions may occur following the first dose. If these reactions occur in patients receiving trovafloxacin or alatrofloxacin, the drug should be discontinued and appropriate measures instituted. (See **PRECAUTIONS: General, Information for Patients, Drug Interactions** and **ADVERSE REACTIONS**.)

As with other quinolones, TROVAN should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral atherosclerosis, epilepsy, and other factors that predispose to seizures. (See **ADVERSE REACTIONS**.)

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions.

TROVAN should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS**.)

Serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have been reported in patients receiving therapy with all antimicrobials. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and

aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Although not seen in TROVAN clinical trials, ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. TROVAN should be discontinued if the patient experiences pain, inflammation or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones.

AZITHROMYCIN

Serious allergic reactions, including angioedema and anaphylaxis, have been reported rarely in patients on azithromycin therapy. (See **CONTRAINDICATIONS**.) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure**. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

General

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including both TROVAN and ZITHROMAX, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS**.)

Neither trovafloxacin nor azithromycin has been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat non-gonococcal urethritis/cervicitis or gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with sexually transmitted urethritis/cervicitis or gonorrhea should have a serologic test for syphilis at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests should be initiated if infection is confirmed.

PRECAUTIONS

General: Trovafloxacin

Moderate to severe phototoxicity reactions have been observed in patients who are exposed to direct sunlight while receiving some drugs in the quinolone class. Therapy should be discontinued if phototoxicity (e.g., a skin eruption, etc.) occurs.

The safety and efficacy of TROVAN in patients with severe cirrhosis (Child-Pugh Class C) have not been studied.

During the post-marketing period, TROVAN-associated liver enzyme abnormalities and/or symptomatic hepatitis have occurred during short-term or long-term therapy. Liver enzyme abnormalities have been reported in both men and women. Liver failure (including acute hepatic necrosis with eosinophilic infiltration) has also been reported rarely. Symptomatic pancreatitis has been reported on therapy. Clinicians should monitor liver function tests and pancreatic tests in patients who develop symptoms consistent with hepatitis and/or pancreatitis as clinically indicated.

General: Azithromycin

Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment; thus, caution should be exercised when prescribing azithromycin in these patients. The following adverse events have not been reported in clinical trials with azithromycin, an azalide; however, they have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsades de pointes*, in individuals with prolonged QT intervals.

Information for Patients:

Patients should be advised:

- that TROVAN Tablets may be taken without regard to meals;

- that vitamins or minerals containing iron, aluminum- or magnesium-base antacids, antacids containing citric acid buffered with sodium citrate, sucralfate or Videx® (Didanosine) chewable/buffered tablets, buffered powder for oral solution, or pediatric powder for oral solution, should be taken at least two hours before or two hours after taking TROVAN Tablets. (See **PRECAUTIONS: Drug Interactions.**);
- that TROVAN may cause lightheadedness and/or dizziness. Dizziness and/or lightheadedness was the most common adverse reaction reported, and for females under 45 years, it was reported significantly more frequently than in other groups. The incidence of dizziness may be substantially reduced if TROVAN Tablets are taken at bedtime or with food. Patients should know how they react to trovafloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination. (See **WARNINGS** and **ADVERSE REACTIONS.**);
- that TROVAN®/Zithromax® Compliance Pak has been associated with nausea, vomiting, and diarrhea within 2 hours of administration. Nausea was the most common adverse event, seen in 10/20 (50%) of participants in a pharmacokinetic trial, followed by abdominal pain seen in 5/20 (25%) of the study subjects.
- to discontinue treatment and inform their physician if they experience pain, inflammation or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded;
- that TROVAN may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction. (See **WARNINGS** and **ADVERSE REACTIONS.**);
- to avoid excessive sunlight or artificial ultraviolet light (e.g., tanning beds) while taking TROVAN and to discontinue therapy if phototoxicity (e.g., sunburn-like reaction or skin eruption) occurs;
- that ZITHROMAX® for oral suspension in single 1-g packets can be taken with or without food after constitution;
- that they should not take aluminum- and magnesium-containing antacids and azithromycin simultaneously;
- that they should discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Drug Interactions:

Trovafloracin

No significant interactions with theophylline, cimetidine, digoxin, warfarin, or cyclosporine have been observed with TROVAN Tablets. (See **CLINICAL PHARMACOLOGY**.)

Minor pharmacokinetic interactions without clinical significance have been observed with co-administration of TROVAN Tablets with caffeine, omeprazole and calcium carbonate. (See **CLINICAL PHARMACOLOGY**.)

Antacids, Sucralfate, and Iron: The absorption of oral trovafloracin is significantly reduced by the concomitant administration of some antacids containing magnesium or aluminum, citric acid/sodium citrate (Bicitra®), as well as sucralfate, and iron (as ferrous ions). These agents, as well as formulations containing divalent or trivalent cations or other buffering ingredients, such as Videx®, (Didanosine), chewable/buffered or the pediatric oral solution, should be taken at least two hours before or two hours after oral trovafloracin administration. (See **CLINICAL PHARMACOLOGY**.)

Morphine: Co-administration of intravenous morphine significantly reduces the absorption of oral trovafloracin. Intravenous morphine should be administered at least 2 hours after oral TROVAN dosing in the fasted state and at least 4 hours after oral TROVAN is taken with food. Trovafloracin administration had no effect on the pharmacokinetics of morphine or its metabolite, morphine-6-β-glucuronide. (See **CLINICAL PHARMACOLOGY**.)

Azithromycin

Aluminum- and magnesium-containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of azithromycin (500 mg) absorption.

Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin (500 mg) absorption.

Azithromycin (500 mg Day 1, 250 mg Days 2-5) did not affect the plasma levels or pharmacokinetics of theophylline administered as a single intravenous dose. The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses resulting in therapeutic steady-state levels of theophylline is not known. However, concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Therefore, until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.

Azithromycin (500 mg Day 1, 250 mg Days 2-5) did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

The following drug interactions have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin - elevated digoxin levels.

Ergotamine or dihydroergotamine - acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Triazolam - decreases the clearance of triazolam and thus may increase the pharmacologic effect of triazolam.

Drugs metabolized by the cytochrome P⁴⁵⁰ system - elevations of serum carbamazepine, cyclosporine, hexobarbital, and phenytoin levels.

Laboratory Test Interactions: There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Trovafloracin

Trovan did not shorten the time to development of UV-induced skin tumors in hairless albino (Skh-1) mice; thus, it was not photo co-carcinogenic in this model. These mice received oral trovafloracin and concurrent irradiation with simulated sunlight 5 days per week for 40 weeks followed by a 12-week treatment-free observation period. The daily dose of UV radiation used in this study was approximately 30% of the minimal dose of UV radiation that would induce erythema in Caucasian humans. The median time to the development of skin tumors in the hairless mice (42-43 weeks) was similar in the vehicle control group and those given 10 or 30 µg /kg of trovafloracin daily. At a dose level of 30 mg/kg/day, the mice had skin trovafloracin concentrations of approximately 7 mg/g. Following multiple 200 mg daily doses of trovafloracin, the amount in human skin is estimated maximally to be about 3 µg/g, based upon peak plasma concentrations measured at this dose level and the skin to serum penetration ratio approximately 1.0.

Trovafloracin was not mutagenic in the Ames Salmonella reversion assay or CHO/HGPRT mammalian cell gene mutation assay and it was not clastogenic in mitogen-stimulated human lymphocytes or mouse bone marrow cells. A mouse

micronucleus test conducted with alatrofloxacin was also negative. The positive response observed in the *E. coli* bacterial mutagenicity assay may be due to the inhibition of DNA gyrase by trovafloxacin.

Trovafloxacin and alatrofloxacin did not affect the fertility of male or female rats at oral and I.V. doses of 75 mg/kg/day and 50 mg/kg/day, respectively. These doses are 15 and 10 times the recommended maximum human dose based on mg/kg or approximately 2 times based on mg/m². However, oral doses of trovafloxacin at 200 mg/kg/day (40 times the recommended maximum human dose based on mg/kg or about 6 times based on mg/m²) were associated with increased preimplantation loss in rats.

Azithromycin

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.

Pregnancy: Teratogenic Effects

Trovafloxacin: Pregnancy Category C

An increase in skeletal variations was observed in rat fetuses after daily oral 75 mg/kg maternal doses of trovafloxacin (approximately 15 times the highest recommended human dose based on mg/kg or two times based upon body surface area) were administered during organogenesis. However, fetal skeletal variations were not observed in rats dosed orally with 15 mg/kg trovafloxacin. Evidence of fetotoxicity (increased perinatal mortality and decreased body weights) was also observed in rats at 75 mg/kg. Daily oral doses of trovafloxacin at 45 mg/kg (approximately 9 times the highest recommended human dose based on mg/kg or 2.7 times based upon body surface area) in the rabbit were not associated with an increased incidence of fetal skeletal variations or malformations.

An increase in skeletal variations and malformations was observed in rat fetuses after daily intravenous doses of alatrofloxacin at ≥ 20 mg/kg/day (approximately 4 times the highest recommended human dose based on mg/kg or 0.6 times based upon body surface area) were administered to dams during organogenesis. In the rabbit, an increase in fetal skeletal malformations was also observed when 20 mg/kg/day (approximately equal to the highest recommended human dose based upon body surface area) of alatrofloxacin was given intravenously during the period of organogenesis. Intravenous dosing of alatrofloxacin at 6.5 mg/kg in the rat or rabbit was not associated with an increased incidence of skeletal variations or malformations. Fetotoxicity and fetal skeletal malformations have been associated with other quinolones.

Oral doses of trovafloxacin >5 mg/kg were associated with an increased gestation time in rats, and several dams at 75 mg/kg experienced uterine dystocia.

There are no adequate and well-controlled studies in pregnant women. TROVAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

Pregnancy: Teratogenic Effects

Azithromycin: Pregnancy Category B

Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose levels (i.e., 200 mg/kg/day). These doses, based on a mg/m² basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg.

No evidence of impaired fertility or harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers:

Trovafloracin

Trovafloracin is excreted in human milk and was found in measurable concentrations in the milk of lactating subjects. (See **CLINICAL PHARMACOLOGY, Distribution**.)

Because of the potential for unknown effects from trovafloracin in nursing infants from mothers taking trovafloracin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Azithromycin

It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Pediatric Use:

The safety and effectiveness of the TROVAN/ZITHROMAX Compliance Pak in pediatric populations less than 18 years of age have not been established. Quinolones, including trovafloracin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See **WARNINGS**.)

Geriatric Use:

Trovafloracin

In multiple-dose clinical trials of trovafloracin, 27% of patients were ≥ 65 years of age and 12% of patients were ≥ 75 years of age. The overall incidence of drug-related

adverse reactions, including central nervous system and gastrointestinal side effects, was less in the ≥ 65 year group than the other age groups.

Azithromycin

Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen. (See **CLINICAL PHARMACOLOGY**.)

ADVERSE REACTIONS

TROVAN®/Zithromax® Compliance Pak

Twenty healthy subjects participated in a Phase 1 pharmacokinetic study to assess the safety of the TROVAN®/Zithromax® Compliance Pak.

Treatment-Related Adverse Events (>1%) Associated with TROVAN Use Alone or in Combination with ZITHROMAX

Adverse Event	Trovafoxacin 100-mg tablet (N = 20)		Trovafoxacin 100-mg tablet and Azithromycin 1-gm oral suspension (N = 20)	
	n	%	n	%
Nausea	0	-	10	50
Abdominal Pain	0	-	5	25
Vomiting	0	-	2	10
Diarrhea	0	-	2	10
Dizziness/Lightheadedness	2	10	3	15
Nausea and Vomiting	0	-	2	10
Abdominal Pain & Nausea	0	-	3	15
Abdominal Pain & Diarrhea	0	-	1	5
Abdominal Pain & Headache	0	-	1	5
Flatulence	0	-	1	5
Cumulative Treatment-Related Adverse Event Rate	2/20	10	12/20	60

The adverse events listed in the table above were obtained from the experience of the 20 healthy volunteers that participated in the study and were described as mild to moderate in nature.

Trovafloracin

Over 6000 patients have been treated with TROVAN in multidose clinical efficacy trials worldwide.

In TROVAN studies, the majority of adverse reactions were described as mild in nature (over 90% were described as mild or moderate). TROVAN was discontinued for adverse events thought related to drug in 5% of patients (dizziness 2.4%, nausea 1.9%, headache 1.1%, and vomiting 1.0%).

Dizziness/lightheadedness on TROVAN is generally mild, lasts for a few hours following a dose, and in most cases, resolves with continued dosing. The incidence of dizziness and lightheadedness in TROVAN patients over 65 years is 3.1% and 0.6%, respectively. (See **PRECAUTIONS: Information for Patients.**)

TROVAN appears to have a low potential for phototoxicity. In clinical trials with TROVAN, only mild, treatment-related phototoxicity was observed in less than 0.03% (2/7096) of patients.

Additional reported drug-related events in clinical trials (remotely, possibly, probably or unknown) that occurred in <1% of TROVAN-treated patients are:

APPLICATION/INJECTION/INSERTION SITE: Application/injection/insertion site device complications, inflammation, pain, edema

AUTONOMIC NERVOUS: flushing, increased sweating, dry mouth, cold clammy skin, increased saliva

CARDIOVASCULAR: peripheral edema, chest pain, thrombophlebitis, hypotension, palpitation, periorbital edema, hypertension, syncope, tachycardia, angina pectoris, bradycardia, peripheral ischemia, edema, dizziness postural

CENTRAL & PERIPHERAL NERVOUS SYSTEM: confusion, paresthesia, vertigo, hypoesthesia, ataxia, convulsions, dysphonia, hypertonia, migraine, involuntary muscle contractions, speech disorder, encephalopathy, abnormal gait, hyperkinesia, hypokinesia, tongue paralysis, abnormal coordination, tremor, dyskinesia

GASTROINTESTINAL: altered bowel habit, constipation, *Clostridium difficile*-associated diarrhea, dyspepsia, flatulence, loose stools, gastritis, dysphagia, increased appetite, gastroenteritis, rectal disorder, colitis, pseudomembranous colitis, enteritis, eructation, gastrointestinal disorder, melena, hiccup

ORAL CAVITY: gingivitis, stomatitis, altered saliva, tongue disorder, tongue edema, tooth disorder, cheilitis, halitosis

GENERAL/OTHER: fever, fatigue, pain, asthenia, moniliasis, hot flushes, back pain, chills, infection (bacterial, fungal), malaise, sepsis, alcohol intolerance, allergic reaction, anaphylactoid reaction, drug (other) toxicity/reaction, weight increase, weight decrease

HEMATOPOIETIC: anemia, granulocytopenia, hemorrhage unspecified, leukopenia, prothrombin decreased, thrombocythemia, thrombocytopenia

LIVER/BILIARY: increased hepatic enzymes, hepatic function abnormal, bilirubinemia, discolored feces, jaundice

METABOLIC/NUTRITIONAL: hyperglycemia, thirst

MUSCULOSKELETAL: arthralgia, muscle cramps, myalgia, muscle weakness, skeletal pain, tendinitis, arthropathy

PSYCHIATRIC: anxiety, anorexia, agitation, nervousness, somnolence, insomnia, depression, amnesia, concentration impaired, depersonalization, dreaming abnormal, emotional lability, euphoria, hallucination, impotence, libido decreased-male, paroniria, thinking abnormal

REPRODUCTIVE: Female: leukorrhea, menstrual disorder;
Male: balanoposthitis

RESPIRATORY: dyspnea, rhinitis, sinusitis, bronchospasm, coughing, epistaxis, respiratory insufficiency, upper respiratory tract infection, respiratory disorder, asthma, hemoptysis, hypoxia, stridor

SKIN/APPENDAGES: pruritus ani, skin disorder, skin ulceration, angioedema, dermatitis, dermatitis fungal, photosensitivity skin reaction, seborrhea, skin exfoliation, urticaria

SPECIAL SENSES: taste perversion, eye pain, abnormal vision, conjunctivitis, photophobia, conjunctival hemorrhage, hyperacusis, scotoma, tinnitus, visual field defect, diplopia, xerophthalmia

URINARY SYSTEM: dysuria, face edema, micturition frequency, interstitial nephritis, renal failure acute, renal function abnormal, urinary incontinence

Azithromycin

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients from the multiple-dose clinical trials discontinued ZITHROMAX[®] (azithromycin) therapy because of treatment-related side effects. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting,

diarrhea, or abdominal pain. Rarely but potentially serious side effects were angioedema and cholestatic jaundice.

Single 1-gram dose regimen: Overall, the most common side effects in patients receiving a single-dose regimen of 1 gram of ZITHROMAX[®] were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Side effects that occurred in patients on the single one-gram dosing regimen of ZITHROMAX[®] with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

LABORATORY CHANGES - Trovafloxacin: Changes in laboratory parameters, without regard to drug relationship, occurring in $\geq 1\%$ of TROVAN-treated patients were: decreased hemoglobin and hematocrit; increased platelets; decreased and increased WBC; eosinophilia; increased ALT (SGPT), AST (SGOT), and alkaline phosphatase; decreased protein and albumin; increased BUN and creatinine; decreased sodium; and bicarbonate. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

The incidence and magnitude of liver function abnormalities with TROVAN were the same as comparator agents except in the only study in which oral TROVAN was administered for 28 days. In this study (chronic bacterial prostatitis) nine percent (13/140) of TROVAN-treated patients experienced elevations of serum transaminases (AST and/or ALT) of ≥ 3 times the upper limit of normal. These liver function test abnormalities generally developed at the end of, or following completion of, the planned 28-day course of therapy, but were not associated with concurrent elevations of related laboratory measures of hepatic function (such as serum bilirubin, alkaline phosphatase, or lactate dehydrogenase). Patients were asymptomatic with these abnormalities, which generally returned to normal within 1-2 months after discontinuation of therapy. (See **ADVERSE REACTIONS: POST-MARKETING EXPERIENCE** subsection.)

TROVAN POST-MARKETING EXPERIENCE:

Adverse reactions reported with TROVAN during the post-marketing period include: anaphylaxis, symptomatic hepatitis (some patients experienced an associated peripheral eosinophilia), liver failure (including acute hepatic necrosis with eosinophilic infiltration), Stevens-Johnson Syndrome, and symptomatic pancreatitis.

During the post-marketing period, TROVAN-associated liver enzyme abnormalities and/or symptomatic hepatitis have occurred during short-term or long-term therapy. (See **PRECAUTIONS.**)

LABORATORY CHANGES – Azithromycin: Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:

With an incidence of 1-2%, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT).

With an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and phosphate.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and one because of a renal function abnormality.

OVERDOSAGE

Trovafloxacin

Trovafloxacin has a low order of acute toxicity. The minimum lethal oral dose in mice and rats was 2000 mg/kg or greater. The minimum lethal I.V. dose for the prodrug, alatrofloxacin, was 50-125 mg/kg for mice and greater than 75 mg/kg for rats. Clinical signs observed included decreased activity and respiration, ataxia, ptosis, tremors and convulsions.

In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given symptomatic and supportive treatment. Adequate hydration should be maintained. Trovafloxacin is not efficiently removed from the body by hemodialysis.

DOSAGE AND ADMINISTRATION

The recommended regimen is a single 100-mg tablet of TROVAN and a single 1-gram (1000 mg) dose of ZITHROMAX for oral suspension. (See **INDICATIONS AND USAGE** section.) These single-regimen medications are available together as a "Compliance Pak", containing a single 100-mg TROVAN (trovafloxacin) tablet and one ZITHROMAX (azithromycin for oral suspension) single-dose packet (1g).

TROVAN

TROVAN can be taken with or without food.

Oral doses should be administered at least two hours before or two hours after antacids containing magnesium or aluminum, as well as sucralfate, citric acid buffered with sodium citrate (e.g., Bicitra®), metal cations (e.g., ferrous sulfate) and Videx® (Didanosine), chewable/buffered tablets, buffered powder for solution, or the pediatric powder for oral solution.

Intravenous morphine should be administered at least 2 hours after oral TROVAN dosing in the fasted state and at least 4 hours after oral TROVAN is taken with food.

IMPAIRED RENAL FUNCTION: No adjustment in the dosage of TROVAN is necessary in patients with impaired renal function. Trovafloxacin is eliminated primarily by biliary excretion. Trovafloxacin is not efficiently removed from the body by hemodialysis.

CHRONIC HEPATIC DISEASE (cirrhosis): No dosage adjustment is necessary for patients with mild or moderate cirrhosis (Child-Pugh Class A and B) receiving the 100-mg TROVAN dose. There are no data in patients with severe cirrhosis (Child-Pugh Class C).

ZITHROMAX

ZITHROMAX® for oral suspension (single-dose 1-g packet) can be taken with or without food after constitution. Not for pediatric use

The ZITHROMAX dose should not be taken with aluminum- or magnesium-containing antacids. Caution should be used when prescribing ZITHROMAX to patients with impaired renal or hepatic function.

DIRECTIONS FOR COMPLIANCE PAK ADMINISTRATION:

The entire contents of the ZITHROMAX single-dose 1-g (1000 mg) packet should be mixed thoroughly with two ounces (approximately 60 mL) of water. Drink the entire contents immediately; add an additional two ounces of water, mix, and rinse. Use the rinse to swallow the TROVAN 100-mg tablet and drink the entire contents to assure complete consumption of dosage. **The single-dose packet should not be used to administer doses other than 1000 mg of azithromycin. This packet is not for pediatric use.**

HOW SUPPLIED

Compliance Pak: One ZITHROMAX[®] single-dose packet of azithromycin dihydrate is equivalent to 1 gram of azithromycin and a single TROVAN[®] tablet containing trovafloxacin mesylate

is equivalent to 100-mg trovafloxacin. The Compliance Pak is available as follows:

Boxes of 3 Compliance Paks

NDC 0049-3770-89

Store Compliance Paks between 15° and 30°C (59° and 86°F).

ANIMAL PHARMACOLOGY

Trovafloxacin

Quinolones have been shown to cause arthropathy in immature animals.

Arthropathy and chondrodysplasia were observed in immature animals given trovafloxacin. (See **WARNINGS**.)

At doses from 10 to 15 times the human dose based on mg/kg or approximately 3 to 5 times based on mg/m², trovafloxacin has been shown to cause arthropathy in immature rats and dogs. In addition, these drugs are associated with an increased incidence of chondrodysplasia in rats compared to controls. There is no evidence of arthropathies in fully mature rats and dogs at doses from 40 or 10 times the human dose based on mg/kg or approximately 5 times based on mg/m² for a 6-month exposure period.

Unlike some other members of the quinolone class, crystalluria and ocular toxicity were not observed in chronic safety studies with rats or dogs with either trovafloxacin or its prodrug, alatrofloxacin.

Quinolones have been reported to have proconvulsant activity that is exacerbated with concomitant use of non-steroidal antiinflammatory drugs (NSAIDs). Neither trovafloxacin administered orally at 500 mg/kg, nor alatrofloxacin administered intravenously at 75 mg/kg, showed an increase in measures of seizure activity in mice at doses when used in combination with the active metabolite of the NSAID, fenbufen.

As with other members of the quinolone class, trovafloxacin at doses 5 to 10 times the human dose based on mg/kg or 1 to 5 times the human dose based on mg/m² produces testicular degeneration in rats and dogs dosed for 6 months.

At a dose of trovafloxacin 10 times the highest human dose based on mg/kg or approximately 5 times based on mg/m², elevated liver enzyme levels which correlated with centrilobar hepatocellular vacuolar degeneration and necrosis were observed in dogs in a 6-month study. A subsequent study demonstrated reversibility of these effects when trovafloxacin was discontinued.

Azithromycin

Phospholipidosis (intracellular phospholipid binding) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs administered doses which, based on pharmacokinetics, are as low as two times greater than the recommended adult human dose and in rats at doses comparable to the recommended adult human dose. This effect has been reversible after cessation of azithromycin treatment. The significance of these findings for humans is unknown.

Rx only.

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2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests--Sixth Edition; Approved Standard, NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997.