CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

17-577/S-032, S-033 &
18-211/S-014, S-016 &
20-897/S-009, S-010

Trade Name: Ditropan Tablets 5 mg
Ditropan Syrup 5 mg/5 ml
Ditropan XL Extended Release Tablets 5, 10, 15 mg

Generic Name: oxybutyin chloride

Sponsor: Ortho-McNeil Pharmaceuticals, Inc.

Approval Date: April 15, 2003

Indications: Ditropan Tablets & Ditropan Syrup: The safety and efficacy of Ditropan (oxybutyin chloride) administration have been demonstrated for pediatric patients 5 years of age and older.

Ditropan XL: For the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-577/S-032, S-033 &
18-211/S-014, S-016 &
20-897/S-009, S-010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-577/S-032, S-033 &
18-211/S-014, S-016 &
20-897/S-009, S-010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-577/S-033 and S-032
NDA 18-211/S-016 and S-014
NDA 20-897/S-009 and S-010

Liliana Arbelaez
Associate Director, Regulatory Affairs
Global Marketed Products
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Ms. Arbelaez:

Please refer to your supplemental new drug applications dated December 7, 2001, received December 7, 2001, submitted under section 505(b) pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act as follows:

NDA Number	Supplement Number	Drug Product
17-577	S-033 and S-032	DITROPAN® (oxybutynin chloride) Tablets
18-211	S-016 and S-014	DITROPAN® (oxybutynin chloride) Syrup
20-897	S-009 and S-010	DITROPAN® XL (oxybutynin chloride) Extended Release Tablets

We acknowledge receipt of your "Response to Approvable Letter", submitted on October 16, 2002.

We also acknowledge receipt of your subsequent submissions dated March 12, 2002, February 28, March 13, March 14, March 31, April 3, April 4, April 7, April 9, and April 10, 2003 for NDA 17-577/S-033, NDA 18-211/S-016, and NDA 20-897/S-009.

Furthermore, we also acknowledge receipt of your submissions, which contained additional proposed labeling, dated July 2 and December 23, 2002, and March 5, March 13, March 31, April 3, April 4, April 7, April 9, and April 10, 2003 for NDA 17-577/S-032, NDA 18-211/S-014, and NDA 20-897/S-010.

These supplemental new drug applications provide for the use of DITROPAN® (oxybutynin chloride) Tablets, DITROPAN® (oxybutynin chloride) Syrup, and DITROPAN® XL (oxybutynin chloride) Extended Release Tablets for the treatment of overactive bladder in children aged six years of age and older.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the attached labeling text. Accordingly, the applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package inserts submitted for NDA 17-577/S-032 and S-033 on April 9, 2003; package inserts submitted for NDA 18-211/S-016 and S-014 on April 9, 2003; and package inserts submitted for NDA 20-897/S-009 and S-010 on April 3, 2003). 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 paper copies of the FPL for NDA 17-577, NDA 18-211, and NDA 20-897 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.

Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 17-577, NDA 18-211, and NDA 20-897", respectively. 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:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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, call Jean King, M.S., R.D., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}
Daniel Shames, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daniel A. Shames
4/15/03 03:42:56 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-577/S-032, S-033 &
18-211/S-014, S-016 &
20-897/S-009, S-010

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-577/S-032

Alza Corporation
Attention: Stephen W. Sherman
Director, Advertising and Labeling Regulatory Affairs
1010 Joaquin Road
P.O. Box 7210
Mountain View, CA 94039-7210

Dear Mr. Sherman:

Please refer to your supplemental new drug application dated September 10, 1999, received September 13, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ditropan (oxybutynin chloride) Tablets.

This supplement proposes changes to the following change **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **OVERDOSAGE** sections. The proposed changes are based on the approved labeling for Ditropan® XL (oxybutynin chloride) Extended Release Tablets, two literature reports to support the revised language concerning metabolism and potential drug-drug interactions, and adverse events reported for the immediate-release formulation of oxybutynin chloride used in three clinical trials for the Ditropan XL.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. **CONTRAINDICATIONS** section: correct the misspelling of "retention" in the first sentence of the section submitted in Section 2: Strikeout/Underlined.

2. **PRECAUTIONS** section:

   a. delete the proposed underlining of all the subsection titles

   b. add the following as a new second sentence to the **General** subsection:

      "Ditropan® may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension [ ] prostatic hypertrophy." b(4)

   c. add the following as a new second sentence to the **Gastrointestinal Disorders** subsection:

      "Administration of Ditropan® to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease."

   d. add the following as a new sixth sentence to the **Drug Interactions** subsection:

"Caution should be used when such drugs are co-administered."

3. **ADVERSE REACTIONS** section:

   a. replace the **ADVERSE REACTIONS** section with similar formatting to the **ADVERSE REACTIONS** Section Ditropan® XL section

   b. change the **ADVERSE REACTIONS** section to:

ADVERSE REACTIONS:

The safety and efficacy of Ditropan® (oxybutynin chloride) was evaluated in a total of 199 patients in three clinical trials [ ] Ditropan® XL (Table 1). These participants were treated [ ] 5-20 mg/day for up to 6 weeks. [ ] b(4)

Table 1
Incidence (%) of Adverse Events Reported by / 5% of Patients Using Ditropan® (5-20 mg/day)

Body System	Adverse Event	Ditropan® (5-20 mg/day) (n=199)
General	Abdominal pain	6.5%
	Headache	6.0%
Digestive	Dry mouth	71.4%
	Constipation	12.6%
	Nausea	10.1%
	Dyspepsia	7.0%
	Diarrhea	5.0%
Nervous	Dizziness	15.6%
	Somnolence	12.6%
Special senses	Blurred vision	[ ]%
	[ ]	[ ]%
Urogenital	Urination impaired	10.6%
	Post void residuals increase	5.0%
	Urinary tract infection	5.0%

b(4)

The most common adverse events reported by patients [ ] 5-20 mg/day Ditropan® were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related. b(4)

In addition, the following adverse events were reported by 2 to <5% of patients using Ditropan® (5-20 mg/day) in all studies. General: asthenia, dry nasal and sinus mucous membranes; Cardiovascular: palpitation; Metabolic and Nutritional System: peripheral edema; Nervous System: insomnia, nervousness, confusion; Skin: dry skin; Special Senses: dry eyes, taste perversion.

Other adverse events [ ] : tachycardia, hallucinations, cycloplegia, mydriasis, impotence, suppression of lactation, vasodilatation, rash, decreased gastrointestinal motility, flatulence, [ ] decreased sweating. b(4)

4. **OVERDOSAGE** section:

a. add "(e.g. restlessness, tremor, irritability, convulsions, delirium, hallucinations)" after the phrase "[ ] excitation" in the proposed third sentence b(4)

b. add a new fourth sentence:

"Other symptoms may include hypotension or hypertension, respiratory failure, paralysis and coma."

c. begin a new paragraph with the proposed third sentence

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDAs (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this/these change(s) prior to approval of this supplemental application.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Susan Allen
4/6/01 08:23:02 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-211/S-014

Alza Corporation
Attention: Stephen W. Sherman
Director, Advertising and Labeling Regulatory Affairs
1010 Joaquin Road
P.O. Box 7210
Mountain View, CA 94039-7210

Dear Mr. Sherman:

Please refer to your new drug application (NDA) dated September 10, 1999, received September 13, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ditropan (oxybutynin chloride) Syrup.

This supplement proposes changes to the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **OVERDOSAGE** sections. The proposed changes are based on the approved product labeling for Ditropan® XL (oxybutynin chloride) Extended Release Tablets, two literature reports to support the revised language concerning metabolism and potential drug-drug interactions, and adverse events reported for the immediate-release formulation of oxybutynin chloride used in three clinical trials for the Ditropan XL.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. **CONTRAINDICATIONS** section: correct the misspelling of "retention" in the first sentence of the section submitted in Section 2.

2. **PRECAUTIONS** section:

   a. delete the proposed underlining of all the subsection titles

   b. add the following as a new second sentence to the **General** subsection:

      "Ditropan® may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension[ ] prostatic hypertrophy." b(4)

   c. add the following as a new second sentence to the **Gastrointestinal Disorders** subsection:

      "Administration of Ditropan® to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease."

d. add the following as a new sixth sentence to the **Drug Interactions** subsection:

"Caution should be used when such drugs are co-administered."

3. **ADVERSE REACTIONS** section:

a. replace the **ADVERSE REACTIONS** section with similar formatting to the **ADVERSE REACTIONS** Section Ditropan® XL section

b. change the **ADVERSE REACTIONS** section to:

ADVERSE REACTIONS:
The safety and efficacy of Ditropan® (oxybutynin chloride) was evaluated in a total of 199 patients in three clinical trials [ ] Ditropan® XL (Table 1). These participants were treated [ ] 5-20 mg/day for up to 6 weeks. [ ] b(4)

Table 1
Incidence (%) of Adverse Events Reported by / 5% of Patients Using Ditropan® (5-20 mg/day)

Body System	Adverse Event	Ditropan® (5-20 mg/day) (n=199)
General	Abdominal pain	6.5%
	Headache	6.0%
Digestive	Dry mouth	71.4%
	Constipation	12.6%
	Nausea	10.1%
	Dyspepsia	7.0%
	Diarrhea	5.0%
Nervous	Dizziness	15.6%
	Somnolence	12.6%
Special senses	Blurred vision	[ ]%
	[ ]	[ ]%
Urogenital	Urination impaired	10.6%
	Post void residuals increase	5.0%
	Urinary tract infection	5.0%

b(4)

The most common adverse events reported by patients [ ] 5-20 mg/day Ditropan® were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related. b(4)

In addition, the following adverse events were reported by 2 to <5% of patients using Ditropan® (5-20 mg/day) in all studies. General: asthenia, dry nasal and sinus mucous membranes; Cardiovascular: palpitation; Metabolic and Nutritional System: peripheral edema; Nervous System: insomnia, nervousness, confusion; Skin: dry skin; Special Senses: dry eyes, taste perversion.

Other adverse events [ ] : tachycardia, hallucinations, cycloplegia, mydriasis, impotence, suppression of lactation, vasodilatation, rash, decreased gastrointestinal motility, flatulence,[ ] decreased sweating. b(4)

4. **OVERDOSAGE** section:

a. add (e.g. restlessness, tremor, irritability, convulsions, delirium, hallucinations) after the phrase "[ ] excitation" in the proposed third sentence b(4)

b. add a new fourth sentence:

"Other symptoms may include hypotension or hypertension, respiratory failure, paralysis and coma."

c. begin a new paragraph with the proposed third sentence

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDAs (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this/these change(s) prior to approval of this supplemental application.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Susan Allen
4/13/01 11:45:37 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-577/S-033
NDA 18-211/S-016
NDA 20-897/S-009

Johnson & Johnson Pharmaceutical Research & Development
Attention: Liliana Arbelaez
Manager, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Ms. Arbelaez:

Please refer to your supplemental new drug applications dated December 7, 2001, received December 7, 2001, submitted under section 505(b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for

NDA Number	Supplement Number	Drug Name
17-577	S-033	DITROPAN® (oxybutynin chloride) Tablets
18-211	S-016	DITROPAN® (oxybutynin chloride) Syrup
20-897	S-009	DITROPAN XL® (oxybutynin chloride) Extended Release Tablets

We acknowledge receipt of your submission dated March 12, 2002.

We also acknowledge receipt of your submission dated July 29, 2002. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

These supplemental new drug applications provide for the use of DITROPAN® (oxybutynin chloride) Tablets, DITROPAN® (oxybutynin chloride) Syrup, and DITROPAN XL® (oxybutynin chloride) Extended Release Tablets for pediatric claims for the treatment of overactive bladder.

We have completed the review of these applications, as amended, and they are approvable. Before the applications may be approved, however, it will be necessary to review the amendment dated July 29, 2002.

In addition, labeling negotiations will be conducted in the next review cycle. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made. If additional information relating to the safety or effectiveness of this/these drug(s) becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may proceed to withdraw the application(s). Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Daniel Shames, M.D.
Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daniel A. Shames
10/7/02 01:45:40 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-577/S-032, S-033 &
18-211/S-014, S-016 &
20-897/S-009, S-010

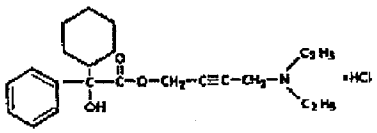
LABELING

NDA 17-577 DITROPAN® (oxybutynin chloride) Tablets (Final Draft submitted 4/9/2003)
NDA 18-211 DITROPAN® (oxybutynin chloride) Syrup (Final Draft submitted 4/9/2003)

DITROPAN®
(oxybutynin chloride)
Tablets and Syrup

DESCRIPTION

Each scored biconvex, engraved blue DITROPAN® (oxybutynin chloride) Tablet contains 5 mg of oxybutynin chloride. Each 5 mL of DITROPAN Syrup contains 5 mg of oxybutynin chloride. Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \bullet HCl$. The structural formula appears below:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alkalis.
DITROPAN Tablets
Also contains: calcium stearate, FD&C Blue #1 Lake, lactose, and microcrystalline cellulose.
DITROPAN Syrup
Also contains: citric acid, FD&C Green #3, glycerin, methylparaben, flavor, sodium citrate, sorbitol, sucrose, and water.
DITROPAN Tablets and Syrup are for oral administration.
Therapeutic Category: Antispasmodic, anticholinergic.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Antimuscarinic activity resides predominately in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in in vitro studies.

Pharmacokinetics

Absorption

Following oral administration of DITROPAN, oxybutynin is rapidly absorbed achieving C_{max} within an hour, following which plasma concentration decreases with an effective half-life of approximately 2 to 3 hours. The absolute bioavailability of oxybutynin is

reported to be about 6% (range 1.6 to 10.9%) for both the tablet and syrup. Wide interindividual variation in pharmacokinetic parameters is evident following oral administration of oxybutynin.

The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 1. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape; Figure 1 shows the profile for R-oxybutynin.

Table 1
Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters
Following Three doses of Ditropan 5 mg administered every 8 hours (n=23)

Parameters (units)	R-oxybutynin	S-oxybutynin
C_{max} (ng/mL)	3.6 (2.2)	7.8 (4.1)
T_{max} (h)	0.89 (0.34)	0.65 (0.32)
AUC_t (ng·h/mL)	22.6 (11.3)	35.0 (17.3)
AUC_{inf} (ng·h/mL)	24.3 (12.3)	37.3 (18.7)

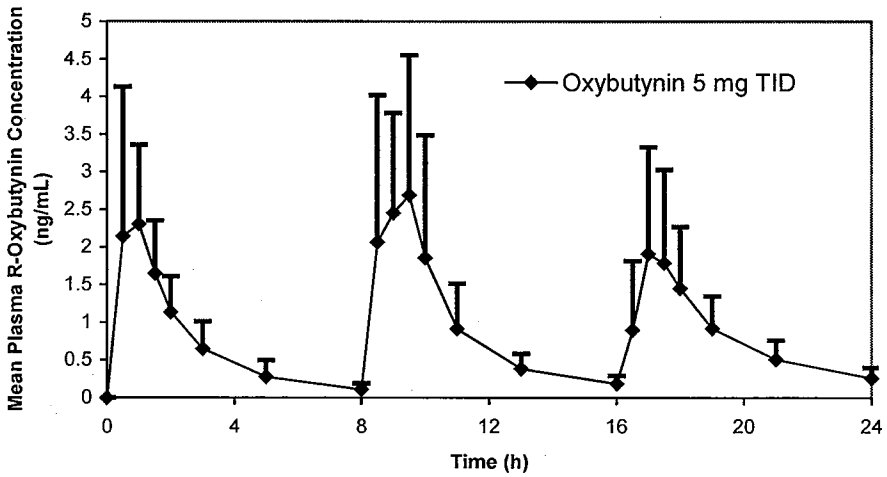


Figure 1. *Mean R-oxybutynin plasma concentrations following three doses of DITROPAN® 5 mg administered every 8 hours for 1 day in 23 healthy adult volunteers*

DITROPAN® steady-state pharmacokinetics was also studied in 23 pediatric patients with detrusor overactivity associated with a neurological condition (e.g., spina bifida). These pediatric patients were on Ditropan tablets (n=11) with total daily dose ranging from 7.5 mg to 15 mg (0.22 to 0.53 mg/kg) or Ditropan syrup (n=12) with total daily dose ranging from 5 mg to 22.5 mg (0.26 to 0.75 mg/kg). Overall, most patients (86.9%) were taking a total daily Ditropan dose between 10 mg and 15 mg. Sparse sampling technique was used to obtain serum samples. When all available data are normalized to

an equivalent of 5 mg twice daily Ditropan, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 2a (for tablet) and Table 2b (for syrup). The plasma-time concentration profile for R- and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are normalized to an equivalent of 5 mg twice daily.

Table 2a
Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15
Following Administration of 7.5 mg to 15 mg Total Daily Dose of Ditropan Tablets (N=11)

All Available Data Normalized to An Equivalent of Ditropan Tablets 5 mg BID or TID at Steady State

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}*(ng/mL)	6.1± 3.2	10.1 ± 7.5	55.4 ± 17.9	28.2 ± 10.0
T_{max} (hr)	1.0	1.0	2.0	2.0
AUC** (ng.hr/mL)	19.8 ± 7.4	28.4 ± 12.7	238.8 ± 77.6	119.5 ± 50.7

*Reflects C_{max} for pooled data

**$AUC_{0\text{-end of dosing interval}}$

Table 2b
Mean ± SD R- and S-oxybutynin and R- and S-desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15
Following Administration of 5 mg to 22.5 mg Total Daily Dose of Ditropan Syrup (N=12)

All Available Data Normalized to An Equivalent of Ditropan Syrup 5 mg BID or TID at Steady State

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}* (ng/mL)	5.7 ± 6.2	7.3 ± 7.3	54.2 ± 34.0	27.8 ± 20.7
T_{max} (hr)	1.0	1.0	1.0	1.0
AUC** (ng.hr/mL)	16.3 ± 17.1	20.2 ± 20.8	209.1 ± 174.2	99.1 ± 87.5

*Reflects C_{max} for pooled data

**$AUC_{0\text{-end of dosing interval}}$

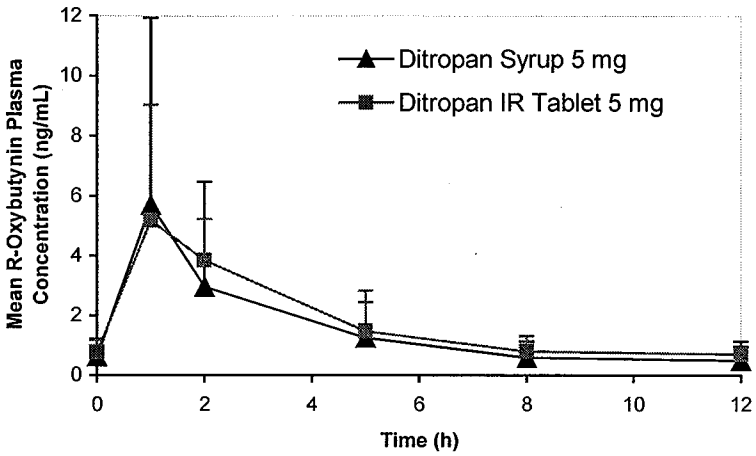


Figure 2. *Mean steady-state (±SD) R-oxybutynin plasma concentrations following administration of total daily Ditropan dose of 5 mg to 30 mg (0.21 mg/kg to 0.77 mg/kg) in children 5-15 years of age. – Plot represents all available data normalized to the equivalent of Ditropan 5 mg BID or TID at steady state*

Food effects
Data in the literature suggests that oxybutynin solution co-administered with food resulted in a slight delay in absorption and an increase in its bioavailability by 25% (n=18).[1]

Distribution
Plasma concentrations of oxybutynin decline biexponentially following intravenous or oral administration. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin chloride.

Metabolism
Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active.

Excretion
Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

Clinical Studies
DITROPAN® was well tolerated in patients administered the drug in controlled studies of 30 days' duration and in uncontrolled studies in which some of the patients received the drug for 2 years.

[1] Yong C et al. Effect of Food on the Pharmacokinetics of Oxybutynin in normal subjects. *Pharm Res.* 1991; 8 (Suppl.): S-320

INDICATIONS AND USAGE

DITROPAN® (oxybutynin chloride) is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria).

CONTRAINDICATIONS

DITROPAN is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

DITROPAN is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

General

DITROPAN should be used with caution in the frail elderly, in patients with hepatic or renal impairment, and in patients with myasthenia gravis.

DITROPAN may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, myasthenia gravis, and prostatic hypertrophy.

Urinary Retention

DITROPAN should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (See **CONTRAINDICATIONS**).

Gastrointestinal Disorders

DITROPAN should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Administration of DITROPAN to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

DITROPAN, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, and intestinal atony.

DITROPAN should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

Information for Patients

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Drug Interactions
The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 3-4 fold higher when DITROPAN® (oxybutynin chloride) was administered with ketoconazole, a potent CYP3A4 inhibitor.

Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility
A 24-month study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae* and *Salmonella typhimurium* test systems.

Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility.

Pregnancy
Category B. Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN administered to women who are or who may become pregnant has not been established. Therefore, DITROPAN should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

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

Pediatric Use
The safety and efficacy of DITROPAN® (oxybutynin chloride) administration have been demonstrated for pediatric patients 5 years of age and older (see DOSAGE AND ADMINISTRATION).

The safety and efficacy of Ditropan Tablets and Ditropan Syrup were studied in 30 and in 26 children, respectively, in a 24-week, open-label trial. Patients were aged 5-15 years, all had symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride. Study results demonstrated that the administration of DITROPAN was associated with improvement in clinical and urodynamic parameters.

At total daily doses ranging from 5 mg to 15 mg, treatment with Ditropan Tablets was associated with an increase from baseline in mean urine volume per catheterization from 122 mL to 145 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 168 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 43% to 61%. Urodynamic results in these patients were consistent with the clinical results. Treatment with Ditropan® Tablets was associated with an increase from baseline in maximum cystometric capacity from 230 mL to 279 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 36 cm H_20 to 33 cm H_20, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_20) from 39% to 20%.

At total daily doses ranging from 5 mg to 30 mg, treatment with Ditropan Syrup was associated with an increase from baseline in mean urine volume per catheterization from 113 mL to 133 mL, an increase from baseline in mean urine volume after morning awakening from 143 mL to 165 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 63%. Urodynamic results were consistent with these clinical results. Treatment with Ditropan Syrup was associated with an increase from baseline in maximum cystometric capacity from 192 mL to 294 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 46 cm H_20 to 37 cm H_20, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_20) from 67% to 28%.

As there is insufficient clinical data for pediatric populations under age 5, DITROPAN is not recommended for this age group.

Geriatric Use
Clinical studies of DITROPAN did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between healthy elderly and younger patients; however, a lower initial starting dose of 2.5 mg given 2 or 3 times a day has been recommended for the frail elderly due to a prolongation of the

elimination half-life from 2-3 hours to 5 hours.[2,3,4] In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The safety and efficacy of DITROPAN® (oxybutynin chloride) was evaluated in a total of 199 patients in three clinical trials comparing DITROPAN with DITROPAN XL (see Table 3). These participants were treated with DITROPAN 5-20 mg/day for up to 6 weeks. Table 3 shows the incidence of adverse events judged by investigator to be at least possibly related to treatment and reported by at least 5% of patients.

Table 3
Incidence (%) of Adverse Events Reported by > 5% of Patients Using DITROPAN (5-20 mg/day)

Body System	Adverse Event	DITROPAN (5-20 mg/day) (n=199)
General	Abdominal pain	6.5%
	Headache	6.0%
Digestive	Dry mouth	71.4%
	Constipation	12.6%
	Nausea	10.1%
	Dyspepsia	7.0%
	Diarrhea	5.0%
Nervous	Dizziness	15.6%
	Somnolence	12.6%
Special senses	Blurred vision	9.0%
Urogenital	Urination impaired	10.6%
	Post void residuals increase	5.0%
	Urinary tract infection	5.0%

The most common adverse events reported by patients receiving DITROPAN® 5-20 mg/day were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

In addition, the following adverse events were reported by 2 to <5% of patients using DITROPAN (5-20 mg/day) in all studies. *General:* asthenia, dry nasal and sinus mucous

[2] Hughes KM et al. Measurement of oxybutynin and its *N*-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. *Xenobiotica.* 1992; 22 (7): 859-869.
[3] Ouslander J et al. Pharmacokinetics and Clinical Effects of Oxybutynin in Geriatric Patients. *J. Urol.* 1988; 140: 47-50
[4] Yarker Y et al. Oxybutynin: A review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapeutic Use in Detrusor Instability. *Drugs & Aging.* 1995; 6 (3): 243-262.

membranes; *Cardiovascular:* palpitation; *Metabolic and Nutritional System:* peripheral edema; *Nervous System:* insomnia, nervousness, confusion; *Skin:* dry skin; *Special Senses:* dry eyes, taste perversion.

Other adverse events that have been reported include: tachycardia, hallucinations, cycloplegia, mydriasis, impotence, suppression of lactation, vasodilatation, rash, decreased gastrointestinal motility, flatulence, urinary retention, convulsions and decreased sweating.

OVERDOSAGE

Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

Overdosage with oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation (e.g., restlessness, tremor, irritability, convulsions, delirium, hallucinations), flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Other symptoms may include hypotension or hypertension, respiratory failure, paralysis, and coma.

Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13 year old boy who experienced memory loss, and a 34 year old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

DOSAGE AND ADMINISTRATION

Tablets

Adults: The usual dose is one 5-mg tablet two to three times a day. The maximum recommended dose is one 5-mg tablet four times a day. A lower starting dose of 2.5 mg two or three times a day is recommended for the frail elderly.

Pediatric patients over 5 years of age: The usual dose is one 5-mg tablet two times a day. The maximum recommended dose is one 5-mg tablet three times a day.

Syrup

Adults: The usual dose is one teaspoon (5 mg/5 mL) syrup two to three times a day. The maximum recommended dose is one teaspoon (5 mg/5 mL) syrup four times a day. A lower starting dose of 2.5 mg two or three times a day is recommended for the frail elderly.

Pediatric patients over 5 years of age: The usual dose is one teaspoon (5 mg/5 mL) syrup two times a day. The maximum recommended dose is one teaspoon (5 mg/5mL) syrup three times a day.

HOW SUPPLIED

DITROPAN® (oxybutynin chloride) Tablets are supplied in bottles of 100 tablets (NDC 17314-9200-1). Blue scored tablets (5 mg) are engraved with DITROPAN on one side with 92 and 00, separated by a horizontal score, on the other side.

NDA 17-577 DITROPAN® (oxybutynin chloride) Tablets (Final Draft submitted 4/9/2003)
NDA 18-211 DITROPAN® (oxybutynin chloride) Syrup (Final Draft submitted 4/9/2003)

DITROPAN® Syrup (5 mg/5 mL) is supplied in bottles of 16 fluid ounces (473 mL) (NDC 17314-9201-4).

Pharmacist: Dispense in tight, light-resistant container as defined in the USP.
Store at controlled room temperature (59-86°F).

Rx ONLY

Manufactured by Aventis Pharmaceuticals, Inc., Kansas City, MO 64137

Distributed and Marketed by Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ 08869.

Placeholder for Ortho-McNeil Pharmaceutical, Inc. Logo

Edition: 03/03

50017115

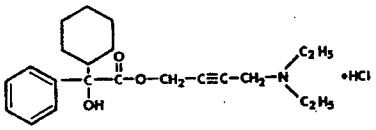
DITROPAN XL®
(oxybutynin chloride)
Extended Release Tablets

DESCRIPTION

DITROPAN XL® (oxybutynin chloride) is an antispasmodic, anticholinergic agent. Each DITROPAN XL Extended Release Tablet contains 5 mg, 10 mg or 15 mg of oxybutynin chloride USP, formulated as a once-a-day controlled-release tablet for oral administration. Oxybutynin chloride is administered as a racemate of R- and S- enantiomers.

Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \cdot HCl$.

Its structural formula is:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alkalis.

DITROPAN XL also contains the following inert ingredients: cellulose acetate, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, synthetic iron oxides, titanium dioxide, polysorbate 80, sodium chloride, and butylated hydroxytoluene.

System Components and Performance

DITROPAN XL uses osmotic pressure to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice in the semipermeable membrane on the drug-layer side of the tablet. In an aqueous environment, such as the gastrointestinal tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and the push layer to expand. This expansion pushes the suspended drug out through the orifice. The semipermeable membrane controls the rate at which water permeates into the tablet core, which in turn controls the rate of drug delivery. The controlled rate of drug delivery into the gastrointestinal lumen is thus independent of pH or gastrointestinal motility. The function of DITROPAN XL depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract. Since the osmotic gradient remains constant, drug delivery remains essentially constant. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Antimuscarinic activity resides predominantly in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in in vitro studies.

Pharmacokinetics

Absorption

Following the first dose of DITROPAN XL® (oxybutynin chloride), oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter steady concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with oxybutynin.

The relative bioavailabilities of R- and S-oxybutynin from DITROPAN XL are 156% and 187%, respectively, compared with oxybutynin. The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 1. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape; Figure 1 shows the profile for R-oxybutynin.

Table 1
Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following a Single Dose of DITROPAN XL 10 mg (n=43)

Parameters (units)	R-Oxybutynin		S-Oxybutynin	
C_{max} (ng/mL)	1.0	(0.6)	1.8	(1.0)
T_{max} (h)	12.7	(5.4)	11.8	(5.3)
$t_{1/2}$ (h)	13.2	(6.2)	12.4	(6.1)
$AUC_{(0-48)}$ (ng·h/mL)	18.4	(10.3)	34.2	(16.9)
AUC_{inf} (ng·h/mL)	21.3	(12.2)	39.5	(21.2)

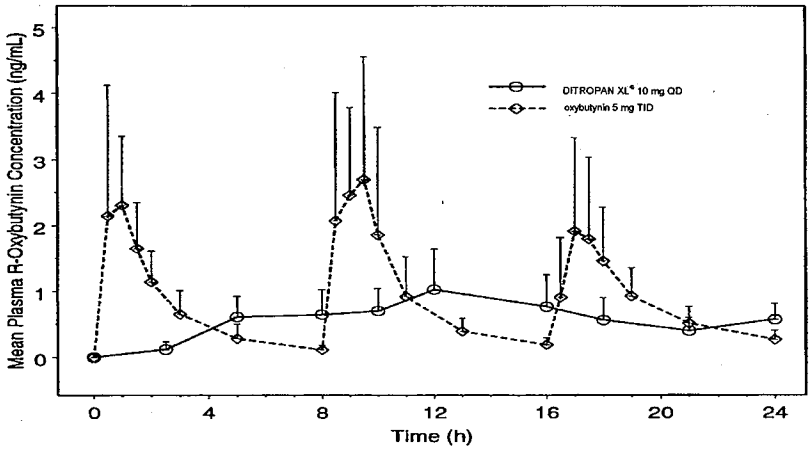


Figure 1. *Mean R-oxybutynin plasma concentrations following a single dose of DITROPAN XL 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment).*

Steady-state oxybutynin plasma concentrations are achieved by Day 3 of repeated DITROPAN XL® (oxybutynin chloride) dosing, with no observed drug accumulation or change in oxybutynin and desethyloxybutynin pharmacokinetic parameters.

DITROPAN XL steady-state pharmacokinetics was studied in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (e.g. spina bifida). The children were on DITROPAN XL total daily dose ranging from 5 to 20 mg (0.10 to 0.77 mg/kg). Sparse sampling technique was used to obtain serum samples. When all available data are normalized to an equivalent of 5mg per day Ditropan XL, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 2. The plasma-time concentration profiles for R- and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are normalized to an equivalent of 5 mg per day.

Table 2
Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5 to 20mg Ditropan XL Once Daily (N=19)

All Available Data Normalized To An Equivalent of Ditropan XL 5 mg Once Daily

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max} (ng/mL)	0.7 ± 0.4	1.3 ± 0.8	7.8 ± 3.7	4.2 ± 2.3
T_{max} (hr)	5.0	5.0	5.0	5.0
AUC (ng.hr/mL)	12.8 ± 7.0	23.7 ± 14.4	125.1 ± 66.7	73.6 ± 47.7

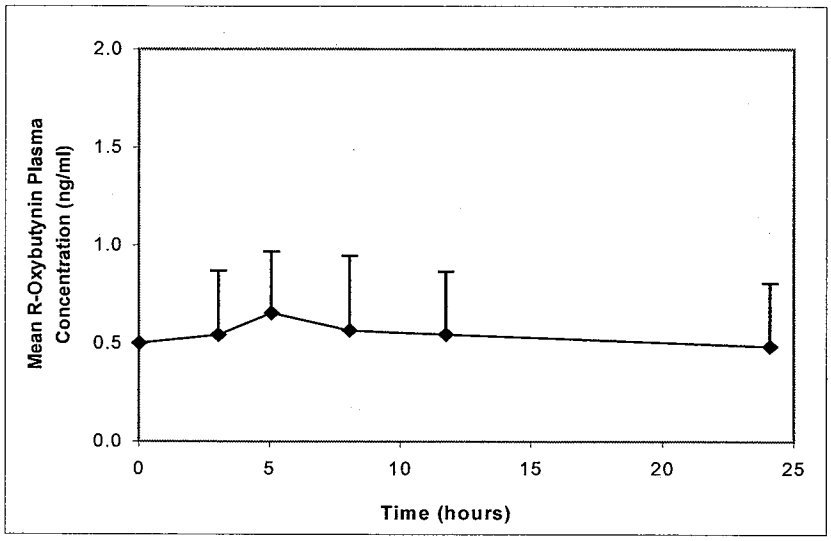


Figure 2. *Mean steady state (±SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg Ditropan XL once daily in children aged 5-15. - Plot represents all available data normalized to an equivalent of Ditropan XL 5 mg once daily*

Food Effects
The rate and extent of absorption and metabolism of oxybutynin are similar under fed and fasted conditions.

Distribution
Plasma concentrations of oxybutynin decline biexponentially following intravenous or oral administration. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin chloride.

Metabolism
Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active. Following DITROPAN XL administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin.

Excretion
Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

Dose Proportionality
Pharmacokinetic parameters of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of 5-20 mg of DITROPAN XL are dose proportional.

Special Populations

Geriatric: The pharmacokinetics of DITROPAN XL® were similar in all patients studied (up to 78 years of age).

Pediatric: The pharmacokinetics of DITROPAN XL (oxybutynin chloride) were evaluated in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida). The pharmacokinetics of DITROPAN XL in these pediatric patients were consistent with those reported for adults (see Tables 1 and 2, and Figures 1 and 2 above).

Gender: There are no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following administration of DITROPAN XL.

Race: Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of DITROPAN XL.

Renal Insufficiency: There is no experience with the use of DITROPAN XL in patients with renal insufficiency.

Hepatic Insufficiency: There is no experience with the use of DITROPAN XL in patients with hepatic insufficiency.

Drug-Drug Interactions: See **PRECAUTIONS:** Drug Interactions.

Clinical Studies

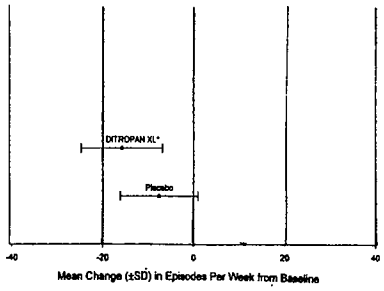
DITROPAN XL was evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (89.0%) and female (91.9%) with a mean age of 59 years (range, 18 to 98 years). Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge) as evidenced by ≥ 6 urge incontinence episodes per week and ≥ 10 micturitions per day. Study 1 was a forced dose escalation design, whereas the other studies used a dose adjustment design in which each patient's final dose was adjusted to a balance between improvement of incontinence symptoms and tolerability of side effects. Controlled studies included patients known to be responsive to oxybutynin or other anticholinergic medications, and these patients were maintained on a final dose for up to 2 weeks.

The efficacy results for the three controlled trials are presented in the following tables and figures.

Number of Urge Urinary Incontinence Episodes Per Week

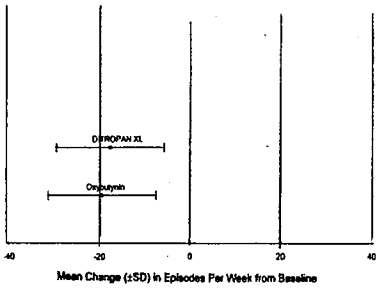
Study 1	N	DITROPAN® XL	N	Placebo
Mean Baseline	34	15.9	16	20.9
Mean (SD) Change from Baseline†	34	-15.8 (8.9)	16	-7.6 (8.6)
95% Confidence Interval for Difference (DITROPAN® XL – Placebo)		(-13.6, -2.8)*		

* The difference between DITROPAN® XL and placebo was statistically significant.
† Covariate adjusted mean with missing observations set to baseline values



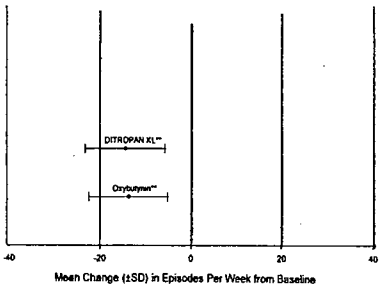
Study 2	N	DITROPAN® XL	N	oxybutynin
Mean Baseline	53	27.6	52	23.0
Mean (SD) Change from Baseline†	53	-17.6 (11.9)	52	-19.4 (11.9)
95% Confidence Interval for Difference (DITROPAN® XL – oxybutynin)		(-2.8, 6.5)		

† Covariate adjusted mean with missing observations set to baseline values



Study 3	N	DITROPAN® XL	N	oxybutynin
Mean Baseline	111	18.9	115	19.5
Mean (SD) Change from Baseline†	111	-14.5 (8.7)	115	-13.8 (8.6)
95% Confidence Interval for Difference (DITROPAN® XL – oxybutynin)		(-3.0, 1.6)**		

** The difference between DITROPAN® XL and oxybutynin fulfilled the criteria for comparable efficacy.
† Covariate adjusted mean with missing observations set to baseline values



INDICATIONS AND USAGE

DITROPAN XL® (oxybutynin chloride) is a once-daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

DITROPAN XL is also indicated in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida).

CONTRAINDICATIONS

DITROPAN XL is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

DITROPAN XL is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

General

DITROPAN XL should be used with caution in patients with hepatic or renal impairment and in patients with myasthenia gravis due to the risk of symptom aggravation.

Urinary Retention:
DITROPAN XL should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

Gastrointestinal Disorders:
DITROPAN XL should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

DITROPAN XL, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal atony.

DITROPAN XL should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

As with any other nondeformable material, caution should be used when administering DITROPAN XL to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations.

Information for Patients

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Patients should be informed that DITROPAN XL® (oxybutynin chloride) should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush tablets. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Drug Interactions
The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 2 fold higher when DITROPAN XL was administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility
A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25 and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems.

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility.

Pregnancy: Teratogenic Effects
Pregnancy Category B
Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN XL administration to women who are or who may become pregnant has not been established. Therefore, DITROPAN XL should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers
It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DITROPAN XL® (oxybutynin chloride) is administered to a nursing woman.

Pediatric Use
The safety and efficacy of DITROPAN XL were studied in 60 children in a 24-week, open-label trial. Patients were aged 6-15 years, all had symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride. Study results demonstrated that administration of DITROPAN XL 5 to 20 mg/day was associated with an increase from baseline in mean urine volume per catheterization from 108 mL to 136 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 189 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 51%.

Urodynamic results were consistent with clinical results. Administration of DITROPAN XL resulted in an increase from baseline in mean maximum cystometric capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 cm H_2O to 33 cm H_2O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_2O) from 60% to 28%.

DITROPAN XL is not recommended in pediatric patients who can not swallow the tablet whole without chewing, dividing, or crushing, or in children under the age of 6 (**see DOSAGE AND ADMINISTRATION**).

Geriatric Use
The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar (See **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, ***Special Populations***: *Gender*).

ADVERSE REACTIONS
Adverse Events with DITROPAN XL®
The safety and efficacy of DITROPAN XL was evaluated in a total of 580 participants who received DITROPAN XL in clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5-30 mg/day for up to 4.5 months. Safety information is provided for 429 patients from three controlled clinical studies and one open label study (Table 3). The adverse events are reported regardless of causality.

Table 3
Incidence (%) of Adverse Events Reported by ≥ 5% of Patients Using DITROPAN XL (5-30 mg/day)

Body System	Adverse Event	DITROPAN XL 5-30 mg/day (n=429)
General	headache	9.8
	asthenia	6.8
	pain	6.8
Digestive	dry mouth	60.8
	constipation	13.1
	diarrhea	9.1
	nausea	8.9
	dyspepsia	6.8
Nervous	somnolence	11.9
	dizziness	6.3
Respiratory	rhinitis	5.6
Special senses	blurred vision	7.7
	dry eyes	6.1
Urogenital	urinary tract infection	5.1

The most common adverse events reported by patients receiving 5-30 mg/day DITROPAN XL® were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

The discontinuation rate for all adverse events was 6.8%. The most frequent adverse event causing early discontinuation of study medication was nausea (1.9%), while discontinuation due to dry mouth was 1.2%.

In addition, the following adverse events were reported by 2 to < 5% of patients using DITROPAN XL (oxybutynin chloride) (5-30 mg/day) in all studies. *General:* abdominal pain, dry nasal and sinus mucous membranes, accidental injury, back pain, flu syndrome; *Cardiovascular:* hypertension, palpitation, vasodilatation; *Digestive:* flatulence, gastroesophageal reflux; *Musculoskeletal:* arthritis; *Nervous:* insomnia, nervousness, confusion; *Respiratory:* upper respiratory tract infection, cough, sinusitis, bronchitis, pharyngitis; *Skin:* dry skin, rash; *Urogenital:* impaired urination (hesitancy), increased post void residual volume, urinary retention, cystitis.

Additional rare adverse events reported from worldwide post-marketing experience with DITROPAN XL include: peripheral edema, cardiac arrhythmia, tachycardia, hallucinations, convulsions, and impotence.

Additional adverse events reported with some other oxybutynin chloride formulations include: cycloplegia, mydriasis, and suppression of lactation.

OVERDOSAGE

The continuous release of oxybutynin from DITROPAN XL (oxybutynin chloride) should be considered in the treatment of overdosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

Overdosage with oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention.

Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13 year old boy who experienced memory loss, and a 34 year old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

DOSAGE AND ADMINISTRATION

DITROPAN XL® must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

DITROPAN XL® may be administered with or without food.

Adults: The recommended starting dose of DITROPAN XL® is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.

Pediatric patients aged 6 years of age and older: The recommended starting dose of DITROPAN XL is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

HOW SUPPLIED

DITROPAN XL® (oxybutynin chloride) Extended Release Tablets are available in three dosage strengths, 5 mg (pale yellow), 10 mg (pink) and 15 mg (gray) and are imprinted with "5 XL", "10 XL" or "15 XL". DITROPAN XL® (oxybutynin chloride) Extended Release Tablets are supplied in bottles of 100 tablets.

5 mg	100 count bottle	NDC 17314-8500-1
10 mg	100 count bottle	NDC 17314-8501-1
15 mg	100 count bottle	NDC 17314-8502-1

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and humidity.

Rx only

For more information call 1-888-395-1232 or visit www.DitropanXL.com

Manufactured by
ALZA Corporation, Mountain View, CA 94043.

An ALZA OROS®
Technology Product

Distributed and Marketed by
Ortho-McNeil Pharmaceuticals, Inc., Raritan, NJ 08869.

Placeholder for Ortho-McNeil Pharmaceuticals, Inc. Logo

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Edition: 3/03

DITROPAN XL®

(oxybutynin chloride)

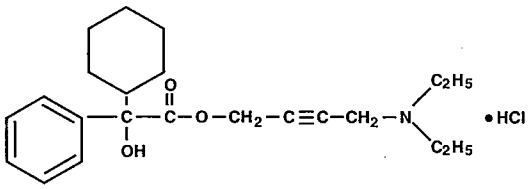
Extended Release Tablets

DESCRIPTION

DITROPAN XL® (oxybutynin chloride) is an antispasmodic, anticholinergic agent. Each DITROPAN XL Extended Release Tablet contains 5 mg, 10 mg, or 15 mg of oxybutynin chloride USP, formulated as a once-a-day controlled-release tablet for oral administration. Oxybutynin chloride is administered as a racemate of R- and S-enantiomers.

Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \cdot HCl$.

Its structural formula is:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alkalis.

DITROPAN XL also contains the following inert ingredients: cellulose acetate, hypromellose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, synthetic iron oxides, titanium dioxide, polysorbate 80, sodium chloride, and butylated hydroxytoluene.

System Components and Performance

DITROPAN XL uses osmotic pressure to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice in the semipermeable membrane on the drug-layer side of the tablet. In an aqueous environment, such as the gastrointestinal tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and the push layer to expand. This expansion pushes the suspended drug out through the orifice. The semipermeable membrane controls the rate at which water permeates into the tablet core, which in turn controls the rate of drug delivery. The controlled rate of drug delivery into the gastrointestinal lumen is thus independent of pH or gastrointestinal motility. The function of DITROPAN XL depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract. Since the osmotic gradient remains constant, drug delivery remains essentially constant. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Antimuscarinic activity resides predominantly in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in *in vitro* studies.

Pharmacokinetics

Absorption

Following the first dose of DITROPAN XL® (oxybutynin chloride), oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter steady concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with oxybutynin.

The relative bioavailabilities of R- and S-oxybutynin from DITROPAN XL are 156% and 187%, respectively, compared with oxybutynin. The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 1. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape; Figure 1 shows the profile for R-oxybutynin.

Table 1
Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following a Single Dose of DITROPAN XL 10 mg (n=43)

Parameters (units)	R-Oxybutynin		S-Oxybutynin	
C_{max} (ng/mL)	1.0	(0.6)	1.8	(1.0)
T_{max} (h)	12.7	(5.4)	11.8	(5.3)
$t_{1/2}$ (h)	13.2	(6.2)	12.4	(6.1)
$AUC_{(0-48)}$ (ng•h/mL)	18.4	(10.3)	34.2	(16.9)
AUC_{inf} (ng•h/mL)	21.3	(12.2)	39.5	(21.2)

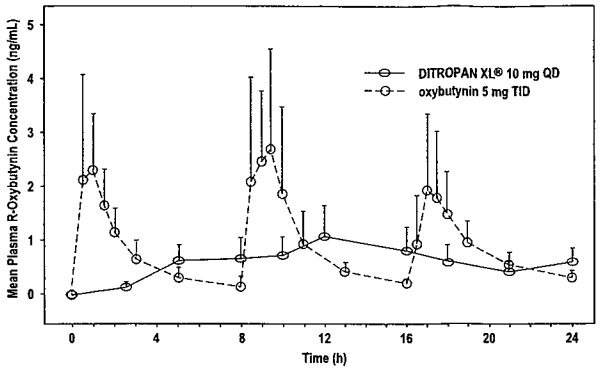


Figure 1. *Mean R-oxybutynin plasma concentrations following a single dose of DITROPAN XL 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment).*

Steady-state oxybutynin plasma concentrations are achieved by Day 3 o repeated DITROPAN XL dosing, with no observed drug accumulation o change in oxybutynin and desethyloxybutynin pharmacokinetic parameters.

DITROPAN XL steady-state pharmacokinetics was studied in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (e.g. spina bifida). The children were on DITROPAN XL total daily dose ranging from 5 to 20 mg (0.10 to 0.77 mg/kg). Sparse sampling technique was used to obtain serum samples. When all available data are normalized to an equivalent of 5 mg per day Ditropan XL, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 2. The plasma-time concentration profiles for R- and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are normalized to an equivalent of 5 mg per day.

Table 2
Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5 to 20 mg DITROPAN XL Once Daily (n=19)
All Available Data Normalized to an Equivalent of DITROPAN XL 5 mg Once Daily

	R-Oxybutynin	S-Oxybutynin	R-Desethyloxybutynin	S-Desethyloxybutynin
C_{max} (ng/mL)	0.7 ± 0.4	1.3 ± 0.8	7.8 ± 3.7	4.2 ± 2.3
T_{max} (hr)	5.0	5.0	5.0	5.0
AUC (ng.hr/mL)	12.8 ± 7.0	23.7 ± 14.4	125.1 ± 66.7	73.6 ± 47.7

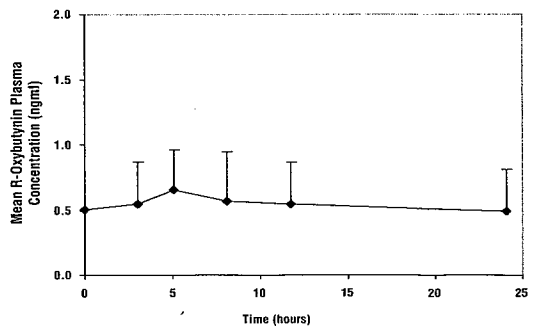


Figure 2. *Mean steady-state (±SD) R-oxybutynin plasma concentration following administration of 5 to 20 mg DITROPAN XL once daily in children aged 5-15. Plot represents all available data normalized to an equivalent o DITROPAN XL 5 mg once daily.*

Food Effects

The rate and extent of absorption and metabolism of oxybutynin are simila under fed and fasted conditions.

DITROPAN XL®

DITROPAN XL®

Distribution

Plasma concentrations of oxybutynin decline biexponentially following intravenous or oral administration. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin chloride.

Metabolism

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active. Following DITROPAN XL administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin.

Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

Dose Proportionality

Pharmacokinetic parameters of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of 5-20 mg of DITROPAN XL are dose proportional.

Special Populations

Geriatric: The pharmacokinetics of DITROPAN XL were similar in all patients studied (up to 78 years of age).

Pediatric: The pharmacokinetics of DITROPAN XL were evaluated in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida). The pharmacokinetics of DITROPAN XL in these pediatric patients were consistent with those reported for adults (see Tables 1 and 2, and Figures 1 and 2 above).

Gender: There are no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following administration of DITROPAN XL.

Race: Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of DITROPAN XL.

Renal Insufficiency: There is no experience with the use of DITROPAN XL in patients with renal insufficiency.

Hepatic Insufficiency: There is no experience with the use of DITROPAN XL in patients with hepatic insufficiency.

Drug-Drug Interactions: See **PRECAUTIONS:** Drug Interactions.

Clinical Studies

DITROPAN XL was evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (89.0%) and female (91.9%) with a mean age of 59 years (range, 18 to 98 years). Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge) as evidenced by ≥ 6 urge incontinence episodes per week and ≥ 10 micturitions per day. Study 1 was a forced dose escalation design, whereas the other studies used a dose adjustment design in which each patient's final dose was adjusted to a balance between improvement of incontinence symptoms and tolerability of side effects. Controlled studies included patients known to be responsive to oxybutynin or other anticholinergic medications, and these patients were maintained on a final dose for up to 2 weeks.

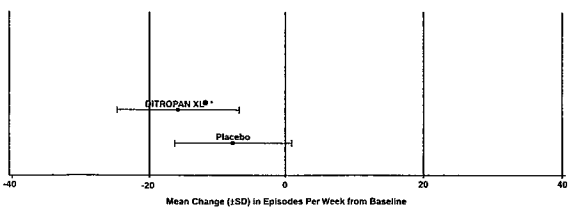
The efficacy results for the three controlled trials are presented in the following tables and figures.

Number of Urge Urinary Incontinence Episodes Per Week

Study 1	n	DITROPAN XL®	n	Placebo
Mean Baseline	34	15.9	16	20.9
Mean (SD) Change from Baseline†	34	-15.8 (8.9)	16	-7.6 (8.6)
95% Confidence Interval for Difference (DITROPAN XL® - Placebo)		(-13.6, -2.8)*		

* The difference between DITROPAN XL® and placebo was statistically significant.

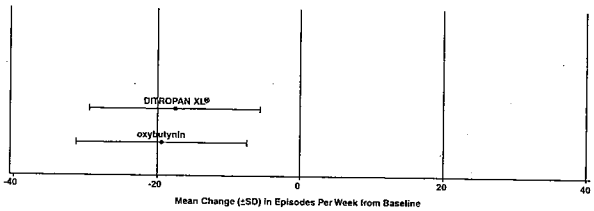
† Covariate adjusted mean with missing observations set to baseline values



Number of Urge Urinary Incontinence Episodes Per Week (continued)

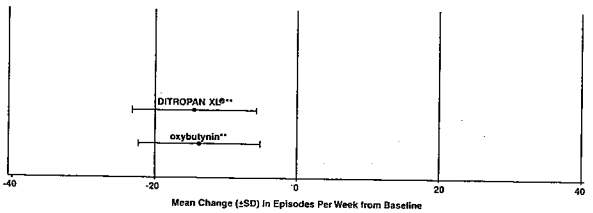
Study 2	n	DITROPAN XL®	n	oxybutynin
Mean Baseline	53	27.6	52	23.0
Mean (SD) Change from Baseline†	53	-17.6 (11.9)	52	-19.4 (11.9)
95% Confidence Interval for Difference (DITROPAN XL® - oxybutynin)		(-2.8, 6.5)		

† Covariate adjusted mean with missing observations set to baseline values



Study 3	n	DITROPAN XL®	n	oxybutynin
Mean Baseline	111	18.9	115	19.5
Mean (SD) Change from Baseline†	111	-14.5 (8.7)	115	-13.8 (8.6)
95% Confidence Interval for Difference (DITROPAN XL® - oxybutynin)		(-3.0, 1.6)**		

** The difference between DITROPAN XL® and oxybutynin fulfilled the criteria for comparable efficacy.
† Covariate adjusted mean with missing observations set to baseline value



INDICATIONS AND USAGE

DITROPAN XL® (oxybutynin chloride) is a once-daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

DITROPAN XL is also indicated in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida).

CONTRAINDICATIONS

DITROPAN XL® (oxybutynin chloride) is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

DITROPAN XL is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

General

DITROPAN XL® (oxybutynin chloride) should be used with caution in patients with hepatic or renal impairment and in patients with myasthenia gravis due to the risk of symptom aggravation.

Urinary Retention

DITROPAN XL should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

Gastrointestinal Disorders

DITROPAN XL should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

DITROPAN XL, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal atony.

DITROPAN XL should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

As with any other nondeformable material, caution should be used when administering DITROPAN XL to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations.

Information for Patients

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Patients should be informed that DITROPAN XL should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush tablets. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Drug Interactions

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 2 fold higher when DITROPAN XL was administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems.

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility.

Pregnancy: Teratogenic Effects

Pregnancy Category B

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN XL administration to women who are or who may become pregnant has not been established. Therefore, DITROPAN XL should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers

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

Pediatric Use

The safety and efficacy of DITROPAN XL were studied in 60 children in a 24-week, open-label trial. Patients were aged 6-15 years, all had symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride. Study results demonstrated that administration of DITROPAN XL 5 to 20 mg/day was associated with an increase from baseline in mean urine volume per catheterization from 108 mL to 136 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 189 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 51%.

Urodynamic results were consistent with clinical results. Administration of DITROPAN XL resulted in an increase from baseline in mean maximum cystometric capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 cm H_2O to 33 cm H_2O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_2O) from 60% to 28%.

DITROPAN XL is not recommended in pediatric patients who can not swallow the tablet whole without chewing, dividing, or crushing, or in children under the age of 6 (see **DOSAGE AND ADMINISTRATION**).

Geriatric Use

The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, ***Special Populations***: *Gender*).

ADVERSE REACTIONS

Adverse Events with DITROPAN XL

The safety and efficacy of DITROPAN XL® (oxybutynin chloride) was evaluated in a total of 580 participants who received DITROPAN XL in clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5-30 mg/day for up to 4.5 months. Safety information is provided for 429 patients from three controlled clinical studies and one open label study (Table 3). The adverse events are reported regardless of causality.

Table 3
Incidence (%) of Adverse Events Reported by ≥ 5% of Patients Using DITROPAN XL (5-30 mg/day)

Body System	Adverse Event	DITROPAN XL® 5-30 mg/day (n=429)
General	headache	9.8
	asthenia	6.8
	pain	6.8
Digestive	dry mouth	60.8
	constipation	13.1
	diarrhea	9.1
	nausea	8.9
	dyspepsia	6.8
Nervous	somnolence	11.9
	dizziness	6.3
Respiratory	rhinitis	5.6
Special senses	blurred vision	7.7
	dry eyes	6.1
Urogenital	urinary tract infection	5.1

The most common adverse events reported by patients receiving 5-30 mg/day DITROPAN XL were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

The discontinuation rate for all adverse events was 6.8%. The most frequent adverse event causing early discontinuation of study medication was nausea (1.9%), while discontinuation due to dry mouth was 1.2%.

In addition, the following adverse events were reported by 2 to <5% of patients using DITROPAN XL (5-30 mg/day) in all studies. *General:* abdominal pain, dry nasal and sinus mucous membranes, accidental injury, back pain, flu syndrome; *Cardiovascular:* hypertension, palpitation, vasodilatation; *Digestive:* flatulence, gastroesophageal reflux; *Musculoskeletal:* arthritis; *Nervous:* insomnia, nervousness, confusion; *Respiratory:* upper respiratory tract infection, cough, sinusitis, bronchitis, pharyngitis; *Skin:* dry skin, rash; *Urogenital:* impaired urination (hesitancy), increased post void residual volume, urinary retention, cystitis.

Additional rare adverse events reported from worldwide post-marketing experience with DITROPAN XL include: peripheral edema, cardiac arrhythmia, tachycardia, hallucinations, convulsions, and impotence.

Additional adverse events reported with some other oxybutynin chloride formulations include: cycloplegia, mydriasis, and suppression of lactation.

OVERDOSAGE

The continuous release of oxybutynin from DITROPAN XL® (oxybutynin chloride) should be considered in the treatment of overdosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

Overdosage with oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention.

Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13-year-old boy who experienced memory loss, and a 34-year-old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

DOSAGE AND ADMINISTRATION

DITROPAN XL® (oxybutynin chloride) must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

DITROPAN XL may be administered with or without food.

Adults: The recommended starting dose of DITROPAN XL is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.

Pediatric patients aged 6 years of age and older: The recommended starting dose of DITROPAN XL is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

HOW SUPPLIED

DITROPAN XL® (oxybutynin chloride) Extended Release Tablets are available in three dosage strengths, 5 mg (pale yellow), 10 mg (pink), and 15 mg (gray) and are imprinted with "5 XL", "10 XL", or "15 XL". DITROPAN XL Extended Release Tablets are supplied in bottles of 100 tablets.

5 mg 100 count bottle
NDC 17314-8500-1

10 mg 100 count bottle
NDC 17314-8501-1

15 mg 100 count bottle
NDC 17314-8502-1

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and humidity.

Rx only

For more information call 1-888-395-1232 or visit www.DITROPANXL.com

Manufactured by
ALZA Corporation, Mountain View, CA 94043

An ALZA OROS® Technology Product

DITROPAN XL® and OROS® are registered trademarks of ALZA Corporation.

Distributed and Marketed by
Ortho-McNeil Pharmaceutical, Inc.,
Raritan, NJ 08869

ORTHO-McNEIL

NDC 17314-8501-1 100 tablets

DITROPAN XL®

(oxybutynin chloride)

Extended-release tablets

10 mg

Rx only

ORTHO-McNEIL

Each tablet contains 10 mg oxybutynin chloride in a controlled-release formulation.

Usual dosage: Once daily.
See package insert for dosage information.
Store at 25°C (77°F) (see insert).
Protect from moisture and humidity.

Manufactured by
ALZA Corporation, Mountain View, CA 94043

Distributed and Marketed by
Ortho-McNeil Pharmaceutical Inc., Raritan, NJ 08869

Ditropan XL® and OROS® are registered trademarks of ALZA Corporation.

609-10-501-1

An ALZA OROS® Technology Product

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Printed in USA
Lot:
Expires:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-577/S-032, S-033 &
18-211/S-014, S-016 &
20-897/S-009, S-010

MEDICAL REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of NDA Efficacy Supplement

NDA	20-897: SE-8 Supplement No. 009 17-577: SE-8 Supplement No. 033 18-211: SE-8 Supplement No. 016
IND	48,930: Clinical Amendment Serial No. [ ] b(4)
Sponsor	ALZA Corporation 1900 Charleston Road P.O. Box 7210 Mountain View, CA 94039-7210
Drug name	NDA 20-897 and IND 48,930: Ditropan XL (oxybutynin chloride) extended release tablets NDA 17-577: Ditropan (oxybutynin chloride) tablets NDA 18-211: Ditropan (oxybutynin chloride) syrup
Drug Class	Muscarinic receptor antagonist
Approved Indications	NDA 20-897: "Ditropan XL is a once-daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency." NDA 17-577 and NDA 18-211: "Ditropan is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e. urgency, frequency, urinary leakage, urge incontinence, dysuria)."
Route of Administration	Oral
Dosage Form/Strengths	NDA 20-897: 5 mg, 10 mg, and 15 mg extended release tablets NDA 17-577: 5 mg immediate release tablet NDA 18-211: immediate release syrup (5 mg/5mL)
Dosing Regimen	NDA 20-897 Ditropan XL *Adults:* The recommended starting dose of Ditropan XL is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals. [Sponsor proposed addition: *Pediatric patients 6 years of age and older*: The recommended starting dose of Ditropan XL is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).] NDA 17-577 Ditropan tablets *Adults*: The usual dose is one 5-mg tablet two to three times a day. The maximum recommended dose is one 5-mg tablet four times a day. *Pediatric patients over 5 years of age*: The usual dose is one 5-mg tablet two times a day. The maximum recommended dose is one 5-mg tablet three times a day. NDA 18-211 Ditropan syrup *Adults*: The usual dose is one teaspoon (5 mg/5 mL) syrup two to three times a day. The maximum recommended dose is one teaspoon (5 mg/5mL)[ ]times a day. *Pediatric patients over 5 years of age*: The usual dose is one teaspoon (5 mg/5 mL) syrup two times a day. The maximum recommended dose is one teaspoon (5 b(4)

mg/5 mL) three times a day [redacted] b(4)

Dates	
Submitted	December 7, 2001
CDER stamp date	December 7, 2001
PDUFA date	October 7, 2002
Related NDAs	None
Related INDs	[redacted] b(4)
Medical Reviewer	Brenda S. Gierhart, MD
Date Review Completed	August 30, 2002

APPEARS THIS WAY
ON ORIGINAL

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EXECUTIVE SUMMARY

1 RECOMMENDATIONS

1.1 Recommendation Regarding Approval

1.1.1 Approvability

It is recommended that the efficacy supplements for NDA 20-897 (SE8-009), NDA 17-577 (SE8-033) and NDA 18-211 (SE8-015) receive an approvable action since satisfactory labeling negotiations with the sponsor have not been concluded to date.

1.1.2 Basis for Recommendation Regarding Approvability (Risk/Benefit Analysis)

The clinical findings in the three 43-volume NDA efficacy supplements submitted on December 7, 2001 to NDA 20-897 (Ditropan XL) as SE8-009, to NDA 17-577 (Ditropan tablets) as SE8-033, and NDA 18-211 (Ditropan syrup) as SE8-015 are summarized as follows:

- In Study **C-2000-043-00**, a statistically significant change in the mean maximal cystometric capacity (p=0.0054) from baseline (104 mL) to end of study (175 mL) was demonstrated. A statistically significantly change in the number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 (p=0.0039) from baseline (n=11) to end of study (n=2) was also demonstrated. No significant change from baseline in mean detrusor pressure at maximal cystometric capacity or in mean intravesical pressure at maximal cystometric capacity was noted.
- In Study **C-2000-042-01** for the enrolled patients, statistically significant changes in the mean volume of urine per catheterization (p<0.0001) from baseline (113.2 mL) to last visit (133.7 mL), mean maximal cystometric capacity (<0.0001) from baseline (196.8 mL) to last visit (244.0 mL), mean detrusor pressure at maximal cystometric capacity (p=0.0009) from baseline (43.0 cmH_20) to last visit (36.3 cmH_20), mean intravesical pressure at maximal cystometric capacity (p=0.0013) from baseline (55.4 cmH_20) to last visit (51.4 cmH_20), and number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 (p=<0.001) from baseline (n=65) to end of study (n=24) were documented.
- No new and unlabeled safety issues were identified.
- The results of C-2000-042-01 and C-2000-043-00 may be seriously compromised by the large number of patients who were protocol violators and protocol deviators.

Following the review of the three 43-volume NDA efficacy supplements submitted on December 7, 2001, the clinical reviewer has reached the following conclusions:

- Administration of Ditropan tablets, Ditropan syrup, and Ditropan XL for a duration of up to 24 weeks was demonstrated to be effective and safe for the treatment of detrusor hyperreflexia in 116 pediatric patients with spina bifida 6 years of age and older.
- [redacted] b(4)
- Neither study supports the efficacy and safety of oxybutynin chloride for the treatment of overactive bladder in pediatric patients.
- No clear relationship between the total daily dose (by mg or by mg/kg) administered of Ditropan tablets, Ditropan syrup, or Ditropan XL and the pharmacokinetic results in pediatric patients with spina bifida was identified.

- No clear dose-response or concentration-response relationships between the total daily dose administered of Ditropan tablets, Ditropan syrup, or Ditropan XL and pharmacodynamic results in pediatric patients with spina bifida were identified.
- [redacted] b(4)
- [redacted] b(4)

The clinical reviewer recommends that any approved labeling changes based upon the results of these two clinical trials clearly state that they are pertinent[redacted] to pediatric patients with detrusor hyperreflexia due to spina bifida. Specifically regarding the Ditropan XL proposed labeling changes, the clinical reviewer recommends clarifying that Ditropan XL is indicated only in adults for the treatment of overactive bladder and granting the new pediatric indication as follows: "DITROPAN XL® is also indicated[redacted] b(4) b(4)

1.2 Specific Recommendations to the Sponsor

1. Provide appropriately revised drug labeling regarding:
   a) **CLINICAL PHARMACOLOGY** Sections of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.
   b) **PRECAUTIONS** Section, **Pediatric Use.** Subsection of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.
   c) **DOSAGE AND ADMINISTRATION** Sections of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.
   d) **INDICATIONS AND USES** Section of the Ditropan XL Physician Insert.

2 SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

2.1.1 Drug

Oxybutynin chloride is an antispasmodic, anticholinergic medication first approved as immediate release tablets in 1975. It is currently available from the sponsor in three different formulations: Ditropan tablets (5 mg immediate release tablets), Ditropan Syrup (5 mg/5mL supplied in 16 fluid ounce bottles), and Ditropan XL (5, 10, and 15 mg extended release tablets). Ditropan syrup was approved on November 29, 1979. Ditropan XL was approved on December 16, 1998.

2.1.2 Clinical Program

Ever since Ditropan (oxybutynin chloride) tablets were approved for marketing in 1975 by the Agency, the medical management of detrusor hyperreflexia due to neurogenic conditions (e.g. spina bifida) in pediatric patients in the United States has primarily consisted of treatment with Ditropan syrup or tablets. Despite the widespread use of oxybutynin in pediatric patients with spina bifida, the current approved Ditropan Tablet and Syrup combined labeling contains no pediatric pharmacokinetic information, no adult pharmacokinetic information, and limited pediatric dosing regimen

recommendations that are only for pediatric patients 6 years of age and older. The current approved Ditropan XL extended release tablet labeling contains no pediatric information.

The Agency felt that the management of pediatric patients with detrusor hyperreflexia due to spina bifida would be improved if pediatric pharmacokinetic and additional pediatric dosing regimen information for this population was added to the Ditropan Tablets, Ditropan Syrup, and Ditropan XL labeling. In order to encourage the generation of this data by conducting clinical trials, the Agency issued a Written Request (WR) to the sponsor on November 30, 2000 requesting two clinical trials in pediatric patients with detrusor hyperreflexia due to spina bifida and two critical analyses. On December 7, 2001, the sponsor responded to the WR by submitting a 43-volume NDA supplement to each of their three oxybutynin NDAs: SE8-009 to NDA 20-897 (Ditropan XL), SE8-033 to NDA 17-577 (Ditropan tablets), and SE8-015 to NDA 18-211 (Ditropan syrup). Each NDA supplement contained an interim study report for C-2000-042-01 (Study #2 in the Written Request), a final study report for C-2000-043-00 (Study #1 in the Written Request), and a report containing the requested two critical analyses. Study **C-2000-042-01** evaluated the effects of administering Ditropan tablets, Ditropan syrup, and Ditropan XL for a duration of up to 24 weeks for the treatment of detrusor hyperreflexia in 116 pediatric patients with spina bifida 6 years of age and older. Study **C-2000-043-00** evaluated the effects of short-term administration (13-28 days) of Ditropan syrup for the treatment of detrusor hyperreflexia in 16 pediatric patients with spina bifida aged 1 to 5 years.

The Division of Reproductive and Urologic Drug Products (DRUDP or HFD-580) completed a review of the supplements after comparing the submitted two pediatric study reports and report containing the critical analyses with the requirements listed in the WR. The findings of this initial review were presented to the Pediatric Exclusivity on February 1, 2002. The Pediatric Exclusivity Board determined that ALZA's submission SE1-009 "fairly responded" to the WR and recommended granting a six month extension of all remaining exclusivity and patents for all three of the sponsor's oxybutynin formulations, which was done.

This current review was performed to determine if the data from the two clinical studies, **C-2000-042-01** and **C-2000-043-01**, supported the sponsor proposed pediatric labeling changes submitted in the NDA supplements regarding the pharmacokinetic properties, efficacy and safety of the sponsor's three oxybutynin chloride formulations. In the supplements, the sponsor claimed that the submitted clinical trial data from Study C-2000-042-01 demonstrates the efficacy, safety and tolerability of Ditropan XL extended-release tablets for pediatric patients 6 years of age and older with symptoms of overactive bladder. Based on this data, the sponsor has proposed new and broad pediatric labeling changes to the Ditropan XL labeling to treat pediatric patients 6 years of age and older with symptoms of overactive bladder. [

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]

Ditropan XL is currently indicated only for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The Division has not accepted that the syndrome "overactive bladder" exists in pediatric patients. The Division has not accepted that the syndrome "overactive bladder" is the same disease in adults and children. The term "overactive bladder" does not appear in the combined Ditropan tablets and syrup labeling. Ditropan tablets and Ditropan syrup are currently indicated only for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e. urgency, frequency, urinary leakage, urge incontinence, dysuria).

It is again noted that when the NDA supplements were submitted on December 7, 2001, only an interim study report was submitted for C-2000-042-01. On July 29, 2002, the sponsor submitted the final study report for C-2000-042-01 in 21 volumes of new clinical data. It was determined that the new clinical data included in the final study report for C-2000-042-01 was submitted too late in the current 10-month review cycle to be adequately reviewed. Therefore, only the data submitted in the interim report for C-2000-042-01 is included in this review.

2.1.3 Design of the Two Clinical Studies

Study C-2000-042-01. This was a multicenter, 24-week treatment duration, open label, multiple-dose level, dose-response and safety study of oxybutynin (administered either as Ditropan XL, Ditropan tablets, or Ditropan syrup) in 116 pediatric subjects diagnosed with detrusor hyperreflexia due to neurogenic conditions and aged 6 to 15 years. The dose-effect (urodynamic) and concentration-effect (urodynamic) of oxybutynin chloride were evaluated. A PK substudy was conducted in 42 patients at steady state: 12 on Ditropan syrup, 11 on Ditropan tablets, and 19 on Ditropan XL.

Study C-2000-043-00. This was multicenter, open label, repeated dose, multiple-dose level, minimum 2-week treatment duration, pharmacokinetic (PK) and pharmacodynamic (PD [urodynamic]) study of Ditropan syrup in 16 pediatric patients diagnosed with detrusor hyperreflexia due to neurogenic conditions and aged one to five years. The steady state PK profiles and the dose-effect (urodynamic) and concentration-effect (urodynamic) of Ditropan syrup were evaluated.

2.2 Efficacy

2.2.1 Efficacy Endpoints

The primary efficacy assessment in **C-2000-042-01** was the volume of urine collected per catheterization as recorded on the patient diaries. The change from baseline in the measured volume of urine per catheterization (averaged catheterized urine volume and first catheterization after morning awakening) was analyzed during treatment at Weeks 4, 12, and 24 (or early termination). Additional secondary efficacy parameters included:

- The percentage of episodes of leakage between catheterizations documented at baseline, Weeks 4, 12, and 24.
- Urodynamic measurement collected at baseline, Week 12, and Week 24 (or early termination). Of interest were changes over time in maximal bladder capacity, detrusor and intravesical pressure at maximal bladder capacity, and presence of uninhibited detrusor contractions > 15 cm H_2O.

The four efficacy assessments (Pharmacodynamic) in **C-2000-043-00** were determined from the urodynamic study measures:

- Maximal cystometric capacity (measured directly)
- Intravesical pressure at maximal cystometric capacity (measured directly)
- Detrusor pressure (P_{det}) at maximal cystometric capacity, calculated from intravesical pressure (P_{ves}) and abdominal pressure (P_{abd}) as follows: $P_{det} = P_{ves} - P_{abd}$ (P_{abd} was assumed to be equal to P_{rectal})
- Presence/absence of uninhibited contractions > 14 cm H_2O (measured directly)

The **Pharmacokinetic** data for both studies was analyzed for plasma R- and S- oxybutynin and the metabolite enantiomers, R- and S-desethyloxybutynin for C_{max}, T_{max}, C_{min}, T_{min}, K, $t_{1/2}$, AUC_{dose}, $AUC_{dosing\ regimen}$, and Clearance.

2.2.2 Efficacy Results

In Study **C-2000-042-01**, the primary efficacy assessment was the volume of urine collected per catheterization as recorded on the patient diaries. The change from baseline in the measured volume of urine per catheterization (averaged catheterized urine volume and first catheterization after morning awakening) was analyzed during treatment at Weeks 4, 12, and 24 (or early termination). The change from baseline to last visit in average urine volume per catheterization for the All Enrolled patients population (Table 1) was statistically significant ($p<0.0001$).

Table 1 Study C-2000-042-01 Change from baseline in average urine volume per catheterization[a] (All Enrolled patients)

	Baseline (n=115)	Week 4 (n=94)	Week 12 (n=80)	Week 24 (n=60)	Last Visit[b] (n=95)
Statistics					
n	115	94	80	60	95
Mean (SEM)	113.2 (6.58)	133.0 (6.23)	135.0 (6.36)	139.3 (8.42)	133.7 (6.51)
Median	105.0	123.0	122.9	130.4	128.9
Range	13 to 455	9 to 278	34 to 304	38 to 375	9 to 375
Change from Baseline[c]					
n		94	80	60	95
Mean (SEM)		24.0 (4.87)	26.4 (5.58)	26.0 (8.16)	25.1 (5.94)
Median		20.8	31.7	26.7	26.2
Range		-192 to 145	-163 to 146	-292 to 245	-292 to 245
p-value[d]		<0.0001	<0.0001	0.0023	<0.0001

Source: Table 12.1.8.1-1 on pg. 53.3/21

[a] Average urine volume per catheterization = total volume on the diaries divided by the number of catheterizations

[b] Data included are from the last visit completed in the study after baseline

[c] Change from baseline is the value at the visit minus the value at baseline

[d] p-value was calculated using the paired t-test

In Study **C-2000-042-01** for the enrolled patients population, statistically significant changes in the mean detrusor pressure at maximal cystometric capacity ($p=0.0009$) from baseline (43.0 cmH_20) to last visit (36.3 cmH_20), mean intravesical pressure at maximal cystometric capacity ($p=0.0013$) from baseline (55.4 cmH_20) to last visit (51.4 cmH_20), and number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 ($p=<0.001$) from baseline (n=65) to end of study (n=24) were also documented.

The pharmacokinetic results from a subset of subjects in Study **C-2000-042-01** were evaluated and no clear relationship between the total daily dose (in mg) and the pharmacokinetic results was identified. After administering the same total daily dose of the same oxybutynin formulation, a fairly large range of values for C_{max} and $AUC_{(0-t)}$ for R-oxybutynin was noted. In an attempt to correct for differing body weights accounting for this large range of values, C_{max} and $AUC_{(0-t)}$ for R-oxybutynin was then further evaluated by the reviewer by total daily dose in mg/kg and by ranking the data by increasing total daily dose (in mg/kg) by each formulation. Again, no clear relationships were identified with the possible exception that Ditropan XL, C_{max} and $AUC_{(0-t)}$ for R-oxybutynin tended to increase as the total daily dose in mg/kg increased. The reviewer suspects that individual variations in metabolism

and failure to be compliant with dose administration are responsible for the persisting wide range of values despite adjusting the total daily dose for body weight.

In Study **C-2000-043-00**, a statistically significant change in the mean maximal cystometric capacity (p=0.0054) from baseline (104 mL) to end of study (175 mL) was demonstrated. A statistically significantly change in the number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 (p=0.0039) from baseline (n=11) to end of study (n=2) was also demonstrated. No significant change from baseline in mean detrusor pressure at maximal cystometric capacity or in mean intravesical pressure at maximal cystometric capacity was noted. In Study C-2000-043-00, it should be noted that no efficacy assessment was listed as a primary efficacy assessment. In addition, the pharmacodynamic efficacy results from C-2000-043-00 (Table 2) are of limited value due to the small sample size (n=16).

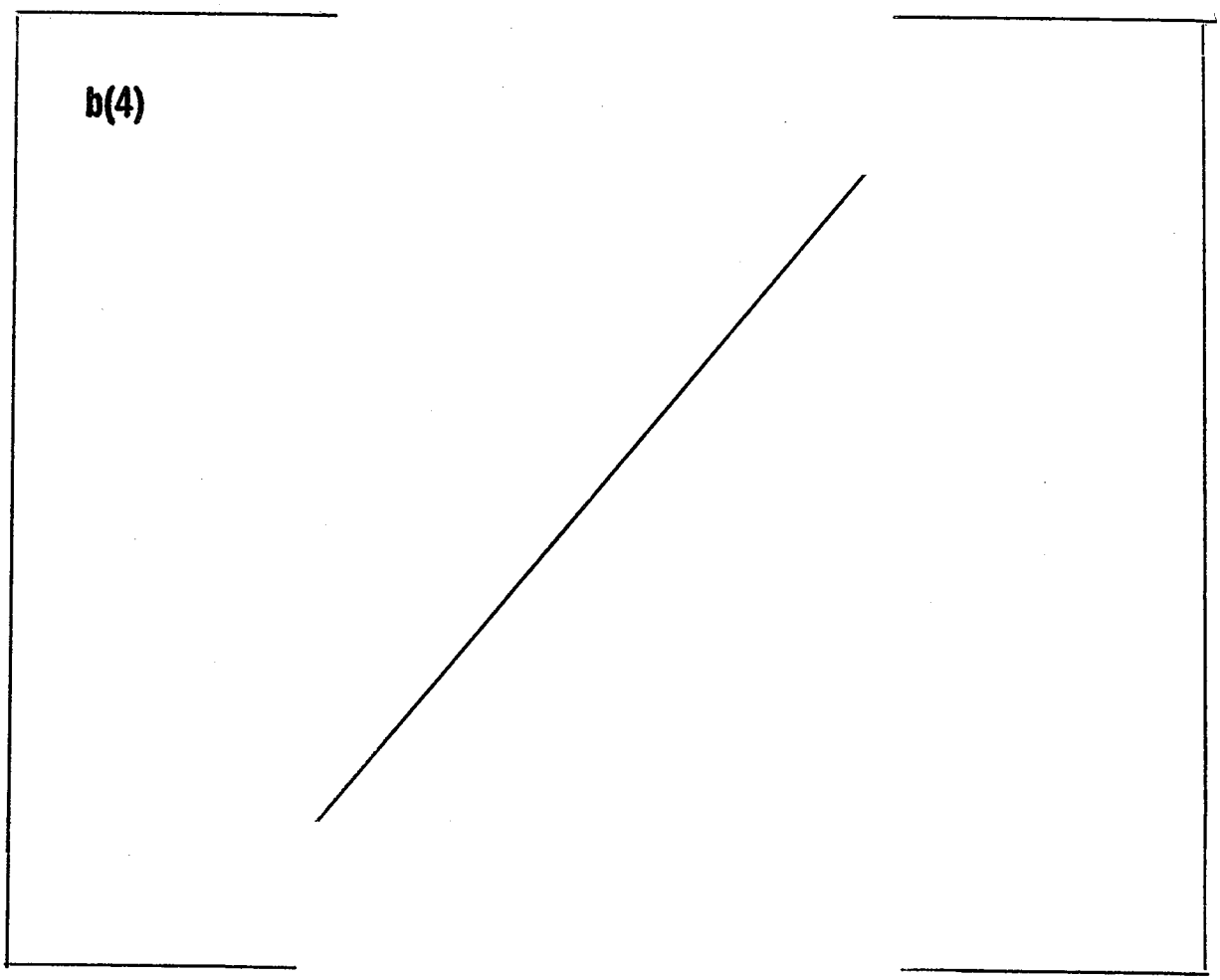
Table 2 Study C-2000-043-00 Pharmacodynamic (Efficacy) Results Summary

	Change from Baseline to End of Study		
Urodynamic Variable	**N**	**Mean (SEM)**	**Range**
Maximal cystometric capacity (mL)	16	+71.5 (21.99)	-29 to +265
Detrusor pressure (cm H_2O)	15	+0.6 (4,79)	-21 to +50
Intravesical pressure (cm H_2O)	15	+0.9 (5.81)	[ ]

b(4)

Source: pg. 53.12/219

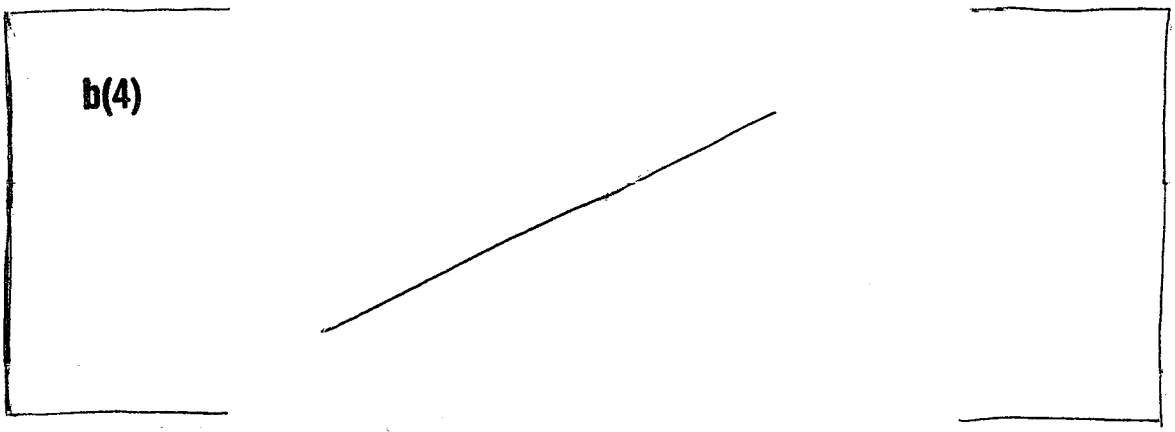
b(4)



[ ] b(4)

2.2.3 Other Efficacy Issues

Regarding Study **C-2000-042-01**, a significant percentage of the enrolled patients failed to adhere to Inclusion/Exclusion criteria and were protocol violators. A significant percentage of the enrolled patients failed to adhere to the study procedures and conduct of Protocol C-2000-042-01 and were protocol deviators. A large number of protocol violators and protocol deviators may commonly occur in pediatric trials, however this finding may seriously compromise the findings of Study C-2000-042-01.



2.2.4 Proposed Label Claim

The sponsor proposed pediatric labeling changes to the following sections of the Physician Insert were not acceptable to the reviewer.

a) **CLINICAL PHARMACOLOGY** Sections of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.

b) **PRECAUTIONS** Section, **Pediatric Use.** Subsection of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.

c) **DOSAGE AND ADMINISTRATION** Sections of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.

d) **INDICATIONS AND USES** Section of the Ditropan XL Physician Insert.

2.3 Safety

No new and unlabeled safety issues were identified during this review.

CLINICAL REVIEW

3 INTRODUCTION AND BACKGROUND

3.1 Drug

Oxybutynin chloride is an antispasmodic, anticholinergic medication first approved as immediate release tablets in 1975. It is currently available from the sponsor in three different formulations: Ditropan tablets (5 mg immediate release tablets), Ditropan Syrup (5 mg/5mL supplied in 16 fluid ounce bottles), and Ditropan XL (5, 10, and 15 mg extended release tablets).

3.2 Overview of Disease and Treatment Options

Ever since Ditropan (oxybutynin chloride) tablets were approved for marketing in 1975 by the Agency, the medical management of detrusor hyperreflexia due to neurogenic conditions (e.g. spina bifida) in pediatric patients in the United States has primarily consisted of treatment with Ditropan syrup or tablets. The sponsor provided an excellent summary of the use of oxybutynin chloride in pediatric patients with detrusor hyperreflexia due to neurogenic conditions in their report containing the two critical analyses. They state:

- Neurogenic bladder refers to abnormal bladder function resulting from a neurologic injury.[1]
- The failure of the spinal column to close properly around the spinal cord (spina bifida) is the most common cause of neurogenic bladder in children.[2]
- Detrusor hyperreflexia is a specific type of neurogenic bladder characterized by bladder overactivity.[3]
- Many children with neurogenic bladders develop incomplete emptying, noncompliant bladders, and elevated detrusor storage pressures, which when combined with untreated detrusor hyperreflexia can result in upper urinary tract deterioration.[4]
- The use of Ditropan and clean intermittent catheterization in these children is felt to prevent upper urinary tract deterioration and to decrease incontinence by diminishing leakage of urine between catheterization.[5]

Despite the widespread use of oxybutynin in pediatric patients with spina bifida, the current approved Ditropan Tablet and Syrup combined labeling contains no pediatric pharmacokinetic information, no adult pharmacokinetic information, and limited pediatric dosing regimen recommendations that are only for pediatric patients 6 years of age and older. The current approved Ditropan XL extended release tablet labeling contains no pediatric information.

3.3 Important Milestones in the Development of Oxybutynin

3.3.1 Significant Regulatory Interactions and Decisions

[ ] b(4)

NDA 17-577 was submitted for Ditropan tablets on March 25, 1974 by Marion Laboratories, Inc. and it was approved on July 16, 1975. The current sponsor listed in DSS is ALZA.

[ ] b(4)

NDA 18-211 was submitted for Ditropan syrup on October 17, 1978 and it was approved on November 29, 1979. The current sponsor listed in DSS is ALZA.

IND 48,930 was opened for Ditropan XL extended release tablets on October 2, 1995 by ALZA. The current sponsor listed in DSS is Johnson and Johnson.

NDA 20-897 was submitted for Ditropan XL extended release tablets on December 17, 1997 by ALZA and it was approved on December 16, 1998. The current sponsor listed in DSS is ALZA.

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[1] NDA 20-897 Supplement SE8-009 pg. 53.15/191
[2] NDA 20-897 Supplement SE8-009 pg. 53.15/193
[3] NDA 20-897 Supplement SE8-009 pg. 53.15/191
[4] NDA 20-897 Supplement SE8-009 pg. 53.15/194
[5] NDA 20-897 Supplement SE8-009 pg. 53.15/195

A Written Request (WR) letter dated November 30, 2000 asked ALZA Corporation to perform two pediatric studies with oxybutynin chloride and to prepare two critical analyses. On December 7, 2001, the sponsor responded to the WR by submitting a 43-volume NDA supplement to each of their three oxybutynin NDAs: SE8-009 to NDA 20-897 (Ditropan XL), SE8-033 to NDA 17-577 (Ditropan tablets), and SE8-015 to NDA 18-211 (Ditropan syrup). Each NDA supplement contained the final study report for C-2000-043-00 (Study #1 in the Written Request), an interim study report for C-2000-042-01 (Study #2 in the Written Request), and two critical analyses. The two clinical studies evaluated the efficacy, safety, tolerability, and the pharmacokinetic properties of the three oxybutynin chloride formulations when administered to pediatric patients with detrusor hyperreflexia (e.g. spina bifida) aged 1 to 15 years.

The Division of Reproductive and Urologic Drug Products (DRUDP or HFD-580) compared the two submitted pediatric study reports and the two submitted critical analyses with the requirements listed in the WR and presented their findings to the Pediatric Exclusivity on February 1, 2002. The Pediatric Exclusivity Board determined that ALZA's submission SE1-009 "fairly responded" to the WR and recommended granting a six month extension of all remaining exclusivity and patents for all three of the sponsor's oxybutynin formulations, which was done.

3.3.2 Issues Arising during Clinical Trials

Protocol **C-2000-042-01** was amended one time during the conduct of the trial. Amendment #1 was dated December 19, 2000 and included the following changes:

- deleted the use of Ditropan XL for the site in the Netherlands, since Ditropan XL was not available in the Netherlands at the time the study was conducted
- revised the exclusion criteria from excluding children with 3 or more days without bowel movement to more than 3 days without bowel movement
- clarified that for the participants taking Ditropan XL, they should take one tablet in the morning per day.
- added obtaining patient weight at Clinic Visit 4-End of Treatment Week 12 and at Clinic Visit 5-End of Treatment Week 24
- added that patients must be on a stable dose of study medication for a minimum of 3 days prior to PK sampling
- clarified that Clinic Visit 1 Screening should occur at Days -4 to -30 days
- modified the cystometry guidelines to be suggested maximum fill rates and allowed for the discontinuation of filling at the discretion of the participant, and added measuring vesical detrusor pressure at maximum cystometric capacity.

No amendments were made to Protocol **C-2000-043-00.**

4 CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

4.1 Toxicology Review

Toxicology review was not conducted. Toxicology review was not considered pertinent since all three formulations of oxybutynin evaluated were approved drug products.

4.2 Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review is not currently available.

5 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

5.1 Pharmacokinetics

The pharmacokinetic data generated by the conduct of Study C-2000-042-01 is reviewed in Appendix A. The pharmacokinetic data generated by the conduct of Study C-200-043-00 is reviewed in Appendix B.

5.2 Pharmacodynamics

The pharmacodynamic data generated by the conduct of Study C-2000-042-01 is reviewed in Appendix A. The pharmacodynamic data generated by the conduct of Study C-200-043-00 is reviewed in Appendix B.

6 DESCRIPTION OF CLINICAL DATA AND SOURCES

6.1 Data Submitted in Support of Supplements

6.1.1 IND Clinical Trial C-2000-042-01

Protocol C-2000-042-01 was still ongoing when the supplements were submitted. The sponsor submitted an interim report C-2000-042-01 [pg. 53.2/10-129] containing full efficacy and safety data only on the 60 subjects in the Initial Cohort. The interim report C-2000-042-01 was submitted to meet the requirement listed in the Written Request dated November 230, 2000 for Study #2. The reviewer considered that the sponsor had not fairly responded to the requirement for a final study report to be submitted, however the Pediatric Exclusivity Board accepted the interim report as satisfying the request for Study #2.

On July 29, 2002, the sponsor submitted the final study report for C-2000-042-01 in 21 volumes of new clinical data. It was determined that the new clinical data included in the final study report for C-2000-042-01 was submitted too late in the current 10-month review cycle to be adequately reviewed. Therefore, only the data submitted in the interim report for C-2000-042-01 is included in this review.

6.1.2 IND Clinical Trial C-2000-043-00

The sponsor submitted the final study report C-2000-043-00 [pg. 53.12/215-300] to meet the requirements listed in the Written Request dated November 30, 2000 for Study #1.

6.1.3 Critical Analyses

The sponsor submitted one report [pg. 53.15/186-406 and 53.16/1-399] to meet the two critical analyses requirements listed in the Written Request dated November 30, 2000.

The report was entitled "Critical Analysis of the Use of Oxybutynin Chloride in Adult and Pediatric Patients with Detrusor Hyperreflexia due to Neurogenic Conditions". It contained 29 pages of text supported by 63 references, two tables entitled "Table 1: Controlled Studies with Ditropan Tablets (NDA 17-577)" and "Table 2: Uncontrolled Studies with Ditropan Tablets or Syrup (NDA 17-577, 18-211), and one Appendix entitled "Rationale for the Duration of Treatment for Efficacy Measurements in the Pivotal Clinical Studies for OROS® (Oxybutynin Chloride)".

6.2 Overview of Clinical Studies Included in the Supplements

Study C-2000-042-01. This was a multicenter, 24-week treatment duration, open label, multiple-dose level, dose-response and safety study of oxybutynin (administered either as Ditropan XL, Ditropan tablets, or Ditropan syrup) in 116 pediatric subjects diagnosed with detrusor hyperreflexia due to neurogenic conditions and aged 6 to 15 years. The dose-effect (urodynamic) and concentration-effect (urodynamic) of oxybutynin chloride were evaluated. A PK substudy was

conducted in 42 patients at steady state: 12 on Ditropan syrup, 11 on Ditropan tablets, and 19 on Ditropan XL.

Study C-2000-043-00. This was multicenter, open label, repeated dose, multiple-dose level, minimum 2-week treatment duration, pharmacokinetic (PK) and pharmacodynamic (PD [urodynamic]) study of Ditropan syrup in 16 pediatric patients diagnosed with detrusor hyperreflexia due to neurogenic conditions and aged one to five years. The steady state PK profiles and the dose-effect (urodynamic) and concentration-effect (urodynamic) of Ditropan syrup were evaluated.

Table 4 provides a more detailed overview of each clinical trial represented in the supplements. Included in Table 4 for each study is information regarding (a) study design, (b) number of patients enrolled, and (c) study treatments.

Table 4 Tabular Listing of Submitted Clinical Investigations

Study No. Study Title	Study Design Status	No. Sites/Country	No. Patients/Sex Age Range Race	No. Patients Treatment Dose/Route/Regimen
C-2000-042-01 A Phase 3, multicenter, open-label, 24-week treatment duration, open label, multiple-dose level, dose response, safety study of oxybutynin chloride (administered either as Ditropan XL, Ditropan tablets, or Ditropan syrup) pediatric subjects aged 6 to 15 years and diagnosed with detrusor hyperreflexia due to neurogenic conditions.	Multicenter Open-label Uncontrolled Ongoing- data through November 9, 2001 was submitted as an interim report	24 sites/USA (100 of all enrolled patients and 56 of the Initial Cohort patients) and Netherlands (6 of all enrolled patients and 4 of the Initial Cohort patients)	116 pediatric patients (55 male and 61 female) with 60 in the Initial Cohort (29 male and 31 female) Range: 4 - 16 yr <6 yr=5 6-10 yr=67 11-15 yr=43 >15 yr=1 PK substudy was conducted in 42 pediatric patients 74 Caucasian 17 African American 23 Hispanic 1 Asian 1 Other	116 pediatric patients on a total daily dose of 10 or 15 mg oxybutynin chloride (administered either as Ditropan XL, Ditropan tablets, or Ditropan syrup). In the Initial Cohort of 60 patients, 17 were exposed to Ditropan syrup, 13 to Ditropan tablets and 31 to Ditropan XL. (Note: one patient switched formulation after enrollment from Ditropan syrup to Ditropan XL and was exposed to more than one formulation) PK substudy was conducted in 42 patients: 12 on Ditropan syrup, 11 on Ditropan tablets, and 19 on Ditropan XL
C-2000-043-00 A multicenter, open-label, repeated dose, multiple-dose level, minimum 2-week treatment duration, pharmacokinetic and pharmacodynamic study of Ditropan syrup in patients aged one to five years and diagnosed with detrusor hyperreflexia due to neurogenic conditions	Multicenter Open-label Uncontrolled Completed	4 sites/USA (6 patients) and Netherlands (10 patients)	16 pediatric patients (11 male and 5 female) Range: 1-5 yr. (1yr.=1; 2yr.=5; 3 yr.=4; 4yr.=4; 5yr.=2) 12 Caucasian 1 African American 3 Hispanic 0 Asian	16 patients on Ditropan syrup with their total daily dose ranging from 3.6 to 9 mg/day. Their total daily dose was split into two, three or four doses per day. 1 patient was on 3.6 mg/day split into 3 doses 1 patient was on 4 mg/day split into 2 doses 1 patient was on 4.5 mg/day split into 3 doses 1 patient was on 5 mg/day split into two doses 1 patient was on 5 mg/day split into four doses 1 patient was on 5.1 mg/day split into 3 doses 5 patients were on 6 mg/day split into 3 doses 3 patients were on 7.5 mg/day split into 3 doses 2 patients were on 9 mg/day split into 3 doses

Source: Modified from December 2001 submission, pg 53.2/8, 53. 2/78, 53.2/81, 53.2/130, 53.13/1, 53.13/246, and 53.14/325-326

6.3 Patient Exposure to Oxybutynin

A total of **16 patients** were exposed to Ditropan syrup in **Study C-2000-043-00** for periods that ranged from **13 to 28 days.** The range of daily dosages was 3.6 to 9 mg/day. No patient had their daily dosage of Ditropan syrup adjusted by the study investigator during the study for the purpose of

balancing tolerability and efficacy. Fourteen patients had been taking Ditropan syrup before the study, which they stopped taking when the washout period began after Visit 1. After washout (at Visit 2), study investigators kept each patient on the same Ditropan Syrup dosage and dosing schedule that he/she had been on prior to washout. Two patients (1002 and 1005) had been taking intravesical oxybutynin chloride before the study, which they stopped at Visit 1. Study investigators determined an appropriate Ditropan syrup dose and dosing scheduled for each of these patients, which the patients were instructed to take for at least 1 week before the washout period. After the washout period (at Visit 2), study investigators prescribed the same Ditropan syrup dosage and dosing schedule for these patients that they had been taking just prior to the washout. The parents of patient 4002 were confused about the dosage between Visit 2 and Visit 3 and gave the patient varying doses, possibly up to 15 mg/day; at Visit 3, study personnel advised the parents about the dosage and dosing schedule so that the correct amount of syrup could be given.

A total of **116 patients** were exposed to oxybutynin in **Study C-2000-042-01**, however data was only provided for these patients and the 60 patients in the Initial Cohort up to November 7, 2001. By that date, 60 of the 116 patients, and 59 of the 60 patients in the Initial Cohort had completed the study.

The range of exposure in **all enrolled** patients up to November 7, 2001 was from **1.1 to 31.0 weeks** with a mean duration of 18.1 weeks. Table 5 shows the duration of treatment for patients in all enrolled patients up to November 7, 2001. Of the 116 enrolled patients, 30 were exposed to Ditropan syrup, 27 to Ditropan tablets, and 60 to Ditropan XL. One patient switched formulation after enrollment from Ditropan syrup to Ditropan XL and was exposed to more than one formulation.

Table 5 Study C-2000-042-01: Duration of Exposure to Oxybutynin for Enrolled Patients up to November 7, 2001

Weeks on Treatment	Patients (n=116)
<2	7
2-<4	11
4-<6	6
6-<8	4
8-<10	1
10-<12	2
12-<14	7
14-<16	1
16-<18	2
18-<20	5
20-<22	5
22-<24	12
24-<26	38
26-<28	11
≥28	4

Source: Appendix 13.2.3-1 on pg. 53.7/217-228.

The range of exposure in the **Initial Cohort** up to November 7, 2001 was from 12.7 to 31.0 weeks with the mean duration 24.8 weeks. Table 6 shows the duration of treatment for patients in the Initial Cohort. Of the 60 patients in the Initial Cohort, 17 were exposed to Ditropan syrup, 13 to Ditropan tablets, and 31 to Ditropan XL.

Table 6 Study C-2000-042-01: Duration of Exposure to Oxybutynin for Patients in Initial Cohort up to November 7, 2001

Weeks on Treatment	Patients (n=60)
<20*	1
20-<22	1
22-<24	8
24-<26	34
26-<28	11
≥28	4

*One patient discontinued early at 12.7 weeks due to person reasons (Patient No. 101)
Source: Appendix 13.2.3-1 on pg. 53.7/217-228.

7 CLINICAL REVIEW METHODS

7.1 Materials Consulted during Medical Review

The following materials were consulted during the conduct of this review:

- NDA 20-897 SE-8 Supplement No. 009; Submission Date of December 7, 2001
  - Volumes 53.1-53.43
- NDA 17-577: SE-8 Supplement No. 033; Submission Date of December 7, 2001
- NDA 18-211: SE-8 Supplement No. 016: Supplement Date of December 7, 2001
- IND 48,930: Clinical Amendment Serial No. [ ] b(4)
- Written Request Letter dated November 30, 2000
- Minutes of all regulatory meetings and telephone conferences with Sponsor that were contained in Division files

7.2 Review Processes and Procedures

7.2.1 Materials Reviewed

The review conducted by this medical officer focused on the two studies (Studies C-2000-043 and C-2000-042) and the report containing the two requested critical analyses submitted on December 7, 2001. All materials submitted on December 7, 2001 in paper format for these studies and report containing the two requested critical analyses were considered during the conduct of this review. Reviews focused on pharmacokinetic and pharmacodynamic data supporting pediatric dose recommendations and safety issues, including drug-related serious adverse events, adverse events leading to patient withdrawal from the clinical trial, deaths, and adverse events.

7.3 Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audits. The Division requested that the Division of Scientific investigation audit [ ] study centers that participated in Study C-2000-042. When the sites were evaluated by the Division for the number of randomized subjects, it was noted that one site had a very large number of randomized subjects (30) and four sites had 8-10 subjects randomized. The [ ] sites that were requested for inspection were: b(7)

1) Israel Franco, M.D. — 30 Randomized Subjects
   Hawthorne, NY 10532

2) Richard Grady, MD — 10 Randomized Subjects

Children's Hospital & Regional
Medical Center
Seattle, WA 98105

[ ] b(7) [ ]

Only Site #1 (Dr. Franco) and Site #2 (Dr. Grady) were selected for inspection by the Good Clinical Practice Branch 1 (GCPBI or HFD-46) of the Division of Scientific Investigations (DSI). Inspections on these two sites were conducted. NAI letters were sent to both Dr. Franco and Dr. Grady. The final conclusion of Roy Blay, Ph. D, Director Regulatory Review Officer, DSI, GCPBI in a Memorandum dated June 11, 2002 regarding these two inspections was that "the data submitted in support of these NDA supplements by Drs. Grady and Franco appear acceptable".

Financial disclosure statements. The sponsor submitted financial disclosure statements for Investigators who participated in two Ditropan clinical trials. This information was reviewed by Jeanine Best, MSN, R.N., Senior Regulatory Associate, HFD-580. The financial disclosure review dated December 14, 2001 concluded that for each of the two studies:

- the information was complete
- appropriate documentation was received
- the information complied with 21 CFR 54
- no disclosable information was reported
- no conflicts of interests were noted
- there was no disclosure of financial interests that could bias the outcome of the trials

Central Laboratory. For Study **C-2000-042-01**, pharmacokinetic measurements (plasma assays for R- and S-oxybutynin and its metabolites R- and S-desethyloxybutynin), using a Liquid Chromatography-Mass Spectroscopy method, were performed for all sites at a [ ] General safety measurements (urinalysis, serum chemistry and complete blood count) were performed for the US sites at a [ ] and for the Netherlands study site at [ ] Switzerland. b(4)

For Study **C-2000-043-00**, pharmacokinetic measurements (plasma assays for R- and S-oxybutynin and its metabolites R- and S-desethyloxybutynin), using a Liquid Chromatography-Mass Spectroscopy method, were performed for all sites at a [ ] General safety measurements (urinalysis, serum chemistry and complete blood count) were performed for the US sites at a [ ] and for the Netherlands study site at [ ] The Netherlands. b(4)

Site Monitoring. For Study **C-2000-042-01** (pg. 53.7/113-115), [ ] US sites ([ ] were responsible for initiating and monitoring sites, handling serious adverse event reports, maintaining the clinical trial database, and disposing of unused supply of investigational drug. b(4)

For Study **C-2000-043-00** (pg. 53.14/159-160), [ ] was responsible for initiating and monitoring sites, handling serious adverse event reports, maintaining the clinical trial database, and disposing of unused supply of investigational drug. [ ] was responsible for initiating and monitoring sites. b(4)

For both studies (pg. 53.12/261 and 53.2/66-67), study auditing, data entry, verification and validation, and subsequent analysis were performed by any or all of ALZA Corporation's Clinical Research and Development, Clinical Pharmacology, Statistics, and Regulatory Compliance Departments or ALZA's representatives for these functions according to GCP. In addition, computerized data entries were checked against CRF images in C-2000-043-00.

Medical Officer's Comments

- **[ ] is a well-known qualified clinical laboratory. [ ] [ ] are well known qualified Contract Research Organizations. Both are widely used by the pharmaceutical industry to conduct and/or monitor drug clinical trials.** b(4)
- **Assay validation procedures and quality control are addressed and reviewed in the Biopharmaceutical Review. Need to still confirm if any areas of concern were identified by the Biopharmaceutical Reviewer.**

8 INTEGRATED REVIEW OF EFFICACY

8.1 Efficacy Assessments

The primary efficacy assessment in **C-2000-042-01** was the volume of urine collected per catheterization as recorded on the patient diaries. The change from baseline in the measured volume of urine per catheterization (averaged catheterized urine volume and first catheterization after morning awakening) was analyzed during treatment at Weeks 4, 12, and 24 (or early termination). Additional secondary efficacy parameters included:

- The percentage of episodes of leakage between catheterizations documented at baseline, Weeks 4, 12, and 24.
- Urodynamic measurement collected at baseline, Week 12, and Week 24 (or early termination). Of interest were changes over time in maximal bladder capacity, detrusor and intravesical pressure at maximal bladder capacity, and presence of uninhibited detrusor contractions > 15 cm H_2O.

The four efficacy assessments (Pharmacodynamic) in **C-2000-043-00** were determined from the urodynamic study measures:

- Maximal cystometric capacity (measured directly)
- Intravesical pressure at maximal cystometric capacity (measured directly)
- Detrusor pressure (P_{det}) at maximal cystometric capacity, calculated from intravesical pressure (P_{ves}) and abdominal pressure (P_{abd}) as follows: $P_{det} = P_{ves} - P_{abd}$ (P_{abd} was assumed to be equal to P_{rectal})
- Presence/absence of uninhibited contractions > 14 cm H_2O (measured directly)

The **Pharmacokinetic** data for both studies was analyzed for plasma R- and S- oxybutynin and the metabolite enantiomers, R- and S-desethyloxybutynin for C_{max}, T_{max}, C_{min}, T_{min}, K, $t_{1/2}$, AUC_{dose}, $AUC_{dosing\ regimen}$, and Clearance.

8.2 Conclusions Regarding Demonstrated Efficacy

In Study **C-2000-042-01**, the primary efficacy assessment was the volume of urine collected per catheterization as recorded on the patient diaries. The change from baseline in the measured volume of urine per catheterization (averaged catheterized urine volume and first catheterization after morning awakening) was analyzed during treatment at Weeks 4, 12, and 24 (or early termination). The change from baseline to last visit in average urine volume per catheterization for the All Enrolled patients was statistically significant ($p<0.0001$).

Table 7 Study C-2000-042-01 Change from baseline in average urine volume per catheterization[a] (All Enrolled patients)

	Baseline (n=115)	Week 4 (n=94)	Week 12 (n=80)	Week 24 (n=60)	Last Visit[b] (n=95)
Statistics					
n	115	94	80	60	95
Mean (SEM)	113.2 (6.58)	133.0 (6.23)	135.0 (6.36)	139.3 (8.42)	133.7 (6.51)
Median	105.0	123.0	122.9	130.4	128.9
Range	13 to 455	9 to 278	34 to 304	38 to 375	9 to 375
Change from Baseline[c]					
n		94	80	60	95
Mean (SEM)		24.0 (4.87)	26.4 (5.58)	26.0 (8.16)	25.1 (5.94)
Median		20.8	31.7	26.7	26.2
Range		-192 to 145	-163 to 146	-292 to 245	-292 to 245
p-value[d]		<0.0001	<0.0001	0.0023	<0.0001

Source: Table 12.1.8.1-1 on pg. 53.3/21

[a] Average urine volume per catheterization = total volume on the diaries divided by the number of catheterizations

[b] Data included are from the last visit completed in the study after baseline

[c] Change from baseline is the value at the visit minus the value at baseline

[d] p-value was calculated using the paired t-test

In Study **C-2000-042-01** for the enrolled patients population, statistically significant changes in the mean detrusor pressure at maximal cystometric capacity (p=0.0009) from baseline (43.0 cmH_20) to last visit (36.3 cmH_20), mean intravesical pressure at maximal cystometric capacity (p=0.0013) from baseline (55.4 cmH_20) to last visit (51.4 cmH_20), and number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 (p=<0.001) from baseline (n=65) to end of study (n=24) were also documented.

The pharmacokinetic results from a subset of subjects in Study **C-2000-042-01** were evaluated and no clear relationship between the total daily dose (in mg) and the pharmacokinetic results was identified. After administering the same total daily dose of the same oxybutynin formulation, a fairly large range of values for C_{max} and $AUC_{(0-t)}$ for R-oxybutynin were noted. In an attempt to correct for differing body weights accounting for this large range of values, C_{max} and $AUC_{(0-t)}$ for R-oxybutynin was then further evaluated by the reviewer by total daily dose in mg/kg and by ranking the data by increasing total daily dose (in mg/kg) by each formulation. Again, no clear relationships were identified with the possible exception that Ditropan XL, C_{max} and $AUC_{(0-t)}$ for R-oxybutynin tended to increase as the total daily dose in mg/kg increased. The reviewer suspects that individual variations in metabolism and failure to be compliant with dose administration are responsible for the persisting wide range of values despite adjusting the total daily dose for body weight.

In Study **C-2000-043-00**, a statistically significant change in the mean maximal cystometric capacity (p=0.0054) from baseline (104 mL) to end of study (175 mL) was demonstrated. A statistically significantly change in the number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 (p=0.0039) from baseline (n=11) to end of study (n=2) was also demonstrated. No significant change from baseline in mean detrusor pressure at maximal cystometric capacity or in mean intravesical pressure at maximal cystometric capacity was noted. In Study C-2000-043-00, it

should be noted that no efficacy assessment was listed as a primary efficacy assessment. In addition, the pharmacodynamic efficacy results from C-2000-043-00 (Table 8) are of limited value due to the small sample size (n=16).

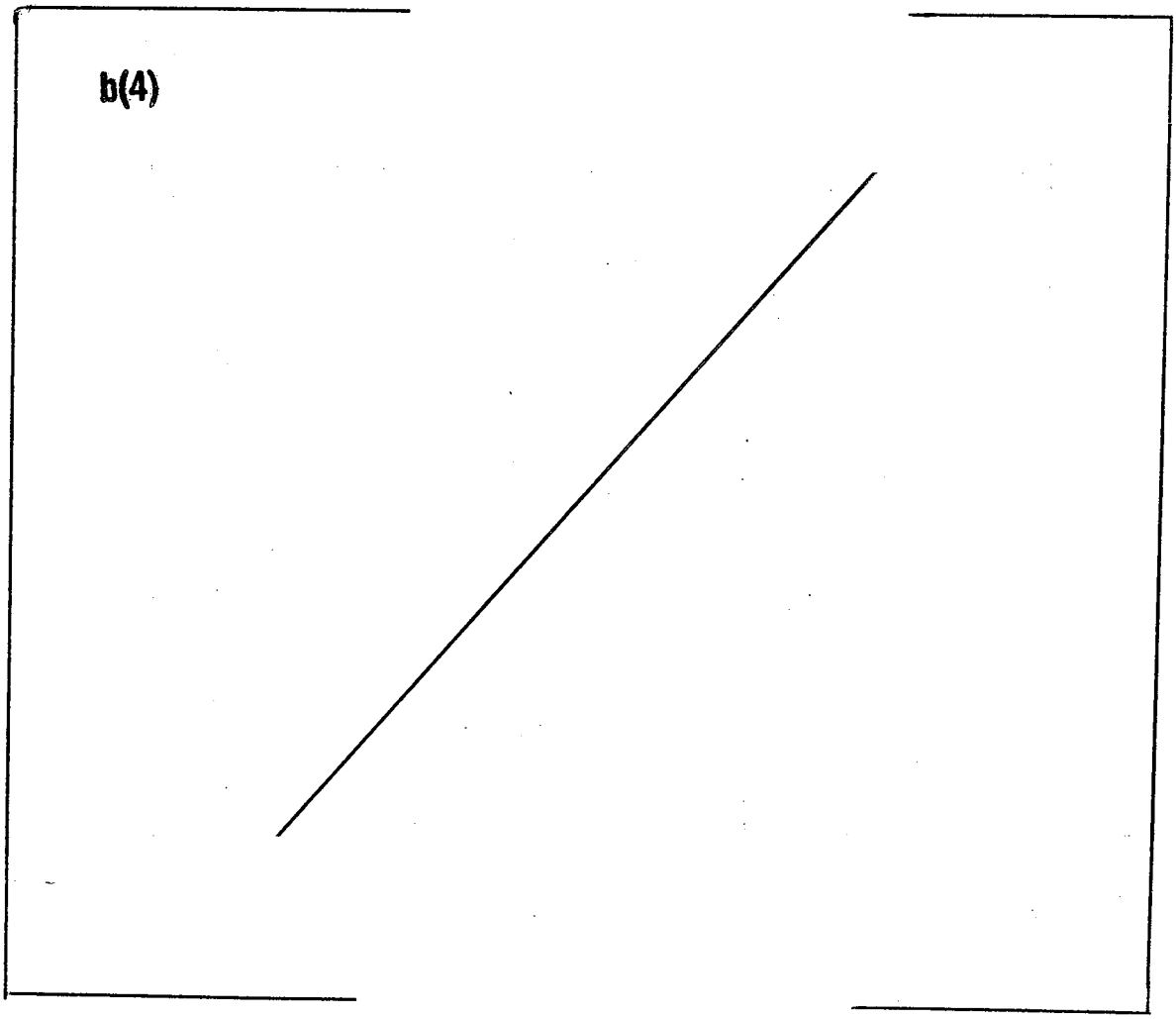
Table 8 Study C-2000-043-00 Pharmacodynamic (Efficacy) Results Summary

	Change from Baseline to End of Study		
Urodynamic Variable	**N**	**Mean (SEM)**	**Range**
Maximal cystometric capacity (mL)	16	+71.5 (21.99)	-29 to +265
Detrusor pressure (cm H_2O)	15	+0.6 (4,79)	-21 to +50
Intravesical pressure (cm H_2O)	15	+0.9 (5.81)	[ ]

b(4)

Source: pg. 53.12/219

b(4)



8.2.1 Achievement of Protocol-Defined Primary Efficacy Endpoints

The sponsor achieved statistical significance for the primary efficacy endpoint for Study C-2000-042-01: change from baseline to last visit in the volume of urine collected per catheterization as recorded

on the patient diaries (p< 0.0001). No efficacy endpoint was designated as primary in the protocol for Study C-2000-043-00.

8.2.2 Support of Label Efficacy Claims

The sponsor did not propose any overt efficacy claims in their proposed pediatric labeling changes, however approving the addition of pediatric information into any of the oxybutynin labeling would give implied pediatric safety and efficacy claims.

8.3 Statistician's Assessment of Efficacy (Protocol-Defined Primary Endpoints)

The FDA statistician performed no statistical review since the study was considered as observational only, no *a prior* criteria were established for efficacy, and the study results are descriptive only.

8.4 Medical Officer's Overall Assessment of Efficacy (Statistical and Clinical Significance)

In Study **C-2000-043-00**, a statistically significant change in the mean maximal cystometric capacity (p=0.0054) from baseline (104 mL) to end of study (175 mL) was demonstrated. A statistically significantly change in the number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 (p=0.0039) from baseline (n=11) to end of study (n=2) was also demonstrated. No significant change from baseline in mean detrusor pressure at maximal cystometric capacity or in mean intravesical pressure at maximal cystometric capacity was noted.

In Study **C-2000-042-01** for the enrolled patients, statistically significant changes in the mean volume of urine per catheterization (p<0.0001) from baseline (113.2 mL) to last visit (133.7 mL), mean maximal cystometric capacity (<0.0001) from baseline (196.8 mL) to last visit (244.0 mL), mean detrusor pressure at maximal cystometric capacity (p=0.0009) from baseline (43.0 cmH_20) to last visit (36.3 cmH_20), mean intravesical pressure at maximal cystometric capacity (p=0.0013) from baseline (55.4 cmH_20) to last visit (51.4 cmH_20), and number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 (p=<0.001) from baseline (n=65) to end of study (n=24) were documented.

The large number of patients who were protocol violators and protocol deviators may seriously compromise the results of C-2000-042-01 [redacted] b(4)

9 INTEGRATED REVIEW OF SAFETY

No integrated review of safety was conducted since the number of pediatric patients exposed was small and safety issues are addressed in the detailed reviews of each clinical trial provided in Appendix A and Appendix B.

10 USE IN SPECIAL POPULATIONS

The number of pediatric patients exposed was too small to conduct a subset safety analyses for the data based on race. The pharmacokinetic data from Study C-2000-042-01 was analyzed according to age (≤10 and >10), oxybutynin formulation, and total daily dose. However, the small number of patients in each subcategory (n=1-6) and the variability of the results prevented drawing a conclusion based on age.

11 PACKAGE INSERT

11.1 Review of DRAFT Ditropan Tablets and Syrup Physician Insert

The sponsor proposes to maintain the current approved labeling for Ditropan Tablets and Syrup except for their proposed changes as outlined in the following Sections 11.1.1 through 11.1.4.

1 Page(s) Withheld

Medical Review (9/6/02)

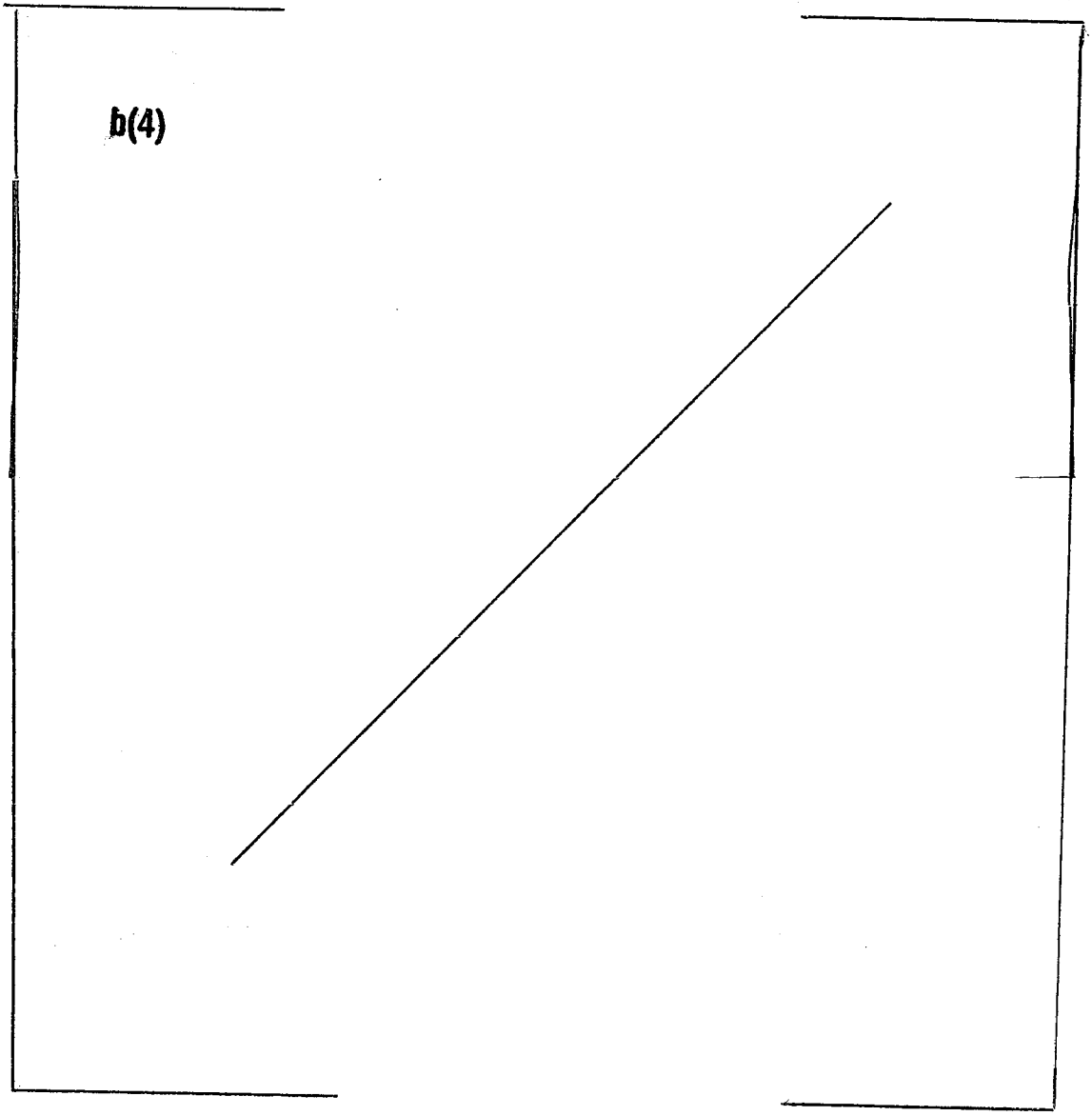
_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)



Medical Officer's Comments

1) The proposed changes are all acceptable to the reviewer.

11.1.5 Medical Reviewer Proposed Changes

The Medical Reviewer proposes no additional changes beyond those outlined in the previous Section 11.1.1-11.1-4 comments.

11.2 Review of DRAFT Ditropan XL Physician Insert

The sponsor proposes to maintain the current approved labeling for Ditropan XL except for their proposed changes as outlined in the following Sections 11.2.1 through 11.2.5.

11.2.1 Sponsor Proposed Changes to CLINICAL PHARMACOLOGY Section, Special Populations Subsection, Pediatric

The sponsor proposes to change the section from:

> *Pediatric:* The pharmacokinetics of DITROPAN XL® were not evaluated in individuals younger than 18 years of age. See PRECAUTIONS: Pediatric Use.

To:

[b(4)]

Medical Officer's Comments

1) [b(4)]

11.2.2 Sponsor Proposed Changes to PRECAUTIONS Section, Pediatric Use Subsection

The sponsor proposes to change the current Pediatric Use Subsection from:

> The safety and efficacy of DITROPAN XL® in pediatric patients have not been established.

To:

> [ ] a 24-week open-label trial, [ ] used clean intermittent catheterization, and were current users of oxybutynin chloride. Study results demonstrated that [ ]. DITROPAN XL® is not recommended in pediatric patients who can not swallow the tablet whole without chewing, dividing, or crushing, or in children under the age of 6 (see **DOSAGE AND ADMINISTRATION**). b(4)

Medical Officer's Comments

1) **It is the opinion of the reviewer that the sponsor is seeking the general indication of treatment of overactive bladder for children above age 6 based on a single trial in 31 spina bifida patients. It is unclear to the reviewer if the symptom complex identified as "overactive bladder" in adult patients exists in children. If changes are permitted in the Ditropan XL label, the reviewer recommends that they be clearly highlighted as being pertinent [ ] for spina bifida patients with detrusor hyperreflexia. [ ]** b(4)

[ ] **The reviewer offers the following change to the current Pediatric Use Subsection of the PRECAUTIONS Section:**

[ ] b(4)

[ ] neurogenic conditions (e.g. spina bifida) [ ] used clean intermittent catheterization, and were current users of oxybutynin chloride [ ] Study results demonstrated that administration of DITROPAN XL® 5 to 20 mg/day was associated with an increase from baseline in [ ] b(4)

11.2.3 Sponsor Proposed Changes to DOSAGES AND ADMINISTRATION Section

The sponsor proposes to change the section from:

> DITROPAN XL® must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.
>
> DITROPAN XL® may be administered with or without food.
>
> The recommended starting dose of DITROPAN XL® is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability [ ] b(4)
>
> [ ]

To:

> DITROPAN XL® must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.
>
> DITROPAN XL® may be administered with or without food.
>
> Adults: The recommended starting dose of DITROPAN XL® is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.
>
> Pediatric patients 6 years of age and older: The recommended starting dose of DITROPAN XL® is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

Medical Officer's Comments

1) **It is the opinion of the reviewer that it is misleading to practitioner to provide dosing for "pediatric patients" since efficacy and safety in pediatric patients with symptoms of overactive bladder have not been demonstrated. The reviewer recommends changing the DOSING AND ADMINISTRATION Section to the following:**

   DITROPAN XL® must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

   DITROPAN XL® may be administered with or without food.

   Adults: The recommended starting dose of DITROPAN XL® is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.

   [ ] [ ] The recommended starting dose of DITROPAN XL® is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day). b(4)

11.2.4 Sponsor Proposed Changes to "Manufactured by", "Distributed by", Edition date, and company logo

The sponsor proposes to change 4 items listed at the very end of the physician insert after

Rx ONLY

For more information call 1-888-395-1232 or visit www.Ditropan XL.com

From:

Manufactured, distributed, and marketed by
ALZA Corporation, Mountain View, CA 94043

Marketed by
UCB Pharma, Inc., Smyrna, GA 30080

Edition: 07/99

00096531

ALZA Logo

To:

Manufactured by
ALZA Corporation, Mountain View, CA 94043

Distributed and Marketed by
Ortho-McNeil Pharmaceuticals, Inc., Raritan, NJ 08869

Edition: 11/01

Placeholder for Ortho-McNeil Pharmaceuticals, Inc Logo

Medical Officer's Comments

1) The proposed changes are all acceptable to the reviewer.

11.2.5 Medical Reviewer Proposed Changes

The Medical Reviewer recommends changing the current **INDICATIONS AND USAGE** Section from:

DITROPAN XL® is a once-daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

To:

DITROPAN XL® is a once-daily controlled-release tablet indicated in adults for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. DITROPAN XL® is also indicated in [ ] b(4)

[ ]

12 CONCLUSIONS AND RECOMMENDATIONS

- In Study **C-2000-043-00**, a statistically significant change in the mean maximal cystometric capacity (p=0.0054) from baseline (104 mL) to end of study (175 mL) was demonstrated. A statistically significantly change in the number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 (p=0.0039) from baseline (n=11) to end of study (n=2) was also demonstrated. No significant change from baseline in mean detrusor pressure at maximal cystometric capacity or intravesical pressure at maximal cystometric capacity was noted.
- In Study C-**2000-042-01** for the enrolled patients, statistically significant changes in the mean volume of urine per catheterization (p<0.0001) from baseline (113.2 mL) to last visit (133.7 mL), mean maximal cystometric capacity (<0.0001) from baseline (196.8 mL) to last visit (244.0 mL), mean detrusor pressure at maximal cystometric capacity (p=0.0009) from baseline (43.0 cmH_20) to last visit (36.3 cmH_20), mean intravesical pressure at maximal cystometric capacity (p=0.0013) from baseline (55.4 cmH_20) to last visit (51.4 cmH_20), and number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 (p=<0.001) from baseline (n=65) to end of study (n=24) were documented.
- No new and unlabeled safety issues were identified.
- Administration of Ditropan tablets, Ditropan syrup, and Ditropan XL for a duration of up to 24 weeks was demonstrated to be effective and safe for the treatment of detrusor hyperreflexia in 116 pediatric patients with spina bifida 6 years of age and older.
- [redacted] b(4)
- No clear relationship between the total daily dose (by mg or by mg/kg) administered of Ditropan tablets, Ditropan syrup, or Ditropan XL and the pharmacokinetic results in pediatric patients with spina bifida was identified.
- No clear dose-response or concentration-response relationships between the total daily dose administered of Ditropan tablets, Ditropan syrup, or Ditropan XL and pharmacodynamic results in pediatric patients with spina bifida were identified.
- [redacted] b(4)
- The large number of patients who were protocol violators and protocol deviators may seriously compromise the results of C-2000-042-01 [redacted] b(4)

12.1 Major Issues with Regard to Sponsor's Proposed Package Insert

[redacted] b(4)

The reviewer recommends that any approved labeling changes based upon the results of these two clinical trials clearly state that they are pertinent [redacted] to pediatric patients with detrusor hyperreflexia due to spina bifida. Specifically regarding the Ditropan XL proposed labeling changes, the reviewer recommends clarifying that Ditropan XL is indicated only in adults for the treatment of overactive bladder and granting the new pediatric indication as follows: "DITROPAN XL® is also indicated [redacted] b(4)

[redacted] b(4)

12.2 Approvability

12.2.1 General Recommendation

It is recommended that the efficacy supplements for NDA 20-897 (SE8-009), NDA 17-577 (SE8-033) and NDA 18-211 (SE8-015) receive an approvable action since satisfactory labeling negotiations with the sponsor have not been concluded to date.

12.2.2 Specific Recommendations

1. Provide appropriately revised drug labeling regarding:

   e) **CLINICAL PHARMACOLOGY** Sections of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.

   f) **PRECAUTIONS** Section, **Pediatric Use.** Subsection of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.

   g) **DOSAGE AND ADMINISTRATION** Sections of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.

   h) **INDICATIONS AND USES** Section of the Ditropan XL Physician Insert.

Brenda S Gierhart MD — Date

Medical Officer, DRUDP

13 APPENDIX A: CLINICAL TRIAL C-2000-042-01

13.1 Summary

Title: "The Safety and Tolerability of Oxybutynin Chloride (Ditropan XL, Ditropan Syrup or Ditropan Tablets) in the Treatment of Detrusor Hyperreflexia due to Neurogenic Conditions in Children Aged 6 to 15 years" dated November 16, 2000 with Amendment #1 dated December 19, 2000.

Protocol **C-2000-042-01** was amended one time during the conduct of the trial. Amendment #1 was dated December 19, 2000 and included the following changes:

- deleted the use of Ditropan XL for the site in the Netherlands, since Ditropan XL was not available in the Netherlands at the time the study was conducted
- revised the exclusion criteria from excluding children with 3 or more days without bowel movement to more than 3 days without bowel movement
- clarified that for the participants taking Ditropan XL, they should take one tablet in the morning per day.
- added obtaining patient weight at Clinic Visit 4-End of Treatment Week 12 and at Clinic Visit 5-End of Treatment Week 24
- added that patients must be on a stable dose of study medication for a minimum of 3 days prior to PK sampling
- clarified that Clinic Visit 1 Screening should occur at Days -4 to -30 days
- modified the cystometry guidelines to be suggested maximum fill rates and allowed for the discontinuation of filling at the discretion of the participant, and added measuring vesical detrusor pressure at maximum cystometric capacity.

First patient treated: February 16, 2001

Last patient completed: November 7, 2001

13.1.1 Objectives

The primary objective was to document the safety and tolerability of oxybutynin chloride (administered as Ditropan XL extended-release tablets, Ditropan tablets, or Ditropan syrup) in children with detrusor hyperreflexia due to neurogenic conditions, e.g. spina bifida, during a 24-week treatment period.

The secondary objectives were to evaluate dose-effect (urodynamic) and concentration-effect (urodynamic) of Ditropan XL extended release tablets and Ditropan tablets, syrup in order to establish safe and effective dosage regiments in the study population.

13.1.2 Overall Design

This Phase 3, multicenter, 24-week treatment duration, open label, multiple-dose level, uncontrolled dose-response and safety study evaluated the safety and tolerability of oxybutynin chloride (a total daily dose of 10 or 15 mg administered as Ditropan XL, Ditropan tablets, or Ditropan syrup) in 116 pediatric subjects aged 6 to 15 years for the treatment of detrusor hyperreflexia due to neurogenic conditions. It had been planned that up to 140 patients would be enrolled with approximately equal numbers of patients in the 6-to-10-year age group and the 11-to-15 year age group. Overall, 131 subjects were screened and 116 enrolled. At the time of submission, this study was ongoing and data through November 9, 2001 was submitted as an interim report. As of that data cut off point, 59 of the 60 patients in the Initial Cohort (i.e. patients enrolled between February 16, 2001 and May 25, 2001)

had completed the trial as well as one of the additional 56 patients. The total number of patients who completed the trial by the data cut-off date of November 9, 2001 was 60.

The study was conducted at 23 sites in the USA and at one site in the Netherlands. The study site in the Netherlands evaluated only the Ditropan tablets and syrup since Ditropan XL was not available in the Netherlands and the protocol specified that patients be continued on the formulation and dose of oxybutynin chloride they had been taking. The dose-effect (urodynamic) and concentration-effect (urodynamic) of oxybutynin chloride were evaluated. A PK substudy was conducted in 42 patients at steady state: 12 on Ditropan syrup, 11 on Ditropan tablets, and 19 on Ditropan XL.

13.2 Study Procedures and Conduct

13.2.1 Schedule of Study Assessments

During the Screening/Baseline Visit (Visit 1), consent and assent was obtained and the patient's eligibility for the study was determined according to the inclusion and exclusion criteria after performing a history, physical examination, vital signs, EKG, urinalysis, serum chemistry profile test and complete blood count with differential. The subject was instructed in diary completion and told to discontinue oxybutynin chloride for a minimum of 3 days prior to Visit 2 (End of Baseline). All patients returned to the clinic for study assessments according to the schedule presented in Table 10.

Blood samples for pharmacokinetic analysis in the PK subgroup were to be collected after 12 weeks of active treatment (or after 24 weeks if not obtained at 12 weeks) of therapy. Urodynamic measurements were to be performed at the end of the washout period and repeated at the end of the 12- and 24-week period.

Table 10 C-2000-042-01 Schedule of Study Assessments

	Clinic Visit 1 Screening/ -4 to –30 days	Clinic Visit 2 Baseline Day 0	Clinic Visit 3 End of Week 4	Clinic Visit 4 End of Week 12	Clinic Visit 5 End of Week 24/Early Termination
Informed consent and assent	X				
History	X				
Physical examination	X				X
EKG	X				X
Hematology/ Clinical chemistry/Urinalysis	X				X
Urine pregnancy test	X	X			X
Vital signs	X	X	X	X	X
Urodynamic study		X		X	X
Review eligibility criteria		X			
Assign participant ID #	X				
Dispense diaries	X[1]	X[2]	X[2]	X[2]	
Dispense study drug[3]		X	X	X	
Review diary		X	X	X	X
PK sampling				X	X[5]
Collect study medication			X	X	X
Adverse events		X	X	X	X
Concomitant medication	X	X	X	X	X
Telephone follow-up instruction	X	X	X	X	X
Telephone reminder PK			X[4]	X[4]	
Dispense urine specimen containers	X	X	X	X	

[1] Diary should be completed for final 2 days during the washout period prior to Visit 2
[2] Diaries should be completed for any 2 consecutive days during treatment Weeks 4, 12, and 24
[3] On the day of PK sampling, the morning dose of study medication should be taken after the first blood draw. If following a TID regimen, no noon dose should be taken, and for BID and TID regimens, the PM dose should be taken after the final PK blood draw.
[4] Call participant with reminder to not take morning dose at home on day of Visit 4 or Visit 5 (if PK blood draws are not obtained at Visit 4)
[5] If PK samples were not obtained at Visit 4, obtain blood samples at Visit 5

13.2.2 Study Drugs

13.2.2.1 Dose Selection

The dose studied was **10 or 15 mg total daily dose** of Ditropan XL extended-release tablets, Ditropan tablets, or Ditropan syrup. Of the 116 enrolled patients, 30 patients were treated with Ditropan syrup, 27 to Ditropan tablets, and 59 to Ditropan XL. Of the 42 PK subgroup patients at the time of the PK testing, 12 patients were on Ditropan syrup, 11 were on Ditropan tablets, and 19 were on Ditropan XL.

Ditropan XL is a once-daily extended-release tablet currently labeled as being indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in adult patients. Ditropan XL does not have an approved indication in any pediatric patient groups and currently states: "The safety and efficacy of Ditropan XL in pediatric patients have not been established". Ditropan XL is available in 5, 10, and 15-mg tablets to be administered QD. Ditropan XL has not been previously studied in pediatric patients with neurogenic bladder. Ditropan XL does not currently have an approved indication specifically for neurogenic bladder in adult or pediatric patients.

Ditropan tablets or syrup has been used as the standard anticholinergic therapy in children with neurogenic bladder for almost 30 years. Ditropan tablets and syrup are currently labeled as being indicated for adults and for pediatric patients over 5 years of age for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex **neurogenic bladder** (i.e. urgency, frequency, urinary leakage, urge incontinence, dysuria).

13.2.2.2 Choice of Comparator

A placebo control was not deemed ethical because all of the patients required the benefits of anticholinergic therapy.

13.2.2.3 Assignment to Study Drug

Qualifying participants would be washed out from their current oxybutynin chloride medication for a minimum of 3 days. Baseline evaluations including catheterization frequency/volume diaries and urodynamic studies would be performed at the end of the washout period. Participants would then start the 24-week treatment period with the same oxybutynin formulation and at the same dose level as used prior to the washout period. Dose adjustments based on the individual optimum tolerability/effectiveness dose ratio could be done during the 24-week treatment period at the investigator's discretion. Patients taking Ditropan XL were instructed to take their tablet each day in the morning.

13.3 Patient Population

13.3.1 Inclusion and Exclusion Criteria

Inclusion Criteria

1) Boys and girls, aged 6 to 15 years, with detrusor hyperreflexia due to neurogenic conditions, e.g. spina bifida, who use clean intermittent catheterization and who are on a total daily dose of 10 or 15 mg oxybutynin chloride (administered as either Ditropan XL extended-release tablets, Ditropan tablets, or Ditropan syrup).

2) Participants who are in good health prior to study participation as determined by medical history; physical examination (general); EKG; blood chemistry profile; CBC with differential and urinalysis.

3) Female participants (if of childbearing potential and sexually active) and male participants (if sexually active with a partner of childbearing potential) who agree to use a medically acceptable and effective birth control method throughout the study and for 1-week following the end of the study. Medically acceptable methods of contraception that may be used by the participant and/or his/her partner include abstinence, birth control pills, diaphragm with spermicide, IUD, condom with foam or spermicide, vaginal spermicidal suppository, surgical sterilization and progestin implant or injection.

4) Female participants at risk of becoming pregnant must have a negative pregnancy test at screening (Visit 1) and prior to Visit 2.

5) Participant who are able to comply with the study visit schedule and are willing and able to complete the protocol-specified assessments.

6) Participants/legal guardians who provide written consent and assent to participate in the study.

7) Participant's caretaker is available to assist with diary completion, if necessary.

Exclusion Criteria

1) Participants with known genitourinary conditions (identified on history or on examination) that may cause incontinence (e.g., interstitial cystitis, bladder exstrophy, urinary tract obstruction, urethral diverticulum or fistula, bladder tumor, bladder stone).

2) Participants with clinically significant medical problems or other organ abnormality or pathology for whom, in the opinion of the investigator, administration of oxybutynin would present undue risk (e.g. medically uncontrolled cardiovascular, pulmonary, gastrointestinal, renal, endocrine, neurological, autoimmune, hematological, urological, psychiatric disorders, significantly reduced hepatic function, or renal impairment).

3) Participants who have undergone bladder augmentation surgery.

4) Participants taking any medications other than oxybutynin chloride affecting bladder contractility (e.g., imipramine, pseudoephedrine, tolterodine, hyoscyamine, flavoxate hydrochloride).

5) Participants with any of the following gastrointestinal problems: partial or complete obstruction pre-existing severe GI narrowing (pathological or iatrogenic)
   - decreased GI motility, such as paralytic ileus, intestinal atony, paralytic ulcerative colitis, chronic and severe constipation (more than 3 days without bowel movement)
   - those at risk of gastric retention
   - gastroesophageal reflux disorder (GERD) and/or who are currently taking drugs (such as biphosphonates) that cause or exacerbate esophagitis.

6) Participants who have taken an investigation drug within a period of 1 month.

7) Participants with known allergy or hypersensitivity to oxybutynin chloride or components of the immediate-release tablets or syrup, or extended-release tablets.

8) Participants with current drug or alcohol abuse.

9) Female participants who are pregnant or breast-feeding.

10) Participants who are unable to swallow a Ditropan XL extended-release tablet without chewing, crushing, biting, dividing, or dissolving the tablet.

13.3.2 Demographics and Baseline Disease Characteristics

Twenty-three US sites and one site in the Netherlands each enrolled 1 or more patients. The US sites enrolled 100 of the All Enrolled patients and 56 of the Initial Cohort patients. The Netherlands site enrolled 6 of the All Enrolled patients and 4 of the Initial Cohort patients. Baseline demographic characteristics for these 116 patients are summarized in Table 11. The majority of the patients in the trial were Caucasian. The second largest ethnic group was comprised of Hispanic patients. Individual ages ranged from 4 to 16 years. Median treatment group weights ranged from 30.4 kg in the All Enrolled group to 30.7 kg in the Initial Cohort group while individual weights ranged from 16 to 100 kg. In the Initial Cohort group, 58.3% of patients reported seven or more bowel movements per week, 33.3% reported no specific bowel regimen, 31.7% reported a history of fecal impaction, and 71.7% reported a history of fecal incontinence. In the All Enrolled group, 55.2% of patients reported seven or more bowel movements per week, 27.6% reported no specific bowel regimen, 36.3% reported a history of fecal impaction, and 75.9% reported a history of fecal incontinence.

The PK Subgroup consisted of 42 patients: 24 males and 18 females; 1 under age 6, 24 aged 6-10 years, and 17 aged 11-15 years; 23 Caucasians, 8 Black, and 11 Hispanic. Twenty-five PK subgroup patients were aged 10 years or less and 17 were aged greater than 10 years.

Table 11 Study C-2000-042-01 Baseline Demographics

	All Enrolled patients (n=116)	Initial Cohort patients (n=60)
Males	55	29
Females	61	31
Race/Ethnicity n[%])		
Caucasian	74	33
African American	17	33
Hispanic	23	16
Asian	1	0
Other	1	0
Age		
<6 yr	5	3
6-10 yr	67	35
11-15 yr	43	21
>15 yr	1	1
Median (range)	10 yr (4 – 16 yrs)	9.5 yr (4 – 16 yrs)
Weight		
Median (range)	30.4 kg (16 to 100 kg)	30.7 kg (16 to 86 kg)

Source: Derived from Table F on pg. 53.2/78 and Tables 12.1.2-1 and 12.1.6-1

13.3.3 Withdrawals, compliance, and protocol violations

As of November 9, 2001, the data cut-off point, two patients had discontinued early:

- Patient 101 in the Initial Cohort discontinued after 12.7 weeks on Ditropan tablets 5 mg TID (15 mg total daily dose) for personal reasons
- Patient 1902 discontinued after 13.6 weeks on Ditropan tablets 5 mg TID (15 mg total daily dose) for lack of efficacy

No patient in the PK subgroup had discontinued early.

The sponsor states (pg. 53.2/57 and 80) that treatment compliance was monitored at the study site at Visits 3, 4, and 5 when all unused study medication was collected, and the number of unused tablets or amount of unused syrup was recorded on the study drug accountability form. Interruptions in dosing of more than 1 day were recorded on the Study Medication and Dose Adjustment Log. No analysis or summary of treatment compliance was found in the interim C-200-042-01 study report.

The reviewer noted 8 patients who were noncompliant with treatment (Appendix 13.2.1-3 on pg. 53.7/134-150 and Appendix 13.2.3-2 on pg. 53.7/229-241):

- Patient 102-stopped treatment for 7 days
- Patient 104-stopped treatment for 11 days due to AE
- Patient 605-discontinued medications for 4 days due to abdominal pain; increased dose to 20 mg
- Patient 611-changed formulation after enrollment
- Patient 620-stopped treatment for 2 days due to AE

- Patient 1002-missed 3 doses equivalent of 1.5 days of study drug, dates unknown
- Patient 1401-interrupted treated twice for total of 6 days due to AE
- Patient 1503-missed several days from taking study drug due to incorrect drug dispensed at Visit 2

The reviewer noted that compliance could not be verified in at least 3 patients:

- Patients 302, 502, 1001- used study medication was not returned

As of November 9, 2001, the reviewer noted that a total of 51 entrance criteria **protocol violations** occurred in 47 of the 116 enrolled patients (Appendix 13.2.1-1 on pg. 53.7/116-132) as follows:

- Inclusion Criteria #1 (e.g. age 6 to 15 with detrusor hyperreflexia)-Incorrect age (6 patients)
- Inclusion Criteria #2 (e.g. total daily dose of oxybutynin 10-15 mg/day)-Patient on higher or lower dose of oxybutynin at screening than stipulated (29 patients)
- Inclusion Criteria #4 (e.g. general good health)-waiver granted (4 patients)
- Inclusion Criteria #7 (e.g. able to comply with schedule)-waiver granted to change schedule (8 patients)
- Exclusion Criteria #1 (e.g. has treatable condition that may cause incontinence)-waiver granted to enroll patient (1 patient)
- Exclusion Criteria #4 (e.g. is taking medication affecting bladder contractility)-waiver granted to allow prohibited medication (3 patients)

As of November 9, 2001, the reviewer noted that a total of 123 **protocol deviations** occurred in 71of the 116 enrolled patient (Appendix 13.2.1-3 on pg. 53.7/134-150 and Appendix 13.2.3-2 on pg. 53.7/229-241). Pertinent deviations included:

- 30 patients did not receive 10 or 15 mg total daily dose Ditropan:
  - Patient 303-took 11.25 mg total daily dose Ditropan syrup
  - Patient 401-increased dose to 20 mg total daily dose Ditropan syrup for 17 days
  - Patient 403-took 7.5 mg total daily dose Ditropan syrup
  - Patient 604-increased dose to 20 mg total daily dose Ditropan XL at Week 14
  - Patient 605-increased dose to 20 mg total daily dose Ditropan XL
  - Patient 612-increased dose to 20 mg total daily dose Ditropan XL at Week 16
  - Patient 614-increased dose to 20 mg total daily dose Ditropan XL at Week 16
  - Patient 618-increased dose to 20 mg total daily dose Ditropan XL at Week 12
  - Patient 707-took 5 mg total daily dose Ditropan XL
  - Patient 802-took 22.5 mg total daily dose Ditropan syrup (had erroneously stated was taking 15 mg Ditropan syrup at Visits 1 and 2)
  - Patient 904-took 30 mg total daily dose Ditropan syrup
  - Patient 1003-took 12 mg total daily dose Ditropan syrup
  - Patient 1203-took 7.5 mg total daily dose Ditropan tablets

- Patient 1503-took 5 mg total daily dose Ditropan XL
- Patient 1701-took 7.5 mg total daily dose Ditropan tablets for 4 weeks
- Patient 1704-took 10.5 mg total daily dose Ditropan syrup
- Patient 1705-took 7.5 mg total daily dose Ditropan tablets
- Patient 1706- took 7.5 mg total daily dose Ditropan tablets
- Patient 2001-took 5 mg total daily dose Ditropan XL
- Patient 2202-took 5 mg total daily dose Ditropan syrup
- Patient 2602-took 20 mg total daily dose Ditropan syrup
- Patient 2603-took 5 mg total daily dose Ditropan XL
- Patient 3302-took 9 mg total daily dose Ditropan syrup
- Patient 3401-took 11.25 mg total daily dose Ditropan syrup
- Patient 3402-took 5 mg total daily dose Ditropan XL
- Patient 3403-took 5 mg total daily dose Ditropan XL
- Patient 3404-took 7.5 mg total daily dose Ditropan XL
- Patient 3408-took 9 mg total daily dose Ditropan syrup
- Patient 3602-took 5 mg total daily dose Ditropan XL for 4 weeks
- Patient 3605-took 7.5 mg total daily dose Ditropan tablets

- 5 patient used dosing schedules not permitted in the protocol
  - Patient 401-increased dosing to QID for 17 days
  - Patient 1701-took Ditropan tablets QID
  - Patient 1703-took Ditropan tablets QID
  - Patient 2602-took Ditropan syrup QID
  - Patient 3607-incorrectly took her Ditropan XL BID
- 1 patient changed formulation after enrollment (Patient 611)
- 2 patients took prohibited medication (pseudoephedrine) (Patient 903, 1902)

Medical reviewer comments:

1) **The sponsor did not specifically analyze treatment compliance in the interim C-2000-042-01 study report (pg. 53.2/80). Scattered incidences of noncompliance were noted in the protocol violation and protocol deviation listings. The sponsor should summarize treatment compliance in the Final Study Report.**

2) **A significant percentage of the enrolled patients failed to adhere to Protocol C-2000-042-01 Inclusion/Exclusion criteria and were protocol violators. A significant percentage of the enrolled patients failed to adhere to the study procedures and conduct of Protocol C-2000-042-01 and were protocol deviators. The large number of protocol violators and protocol deviators may be common in pediatric trials, however this finding may seriously compromise the findings of the clinical trial.**

13.4 Efficacy

13.4.1 Key Efficacy Assessments

The key measurement for efficacy assessment was the volume of urine collected per catheterization as recorded on the patient diaries. The primary efficacy endpoint was the change from baseline in the measured volume of urine per catheterization (averaged catheterized urine volume and first catheterization after morning awakening), which was assessed during treatment at Weeks 4, 12, and 24 (or early termination).

Additional secondary efficacy parameters included:

- The percentage of episodes of leakage between catheterizations documented at baseline, Weeks 4, 12, and 24.
- Urodynamic measurement collected at baseline, Week 12, and Week 24 (or early termination). Of interest were changes over time in maximal bladder capacity, detrusor and intravesical pressure at maximal bladder capacity, and presence of uninhibited detrusor contractions > 15 cm H_2O.

13.4.2 Pharmacokinetic Assessments

Pharmacokinetic plasma samples were to be obtained at Visit 4 in a subset of a minimum of 32 patients (at least 5 on each of the three formulations) prior to the participant taking their morning dose of study medication. Five additional blood samples were to be taken according to the following approximate times post-dose:

Ditropan tablet of syrup	Ditropan XL
1 hour (± 15 minutes)	3 hours (± 0.5 hours)
2 hours (± 0.5 hours)	5 hours (± 1 hours)
5 hours (± 1 hours)	8 hours (± 1 hours)
8 hours (± 1 hours)	12 hours (± 2 hours)
12 hours (± 2 hours)	24 hours (± 2 hours)

If the patient was not able to get the PK samples drawn at Visit 4, they were to be drawn at Visit 5. Specific instructions regarding the blood sample handling and shipment were provided in Appendix 5 to the protocol. The Pharmacokinetic data for both studies was combined and was analyzed for plasma R- and S- oxybutynin and the metabolite enantiomers, R- and S-desethyloxybutynin for C_{max}, T_{max}, C_{min}, T_{min}, K, $t_{1/2}$, AUC_{dose}, $AUC_{dosing\ regimen}$, and Clearance.

13.4.3 Primary Efficacy Endpoint Analysis

The primary efficacy assessment was the volume of urine collected per catheterization as recorded on the patient diaries. The change from baseline in the measured volume of urine per catheterization (averaged catheterized urine volume and first catheterization after morning awakening) was analyzed during treatment at Weeks 4, 12, and 24 (or early termination). The change from baseline in average urine volume per catheterization for the All Enrolled patients is presented in Table 12 and for the Initial Cohort patients in Table 13.

Table 12 Change from baseline in average urine volume per catheterization (All Enrolled patients)

	Baseline (n=115)	Week 4 (n=94)	Week 12 (n=80)	Week 24 (n=60)	Last Visit[a] (n=95)
Average Volume per Catheterization (mL)[b]					
<=50	18 (15.7%)	9 (9.6%)	4 (5.0%)	1 (1.7%)	5 (5.3%)
>50-100	36 (31.3%)	21 (22.3%)	15 (18.8%)	17 (28.3%)	26 (27.4%)
>100-150	37 (32.2%)	25 (26.6%)	34 (42.5%)	21 (35.0%)	32 (33.7%)
>150-200	17 (14.8%)	25 (26.6%)	19 (23.8%)	13 (21.7%)	20 (21.1%)
>200-250	2 (1.7%)	13 (13.8%)	3 (3.8%)	4 (6.7%)	7 (7.4%)
>250	5 (4.3%)	1 (1.1%)	5 (6.3%)	4 (6.7%)	5 (5.3%)
Statistics					
n	115	94	80	60	95
Mean (SEM)	113.2 (6.58)	133.0 (6.23)	135.0 (6.36)	139.3 (8.42)	133.7 (6.51)
Median	105.0	123.0	122.9	130.4	128.9
Range	13 to 455	9 to 278	34 to 304	38 to 375	9 to 375
Change from Baseline[c]					
n		94	80	60	95
Mean (SEM)		24.0 (4.87)	26.4 (5.58)	26.0 (8.16)	25.1 (5.94)
Median		20.8	31.7	26.7	26.2
Range		-192 to 145	-163 to 146	-292 to 245	-292 to 245
p-value[d]		<0.0001	<0.0001	0.0023	<0.0001

Source: Table 12.1.8.1-1 on pg. 53.3/21

[a] Data included are from the last visit completed in the study after baseline

[b] Average Volume per catheterization = total volume on the diaries divided by the number of catheterization

[c] Change from baseline is the value at the visit minus the value at baseline

[d] p-value was calculated using the paired t-test

Table 13 Change from baseline in average urine volume per catheterization (Initial Cohort patients)

	Baseline (n=60)	Week 4 (n=60)	Week 12 (n=59)	Week 24 (n=59)	Last Visit[a] (n=60)
Average Volume per Catheterization (mL)[b]					
<=50	11 (18.3%)	5 (8.3%)	2 (3.4%)	1 (1.7%)	1 (1.7%)
>50-100	16 (26.7%)	10 (16.7%)	10 (16.9%)	17 (28.8%)	26 (28.3%)
>100-150	20 (33.3%)	18 (30.0%)	26 (44.1%)	20 (33.9%)	21 (35.0%)
>150-200	8 (13.3%)	18 (30.0%)	16 (27.1)	13 (22.0%)	13 (21.7%)
>200-250	2 (3.3%)	8 (13.3%)	1 (1.7%)	4 (6.8%)	4 (6.7%)
>250	3 (5.0%)	1 (1.7%)	4 (6.8%)	4 (6.8%)	4 (6.7%)
Statistics					
n	60	60	59	59	60
Mean (SEM)	115.6 (9.27)	138.6 (7.63)	137.6 (7.25)	139.5 (8.56)	139.5 (8.42)
Median	105.0	145.1	125.0	130.8	132.1
Range	24 to 425	24 to 278	38 to 304	38 to 375	38 to 375
Change from Baseline[c]					
n		60	59	59	60
Mean (SEM)		23.0 (6.58)	24.7 (6.63)	25.2 (8.25)	24.0 (8.20)
Median		23.8	33.0	26.2	26.2
Range		-192 to 145	-163 to 136	-292 to 245	-292 to 245
p-value[d]		0.0009	0.0005	0.0035	0.0049

Source: Table 12.1.4.1-1 on pg. 53.2/150

[a] Data included are from the last visit completed in the study after baseline

[b] Average Volume per catheterization = total volume on the diaries divided by the number of catheterization

[c] Change from baseline is the value at the visit minus the value at baseline

[d] p-value was calculated using the paired t-test

The change from baseline in urine volume after morning awakening for the All Enrolled patients is presented in Table 14 and for the Initial Cohort patients in Table 15.

Table 14 Change from baseline in urine volume after morning awakening (All Enrolled patients)

	Baseline (n=115)	Week 4 (n=94)	Week 12 (n=80)	Week 24 (n=60)	Last Visit[a] (n=95)
Volume after morning awakening (mL)[b]					
<=50	9 (7.8%)	7 (7.4%)	5 (6.3%)	2 (3.3%)	5 (5.3%)
>50-100	29(25.2%)	13 (13.8%)	11 (13.8%)	12 (20.0%)	14 (14.7%)
>100-150	30 (26.1%)	23 (24.5%)	22 (27.5%)	11 (18.3%)	24 (25.3%)
>150-200	24 (20.9%)	18 (19.1%)	20 (25.0%)	16 (26.7%)	23 (24.2%)
>200-250	13 (11.3%)	19 (20.2%)	11 (13.8%)	9 (15.0%)	13 (13.7%)
>250	10 (8.7%)	14 (14.9%)	11 (13.8%)	10 (16.7%)	16 (16.8%)
Statistics					
n	115	94	80	60	95
Mean (SEM)	147.5 (8.08)	169.0 (8.25)	172.5 (10.38)	174.7 (12.34)	176.8 (10.31)
Median	135.0	161.3	156.7	162.5	160.0
Range	5 to 540	5 to 375	20 to 453	35 to 550	5 to 550
Change from Baseline[c]					
n		94	80	60	95
Mean (SEM)		28.4 (7.11)	35.2 (8.67)	44.2 (10.72)	36.9 (8.50)
Median		25.0	30.0	38.2	30.0
Range		-270 to 200	-125 to 280	-143 to 450	-165 to 450
p-value[d]		0.0001	0.0001	0.0001	<0.0001

Source: Table 12.1.8.1-2 on pg. 53.3/22

[a] Data included are from the last visit completed in the study after baseline

[b] Average Volume per catheterization = total volume on the diaries divided by the number of catheterization

[c] Change from baseline is the value at the visit minus the value at baseline

[d] p-value was calculated using the paired t-test

Table 15 Change from baseline in urine volume after morning awakening (Initial Cohort patients)

	Baseline (n=60)	Week 4 (n=60)	Week 12 (n=59)	Week 24 (n=59)	Last Visit[a] (n=60)
Volume after morning awakening (mL)[b]					
<=50	6 (10.0%)	4 (6.7%)	4 (6.8%)	2 (3.4%)	2 (3.3%)
>50-100	16 (26.7%)	9 (15.0%)	9 (15.3%)	12 (20.3%)	12 (20.0%)
>100-150	17 (28.3%)	14 (23.3%)	17 (22.0%)	11 (18.6%)	12 (20.0%)
>150-200	10 (16.7%)	11 (18.3%)	17 (28.8%)	15 (25.4%)	15 (25.0%)
>200-250	8 (15.3%)	13 (21.7%)	9 (15.3%)	9 (15.3%)	9 (15.0%)
>250	3 (5.0%)	9 (15.0%)	7 (11.9%)	10 (16.9%)	10 (16.7%)
Statistics					
n	60	60	59	59	60
Mean (SEM)	132.8 (9.23)	170.2 (10.12)	166.3 (10.17)	174.8 (12.55)	174.8 (12.35)
Median	126.7	162.5	160.0	160.0	158.4
Range	10 to 320	33 to 375	20 to 425	35 to 550	35 to 550
Change from Baseline[c]					
n		60	59	59	60
Mean (SEM)		37.3 (7.52)	34.6 (9.89)	43.1 (10.84)	41.5 (10.77)
Median		33.8	35.0	36.6	35.8
Range		-90 to 200	-125 to 280	-143 to 450	-143 to 450
p-value[d]		<0.0001	0.0009	0.0002	0.0003

Source: Table 12.1.4.1-2 on pg. 53.2/151

[a] Data included are from the last visit completed in the study after baseline

[b] Average Volume per catheterization = total volume on the diaries divided by the number of catheterization

[c] Change from baseline is the value at the visit minus the value at baseline

[d] p-value was calculated using the paired t-test

13.4.4 Secondary (Supportive) Efficacy Analyses

Regarding the secondary efficacy parameter, the percentage of episodes of leakage between catheterizations documented at baseline, Weeks 4, 12, and 24 (or early termination), the All Enrolled patient data is presented in Table 16 and the Initial Cohort patients is presented in Table 17.

Table 16 Change from baseline in percentage of catheterizations without a leaking accident (All Enrolled patients)

	Baseline (n=115)	Week 4 (n=94)	Week 12 (n=80)	Week 24 (n=60)	Last Visit[a] (n=95)
% of catheterizations without a leaking accident					
<10	37 (32.2%)	12 (12.8%)	13 (16.3%)	13 (21.7%)	16 (16.8%)
10-<20	12(10.4%)	5 (5.3%)	4 (5.0%)	3 (5.0%)	4 (4.2%)
20-<40	15 (13.0%)	18 (19.1%)	9(11.3%)	9 (15.0%)	16 (16.8%)
40-<60	17 (14.8%)	10 (10.6%)	8 (10.0%)	7 (11.7%)	10 (10.5%)
60-<80	17 (14.8%)	17 (18.1%)	21 (26.3%)	10 (16.7%)	21 (22.1%)
80-<90	7 (6.1%)	10 (10.6%)	9 (11.3%)	7 (11.7%)	9 (9.5%)
>=90	10 (8.7%)	22 (23.4%)	16 (20.0%)	11 (18.3%)	19 (20.0%)
Statistics					
n	115	94	80	60	95
Mean (SEM)	36.2 (3.15)	56.2 (3.53)	56.3 (3.90)	50.6 (4.77)	54.1 (3.63)
Median	27.8	62.5	65.7	51.3	60.0
Range	0 to 100	0 to 100	0 to 100	0 to 100	0 to 100
Change from Baseline[c]					
n		94	80	60	95
Mean (SEM)		21.5 (3.58)	23.8 (3.58)	22.5 (5.04)	19.6 (3.67)
Median		20.0	16.7	11.8	15.5
Range		-100 to 100	-50 to 100	-100 to 100	-100 to 100
p-value[d]		<0.0001	<0.0001	<0.0001	<0.0001

Source: Table 12.1.8.1-3 on pg. 53.3/23

[a] Data included are from the last visit completed in the study after baseline

[b] Percentage of catheterizations without a leaking accident = number of time 'leaking accident since last catheterization' is checked 'No' on the diaries divided by the number of catheterizations.

[c] Change from baseline is the value at the visit minus the value at baseline

[d] p-value was calculated using the Wilcoxon match-pairs signed-ranks test

Table 17 Change from baseline in percentage of catheterizations without a leaking accident (Initial Cohort patients)

	Baseline (n=60)	Week 4 (n=60)	Week 12 (n=59)	Week 24 (n=59)	Last Visit[a] (n=60)
% of catheterizations without a leaking accident					
<10	25 (41.7%)	11 (18.3%)	10 (16.9%)	13 (22.0%)	13 (21.7%)
10-<20	7(11.7%)	3 (5.0%)	4 (6.8%)	3 (5.1%)	3 (5.0%)
20-<40	8 (13.3%)	9 (15.0%)	8 (13.6%)	9 (15.3%)	9 (15.0%)
40-<60	6 (10.0%)	7 (11.7%)	6 (10.2%)	7 (11.9%)	7(11.7%)
60-<80	6 (10.0%)	10 (16.7%)	10 (16.9%)	10 (16.9%)	10 (16.7%)
80-<90	4 (6.7%)	8 (13.3%)	8 (13.6%)	6 (10.2%)	6 (10.0%)
>=90	4 (6.7%)	12 (20.0%)	13 (22.0%)	11 (18.6%)	12 (20.0%)
Statistics					
n	60	60	59	59	60
Mean (SEM)	29.5 (4.28)	53.6 (4.63)	54.4 (4.71)	50.0 (4.82)	507 (4.79)
Median	18.2	59.2	62.5	50.0	51.3
Range	0 to 100	0 to 100	0 to 100	0 to 100	0 to 100
Change from Baseline[c]					
n		60	59	59	60
Mean (SEM)		24.1 (4.84)	25.6 (4.27)	21.4 (5.01)	21.2 (4.93)
Median		20.4	16.7	11.1	11.1
Range		-100 to 100	-50 to 100	-100 to 100	-100 to 100
p-value[d]		<0.0001	<0.0001	<0.0001	<0.0001

Source: Table 12.1.4.1-3 on pg. 53.2/152

[a] Data included are from the last visit completed in the study after baseline

[b] Percentage of catheterizations without a leaking accident = number of time 'leaking accident since last catheterization' is checked 'No' on the diaries divided by the number of catheterizations.

[c] Change from baseline is the value at the visit minus the value at baseline

[d] p-value was calculated using the Wilcoxon match-pairs signed-ranks test

Regarding the secondary efficacy parameter, change from baseline in the number of catheterizations per day, All Enrolled patient data is presented in Table 18 and the Initial Cohort patients is presented in Table 19.

Table 18 Change from baseline in the number of catheterizations per day (All Enrolled patients)

	Baseline (n=115)	Week 4 (n=94)	Week 12 (n=80)	Week 24 (n=60)	Last Visit[a] (n=96)-Check should be 95
Number of catheterizations per day					
<2	0	0	0	0	0
2-<4	12 (10.4%)	9 (9.6%)	7 (8.8%)	3 (5.0%)	6 (6.3%)
4-<6	77 (67.0%)	65 (69.1%)	56 (70.0%)	44 (73.3%)	70 (72.9%)
6-<8	22 (19.1%)	19 (20.2%)	14 (17.5%)	11 (18.3%)	16 (16.7%)
8-<10	3 (2.6%)	1 (1.1%)	3 (3.8%)	2 (3.3%)	3 (3.1%)
>=10	0	0	0	0	1 (1.0%)
Statistics					
n	115	94	80	60	96-Check should be 95
Mean (SEM)	4.8 (0.12)	4.6 (0.10)	4.6 (0.12)	4.6 (0.12)	4.7 (0.12)
Median	4.7	4.3	4.2	4.4	4.5
Range	2 to 10	3 to 8	3 to 9	3 to 8	3 to 10
Change from Baseline[c]					
n		94	80	60	95
Mean (SEM)		0.2 (0.09)	0.2 (0.09)	-0.0 (0.12)	0.2 (0.09)
Median		0.0	0.0	0.0	0.0
Range		-2 to 3	-3 to 4	-3 to 3	-3 to 3
p-value[d]		0.0129	0.0654	0.8640	0.0496

Source: Table 12.1.8.1-4 on pg. 53.3/24

[a] Data included are from the last visit completed in the study after baseline

[b] Number of catheterizations per day = Total number catheterizations on the diaries divided by the number of diaries.

[c] Change from baseline is the value at the visit minus the value at baseline

[d] p-value was calculated using the paired t-test

Table 19 Change from baseline in the number of catheterizations per day (Initial Cohort patients)

	Baseline (n=60)	Week 4 (n=60)	Week 12 (n=59)	Week 24 (n=59)	Last Visit[a] (n=60)
Number of catheterizations per day					
<2	0	0	0	0	0
2-<4	5 (8.3%)	7 (11.7%)	5 (8.5%)	3 (5.1%)	3 (5.0%)
4-<6	44 (73.3%)	41 (68.3%)	41 (69.5%)	43 (72.9%)	44 (73.3%)
6-<8	8 (13.3%)	12 (20.0%)	11 (18.6%)	11 (18.6%)	11(18.3%)
8-<10	3 (5.0%)	0	2 (3.4%)	2 (3.4%)	2 (3.3%)
>=10	0	0	0	0	0
Statistics					
n	60	60	59	59	60
Mean (SEM)	4.7 (0.16)	4.5 (0.12)	4.6 (0.13)	4.7 (0.13)	4.7 (0.12)
Median	4.5	4.0	4.5	4.5	4.5
Range	2 to 9	3 to 7	3 to 8	3 to 8	3 to 8
Change from Baseline[c]					
n		60	59	59	60
Mean (SEM)		0.1 (0.13)	0.1 (0.12)	-0.0 (0.12)	-0.0 (0.12)
Median		0.0	0.0	0.0	0.0
Range		-2 to 3	-3 to 4	-3 to 3	-3 to 3
p-value[d]		0.2576	0.6083	0.8079	0.8868

Source: Table 12.1.4.1-4 on pg. 53.2/153
[a] Data included are from the last visit completed in the study after baseline
[b] Number of catheterizations per day = Total number catheterizations on the diaries divided by the number of diaries.
[c] Change from baseline is the value at the visit minus the value at baseline
[d] p-value was calculated using the paired t-test

Also evaluated were the urodynamic measurements (in particular changes over time in maximal bladder capacity, detrusor and intravesical pressure at maximal bladder capacity, and presence of uninhibited detrusor contractions > 15 cm H_2O) collected at baseline, Week 12, and Week 24 (or early termination) as presented in Tables 12.1.4.1-6 through 12.1.4.1-10 on pg. 53.2/155-159 and in Tables 12.1.8.1-6 through 12.1.8.1-10 on pg 53.3/26-30. These measurements were reviewed, as well as the efficacy summaries provided by the sponsor by age group (Tables 12.1.4.2-1 through 12.1.4.2.9 on pg. 53.2/160-177 and Tables 12.1.8.2-1 through 12.1.8.2-9 on pg. 53.3/31-48), by total daily dose of Ditropan (Tables 12.1.4.3-1 through 12.1.4.3-9 on pg. 53.2/178-221 and Tables 12.1.8.3-1 through 12.1.8.3-9 on pg. 53.3/49-93), by total daily dose per kilogram body weight of Ditropan (Tables 12.1.4.4-1 through 12.1.4.4-9 on pg 53.2/223-267 and Tables 12.1.8.4-1 on pg. 53.3/94-138), and by formulation of Ditropan (Tables 12.1.4.5-1 through 1.2.1.4.5-9 on pg. 53.2/268-294 and Tables 12.1.8.5-1 through 12.1.8.5-9 on pg. 53.3/139-165).

13.4.5 Pharmacokinetic Data Summary (PK Subgroup)

The PK subgroup dosing at the time of PK testing is summarized in Table 20.

Table 20 Dosing at Time of PK Testing (PK Subgroup)

	PK Subgroup (n=42)
Formulation of Ditropan	
Syrup	12 (28.2%)
Immediate-release tablets	11 (26.2%)
Ditropan XL	19 (45.2%)
Total Daily Dose of Ditropan (mg)	
5-9.99	3 (7.2%)
10	18 (42.9%)
10.01-14.99	1 (2.4%)
15	17 (40.5%)
15.01-30	3 (7.1%)
Total Daily Dose of Ditropan (mg/kg)	
<0.20	3 (7.1%)
0.20-<0.40	21 (50.0%)
0.40-<0.60	13 (31.0%)
0.60-<0.08	5 (11.9%)

Source: Appendix 12.1.9.1-3 on pg. 53.3/168

The majority of the patients in the PK subgroup were Caucasian (n=23 or 54.8%), were aged 6-10 years (n=24 or 57.1%), were on Ditropan XL (n=19 or 45.2%), and were on a total daily dose of 0.20-<0.40 mg/kg (n=21 or 50%). The distribution of patients in the PK subgroup according to age group, total daily dose (mg/kg), and formulation of oxybutynin chloride is presented in Table 21.

Table 21 Distribution of PK Subgroup according to Age Group, Total daily dose (mg/kg), and formulation of oxybutynin chloride

Age group (years)	Formulation	Total Daily Dose (mg/kg)	Number of Patients from PK Subgroup (n=42)
<=10 (n=25)	Syrup	<0.20	0
		0.20-<0.40	3 (7.1%)
		0.40-<0.60	3 (7.1%)
		0.60-<0.80	3 (7.1%)
		>=0.80	0
	Immediate-release tablets	<0.20	0
		0.20-<0.40	2 (4.8%)
		0.40-<0.60	3 (7.1%)
		0.60-<0.80	0
		>=0.80	0
	Ditropan XL	<0.20	0
		0.20-<0.40	4 (9.5%)
		0.40-<0.60	5 (11.9%)
		0.60-<0.80	2 (4.8%)
		>=0.80	0
>10 (n=17)	Syrup	<0.20	0
		0.20-<0.40	3 (7.1%)
		0.40-<0.60	0
		0.60-<0.80	0
		>=0.80	0
	Immediate-release tablets	<0.20	0
		0.20-<0.40	5 (11.9%)
		0.40-<0.60	1 (2.4%)
		0.60-<0.80	0
		>=0.80	0
	Ditropan XL	<0.20	3 (7.1%)
		0.20-<0.40	4 (9.5%)
		0.40-<0.60	1 (2.4%)
		0.60-<0.80	0
		>=0.80	0

Source: Appendix 12.1.9.1-5 on pg. 53.3/170

The Pharmacokinetics results for R-oxybutynin, S-oxybutynin, R-desethyloxybutynin, and S-desethyloxybutynin all by dosage form, by total daily dose (in mg) and by age groups (<=10 years and >10 years) were presented in Tables 12.1.9.2-1 through 12.1.9.2-26 on pages 53.3/171 through 53.4/74 and were reviewed. Mean (SD) Pharmacokinetic parameters for R-oxybutynin, S-oxybutynin, R-desethyloxybutynin, and S-desethyloxybutynin all by dosage form, by total daily dose (in mg) and by age groups (<=10 years and >10 years) were presented in Tables Z, AA, BB, and CC on pages 53.2/118-121 and were reviewed. The small numbers of patients in each subcategory (n=1-6) and the variability of the results prevented a proper comparison by formulation, dose, and age.

Medical reviewer's comment:

1) **The pharmacokinetic results were not presented by total daily dose (in mg/kg). To explore for a relationship between total daily dose and the pharmacokinetic results, C_{max} and $AUC_{(0-t)}$ for R-oxybutynin was evaluated in Table 22 by total daily dose (in mg) after ranking data by increasing C_{max} and by total daily dose within each formulation. No clear relationship between the total daily dose (in mg) and the pharmacokinetic results was identified. After administering the same total daily dose of the same oxybutynin formulation, a fairly large range of values for C_{max} and $AUC_{(0-t)}$ for R-oxybutynin were noted. In an attempt to correct for differing body weights accounting for this large range of values, C_{max} and $AUC_{(0-t)}$ for R-oxybutynin was then evaluated in Table 23 by total daily dose in mg/kg after ranking data by increasing total daily dose (in mg/kg) by each formulation. No clear relationships were identified with the possible exception that Ditropan XL, C_{max} and $AUC_{(0-t)}$ for R-oxybutynin tended to increase as the total daily dose in mg/kg increased. The reviewer suspects that individual variations in metabolism and failure to be compliant with dose administration are responsible for the persisting wide range of values despite adjusting the total daily dose for body weight.**

Table 22 R-oxybutynin C_{max} and AUC $_{(0-t)}$ by dosage form and total daily dose (mg)

Formulation	Patient number	Total daily dose (mg)	C_{max} (ng/mL)	$AUC_{(0-t)}$
Syrup	2202	5	1.4	3.21
	104	10	1.41	5.12
	301	10	1.45	7.35
	901	10	4.43	15.17
	1901	10	12.80	38.02
	1704	10.5	1.38	6.39
	704	15	0.69	3.65
	801	15	1.61	4.40
	803	15	3.59	10.23
	607	15	11.20	34.08
	2201	15	15.60	44.86
	802	22.5	3.21	7.91
Immediate-release tablet	1705	7.5	2.29	9.13
	1701	10	4.71	15.35
	1001	10	5.19	19.42
	706	10	5.31	16.91
	106	10	5.49	16.27
	105	10	5.64	36.78
	1703	10	6.79	12.61
	1702	15	2.34	11.50
	705	15	3.05	Unknown*
	102	15	4.20	11.50
	302	15	7.95	20.15
Ditropan XL	1503	5	0.49	5.63
	806	10	0.57	11.83
	1002	10	0.66	13.67
	902	10	1.20	20.07
	809	10	1.23	22.38
	903	10	1.46	27.56
	622	10	1.49	15.89
	1903	10	1.63	25.20
	1201	10	2.79	56.36
	701	15	0.78	11.23
	1502	15	1.31	27.51
	501	15	1.39	28.07
	624	15	1.78	26.93
	804	15	2.96	42.77
	604	15	3.20	60.79
	603	15	3.54	77.88
	807	15	4.89	70.90
	614	20	2.29	39.42
	605	20	3.62	62.25

Source: Constructed from data listed in Appendix 13.2.2-1 on pg. 53.7/151-199, in Table 12.1.9.2-1 on pg. 53.3/171-179, and Table 12.1.9.2-9 on pg. 231-240. *Patient 705 had only 3 concentration points so the AUC values are not accurately estimable; Regarding AUC (0-t), t=12 hours for syrup and immediate release tablets and t=24 hours for Ditropan XL

Table 23 R-oxybutynin C_{max} and $AUC_{(0-t)}$ by dosage form and total daily dose (mg/kg)

Formulation	Patient number	Total daily dose (mg)	Weight (kg)	Total daily dose (mg/kg)	C_{max} (ng/mL)	$AUC_{(0-t)}$
Syrup	2202	5	19.3	0.2590	1.4	3.21
	901	10	27.0	0.3703	4.43	15.17
	1704	10.5	27.0	0.3888	1.38	6.39
	704	15	37.6	0.3989	0.69	3.65
	104	10	25.0	0.4000	1.41	5.12
	1901	10	23.1	0.4329	12.80	38.02
	607	15	34.5	0.4347	11.20	34.08
	301	10	20.9	0.4784	1.45	7.35
	803	15	28.1	0.5338	3.59	10.23
	801	15	25.0	0.6000	1.61	4.40
	802	22.5	33.1	0.6797	3.21	7.91
	2201	15	19.6	0.7653	15.60	44.86
Immediate-release tablet	1001	10	47.7	0.2096	5.19	19.42
	1703	10	42.1	0.2375	6.79	12.61
	706	10	39.7	0.2518	5.31	16.91
	1705	7.5	29.0	0.2586	2.29	9.13
	105	10	37.5	0.2666	5.64	36.78
	1702	15	51.0	0.2941	2.34	11.50
	102	15	45.0	0.3333	4.20	15.06
	1701	10	24.0	0.4166	4.71	15.35
	705	15	35.4	0.4237	3.05	Unknown*
	302	15	33.1	0.4531	7.95	20.15
	106	10	18.8	0.5319	5.49	16.27
Ditropan XL	1503	5	44.2	0.1131	0.49	5.63
	902	10	85.8	0.1165	1.20	20.07
	1201	10	59.0	0.1694	2.79	56.36
	604	15	72.6	0.2066	3.20	60.79
	1002	10	47.0	0.2127	0.66	13.67
	701	15	70.4	0.2130	0.78	11.23
	501	15	54.9	0.2732	1.39	28.07
	903	10	36.1	0.2770	1.46	27.56
	806	10	30.4	0.3289	0.57	11.83
	1903	10	27.7	0.3610	1.63	25.20
	1502	15	40.5	0.3703	1.31	27.51
	809	10	25.0	0.4000	1.23	22.38
	624	15	30.4	0.4934	1.78	26.93
	622	10	20.0	0.5000	1.49	15.89
	804	15	29.5	0.5084	2.96	42.77
	603	15	29.5	0.5084	3.54	77.88
	807	15	27.7	0.5415	4.89	70.90
	605	20	32.7	0.6116	3.62	62.25
	614	20	25.4	0.7874	2.29	39.42

Source: Constructed from data listed in Appendix 13.2.2-1 on pg. 53.7/151-199, in Table 12.1.9.2-1 on pg. 53.3/171-179,
*Patient 705 had only 3 concentration points so the AUC values are not accurately estimable

13.5 Safety

13.5.1 Safety Measurements

All participants who received at least one dose of study medication were to be included in the summaries and listings of safety data. Premature termination, adverse events, vital signs, concomitant medications, and laboratory data were also to be summarized. The COSTART IV Thesaurus was to be used to map adverse event verbatim to body system and preferred term.

The following safety measurements were evaluated:

- Participant's reports of adverse events
- Laboratory assessment (hematology, serum chemistries, and urinalysis) at screening and study termination
- Physical examination and EKG at screening and end of Week 24 or early termination visit
- Vital signs at all clinic visits.

13.5.2 Extent of exposure

At the data cutoff date of November 7, 2001, 59 of the 60 patients in the Initial Cohort had completed the study and the duration of exposure is summarized in Table 24. The mean duration of exposure for the Initial Cohort group was 24.8 weeks (range 13 to 31 weeks). Since the trial is ongoing, duration of exposure for the All Enrolled group is not pertinent. Of the 60 patients in the Initial Cohort, 17 were started on Ditropan syrup, 13 on Ditropan tablets, and 31 on Ditropan XL. 13 (21.7%) patients had at least one change in the total daily dose: doses were increased in 13 (21.7%), decrease in 2 (3.3%) and interrupted in 3 (5.0%).

Table 24 Duration of Treatment for Patients in the Initial Cohort

Weeks on Treatment	Patients (n=60)
<20	1
20-<22	1
22-<24	8
24-<26	35
26-<28	11
>28	4

Source: Table G on pg. 53.2/81

13.5.3 Serious adverse events

Deaths: there were no deaths

Premature termination due to safety reasons: no patients terminated prematurely form the study because of safety reasons.

Serious adverse events: As of the data cutoff date of November 7, 2001, nine patients (six were in the initial cohort) reported a serious adverse event (see Table 25). None of the serious adverse events were considered by the investigator to be related to study treatment.

Table 25 Serious Adverse Events by Treatment Group (All Enrolled Patients as of November 9, 2001)

Patient #	Age (years)	Formulation	Total Daily Dose (mg)	Serious Adverse Event	Relationship to Treatment
303	10	Ditropan syrup	11.25	Surgery: bilateral pelvic osteotomies (for correction of congenital bilateral hip dysplasia)	Not related
1704*	11	Ditropan syrup	10.5	Hospitalized: evaluation of nocturnal hypoventilation [ ] and Surgery: release tethered cord [ ]	Not related
2201	8	Ditropan syrup	15	Hospitalized: pyelonephritis	Not related
1001*	12	Ditropan tablets	10	Surgery: elective exploration of ventriculoperitoneal shunt	Not related
1203*	7	Ditropan tablets	7.5	Surgery : release of tight right hip flexor	Not related
601*	5	Ditropan XL	10	Hospitalized: Pyelonephritis x 5 days	Not related
617*	10	Ditropan XL	10	Surgery: release of tethered cord	Not related
1201*	14	Ditropan XL	10	Surgery: replacement of nonfunctioning ventriculoperitoneal shunt	Not related
1401	11	Ditropan XL	10	Surgeries: release of tethered cord [ ] ventriculoperitoneal shunt revision [ ]	Not related

b(6)

b(6)

Source: Table R on pg. 53.2/95 and Attachment 12.3.1 on pg. 53.4/245-249
*Initial Cohort patient

Medical Reviewer's comment:

1) **Narratives for the nine serious adverse events (Attachment 12.3.1 on pg. 53.4/245-249) were reviewed. The two cases of pyelonephritis could be related to study drug if the larger volumes per void on treatment resulted in an increased tendency to reflux urine. However all patients were being catheterized multiple times each day, so the reviewer considers the two serious adverse events of pyelonephritis to be expected.**

13.5.4 Frequent adverse events

The adverse event frequency is difficult to evaluate since the trial is ongoing. At least one adverse event was reported by 69 (59.5%) of the All Enrolled patient group. The most frequent adverse events were urinary tract infections, headache, constipation, pain, and rhinitis. Table 26 presents the adverse events occurring in ≥5% in the All Enrolled patient group and Table 27 presents the adverse events occurring in ≥5% in the Initial Cohort Patient group both as of the data cut-off date of November 9, 2001.

Table 26 Adverse Events Reported by ≥5% of Total Patients in the All Enrolled Patient Group as of November 9, 2001

	Ditropan Syrup (n=30)	Ditropan tablets (n=27)	Ditropan XL (n=60)	Total n=116
Urinary tract infections	10 (33.3%)	7 (25.9%)	21 (35.0%)	38 (32.8%)
Headache	2 (6.7%)	3 (11.1%)	2 (3.3%)	7 (6.0%)
Constipation	0	1 (3.7%)	5 (8.3%)	6 (5.2%)
Pain	1 (3.3%)	1 (3.7%)	4 (6.7%)	6 (5.2%)
Rhinitis	1 (3.3%)	2 (7.4%)	3 (5.0%)	6 (5.2%)

Source: Table O on pg. 53.2/92 and Table 12.1.11-1 on pg. 53.4/133-135.

Table 27 Adverse Events Reported by ≥5% of Total Patients in the Initial Cohort Patient Group as of November 9, 2001

	Ditropan Syrup (n=17)	Ditropan tablets (n=13)	Ditropan XL (n=31)	Total (n=60)
Urinary tract infections	9 (52.9%)	4 (30.8%)	15 (48.4%)	28 (46.7%)
Constipation	0	1 (7.7%)	5 (16.1%)	6 (10.0%)
Rhinitis	1 (5.9%)	2 (15.4%)	3 (9.7%)	6 (10.0%)
Headache	1 (5.9%)	3 (23.1%)	0	4 (6.7%)
Pain	1 (5.9%)	1 (7.7%)	2 (6.5%)	4 (6.7%)
Otitis media	1 (5.9%)	1 (7.7%)	1 (3.2%)	3 (5.0%)
Rash	0	0	3 (9.7%)	3 (5.0%)
Surgical procedure	0	1 (7.7%)	2 (6.5%)	3 (5.0%)
Upper respiratory tract infection	1 (5.9%)	1 (7.7%)	1 (3.2%)	3 (5.0%)

Source: Table J on pg. 53.2/83 and Table 12.1.10-1 on pg. 53.4/75-77.

At least one adverse event related to study medication was reported by 14 (12.1%) of the All Enrolled patient group The most frequently reported adverse event felt by the investigator to be **related to treatment** was constipation (n=6, 5.2%). One patient (#601) in the Initial Cohort had a normal EKG at baseline (heart rate=91 bpm, PR interval=95 msec) and had first degree atrioventricular (AV) block (heart rate=180 bpm, PR interval=200 msec) at the end of the study. The EKG change was considered by the investigator to be related to study treatment. No severe adverse events related to study medication were reported. The one adverse event potentially related to patient age was constipation: five of the 6 patients who reported constipation were in the younger age group (i.e. 10 years old or younger).

Anticholinergic adverse events were reported by 15 (12.9%) of the All Enrolled patients by the data cutoff date. Constipation (6 patients, 5.2%) and vomiting (4 patients, 3.4%) were the most frequently reported events.

Medical Reviewer's comment:

1) **It was unusual for an anticholinergic drug that only 1 of the 116 All Enrolled patients reported dry mouth as an adverse event.**

13.5.5 Laboratory Values

The serum chemistry, hematology, and urinalysis test results were reviewed. Shift tables were provided in Tables 12.1.11-13, 12.1.11-15, and 12.1.11-17 on pg. 53.4/181-3, 53.4/190-192, and 53.4/195 and were reviewed. No clinically significant changes in the laboratory values were noted.

13.5.6 Concomitant Medications

In the All Enrolled patient group, the five most common concomitant medication was all antibiotics: Bactrim (n=5, 4.3%), Suprax (n=5, 4.3%), Amoxicillin (n=4, 4.3%), Macrobid (n=4, 4.3%), and Macrodantin (n=4, 3.4%).

13.5.7 Vital Signs

In the All Enrolled patient group, the heart rate and blood pressure values by visit (Table 12.1.11-10 on pg. 53.4/173 and Table 12.2.11-11 on pg. 53.4/174) were reviewed. For the heart rate values, no change in mean or median or range of values was noted. For blood pressure values, a slight increase in mean (63.9 to 67.0) and median (63.0 to 68.0) diastolic blood pressure was noted.

13.5.8 Reviewer's assessment of efficacy and safety

In Study C-**2000-042-01,** administration of Ditropan tablets, Ditropan syrup, and Ditropan XL for a duration of up to 24 weeks was demonstrated to be effective and safe for the treatment of detrusor hyperreflexia in 116 pediatric patients with spina bifida 6 years of age and older.

For the enrolled patients population, statistically significant changes in the mean volume of urine per catheterization ($p<0.0001$) from baseline (113.2 mL) to last visit (133.7 mL), mean maximal cystometric capacity (<0.0001) from baseline (196.8 mL) to last visit (244.0 mL), mean detrusor pressure at maximal cystometric capacity ($p=0.0009$) from baseline (43.0 cmH_20) to last visit (36.3 cmH_20), mean intravesical pressure at maximal cystometric capacity ($p=0.0013$) from baseline (55.4 cmH_20) to last visit (51.4 cmH_20), and number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 (p=<0.001) from baseline (n=65) to end of study (n=24) were documented.

No new and unlabeled safety issues were identified.

No clear relationship between the total daily dose (by mg or by mg/kg) administered of Ditropan tablets, Ditropan syrup, or Ditropan XL and the pharmacokinetic results in pediatric patients with spina bifida was identified.

No clear dose-response or concentration-response relationship between the total daily dose administered of Ditropan tablets, Ditropan syrup, or Ditropan XL and pharmacodynamic results in pediatric patients with spina bifida were identified.

[ ] b(4)

It should be noted that the large number of patients who were protocol violators and protocol deviators might seriously compromise the results of these studies.

14 APPENDIX B: CLINICAL TRIAL C-2000-043-00

14.1 Summary

Title: "The Pharmacokinetics and Pharmacodynamic Effects of oxybutynin Chloride (Ditropan Syrup) in the Treatment of Detrusor Hyperreflexia due to Neurogenic Conditions in Children Aged 1 to 5 years" dated December 18, 2000.

No amendments were made to Protocol **C-2000-043-00**.

First patient treated: April 20, 2001

Last patient completed: October 15, 2001

14.1.1 Objectives

The objectives of this study were:

- to evaluate the steady state pharmacokinetics of Ditropan syrup
- to evaluate the effect (urodynamic) as a function of oxybutynin dose and concentration following Ditropan syrup
- to examine whether children on oxybutynin chloride require drug therapy based on comparison of urodynamic outcome at the end of study relative to baseline.

The population was to be up to 16 children aged 1 to 5 years with detrusor hyperreflexia due to neurogenic conditions, e.g. spina bifida, and who were on a stable daily dose of oxybutynin chloride.

14.1.2 Overall Design

This Phase 3, multicenter, minimum 2-week treatment duration (anticipated 3 to 5 week treatment duration), open label, multiple-dose level, repeated dose, uncontrolled pharmacokinetic (PK) and pharmacodynamic (PD [urodynamic]) study designed to evaluate the steady state PK profiles and the dose-effect (urodynamic) and concentration-effect (urodynamic) of Ditropan (oxybutynin chloride) syrup in 16 pediatric subjects aged 1 to 5 years for the treatment of detrusor hyperreflexia due to neurogenic conditions. The total daily dose of Ditropan syrup that was evaluated ranged from 3.6 to 9 mg/day. The daily dose was split into two, three, or four doses per day. Qualified patients washed out from their current medication for a minimum of 3 days and not more than 7 days before the next clinic visit at which time the urodynamic evaluation was performed. Patients then started treatment with Ditropan syrup. Dose adjustments were made at the investigator's discretion. The patient was to be on the same daily dose and regimen for at least 2-weeks prior to the end of study urodynamic and pharmacokinetic evaluation.

The study was conducted at 3 sites in the USA and at one site in the Netherlands. Both the dose-effect (urodynamic) and concentration-effect (urodynamic) of oxybutynin chloride were evaluated.

14.2 Study Procedures and Conduct

14.2.1 Schedule of Study Assessments

During the Screening/Baseline Visit (Visit 1), consent and assent was obtained and the patient's eligibility for the study was determined according to the inclusion and exclusion criteria after performing a history, physical examination, vital signs, EKG, urinalysis, serum chemistry profile test and complete blood count with differential. The parent/guardian was instructed to discontinue the patient's oxybutynin chloride for a minimum of 3 days and not more than 7 days prior to Visit 2 (End of Baseline). All patients returned to the clinic for study assessments according to the schedule presented in Table 28.

Table 28 Study C-2000-043-00 Schedule of Study Assessments

	Clinic Visit 1 Screening/ -4 to –30 days	Clinic Visit 2 Baseline End of Washout	Clinic Visit 3 End of 2 week treatment or Early Termination
Informed consent and assent	X		
History	X		
Physical examination	X		
EKG	X		
Hematology/ Clinical chemistry/Urinalysis	X		
Vital signs	X	X	X
Urodynamic study[2]		X	X
Review eligibility criteria		X	
Assign participant ID #	X		
Dispense study drug[3]		X	X
PK sampling			X[1,2]
Collect study medication			X
Adverse events		X	X
Concomitant medication	X	X	X
Telephone follow-up instruction	X	X	

[1] On the day of PK sampling, the morning dose of study medication should be taken after the first blood draw. [4] Call participant with reminder to not take morning dose at home on day of Visit 4 or Visit 5 (if PK blood draws are not obtained at Visit 4)
[2]Refer to Appendix 4 of the protocol for blood collection and shipment instructions for PK sampling and to Appendix 3 for instructions for completion of urodynamic studies.

14.2.2 Study Drug

14.2.2.1 Dose Selection

The drug studied was Ditropan syrup with the total daily dose for the 16 enrolled patients ranging from 3.6 to 9 mg/day. The patient's total daily dose was split into two, three or four doses per day.

1 patient was on 3.6 mg/day split into 3 doses
1 patient was on 4 mg/day split into 2 doses
1 patient was on 4.5 mg/day split into 3 doses
1 patient was on 5 mg/day split into two doses
1 patient was on 5 mg/day split into four doses
1 patient was on 5.1 mg/day split into 3 doses
5 patients were on 6 mg/day split into 3 doses
3 patients were on 7.5 mg/day split into 3 doses
2 patients were on 9 mg/day split into 3 doses

Ditropan syrup has been used as the standard anticholinergic therapy in children with neurogenic bladder for almost 30 years. Ditropan syrup is currently labeled as being indicated for adults and for pediatric patients over 5 years of age for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex **neurogenic bladder** (i.e. urgency, frequency, urinary leakage, urge incontinence, dysuria)

14.2.2.2 Choice of Comparator

A placebo control was not deemed ethical because all of the patients required the benefits of anticholinergic therapy.

14.2.2.3 Assignment to Study Drug

Qualifying participants would be washed out from their current oxybutynin chloride medication for a minimum of 3 days and no more than 7 days before the next clinic visit at which time the urodynamic evaluation will be performed (Visit 2). Participants would then start the minimum 2-week treatment period on Ditropan syrup at the dose level used prior to the washout period. Dose adjustments based on the individual optimum tolerability/effectiveness dose ratio could be made at the investigator's discretion within approximately 2 weeks of initiation of therapy. However, the patient should be on the same daily dose and regimen for at least 2 weeks before the end of study urodynamic and pharmacokinetic evaluation (Visit 3).

14.3 Patient Population

14.3.1 Inclusion and Exclusion Criteria

Inclusion Criteria

1. Boys and girls, aged 1 to 5 years, with detrusor hyperreflexia due to neurogenic conditions, who use clean intermittent catheterization and who are on a stable daily dose of oxybutynin chloride and who would be able to go on to oral oxybutynin 5-15 mg/day in two-to-three divided doses.

2. Participants who are in good general health prior to study participation as determined by medical history; physical examination (general); EKG; blood chemistry profile; CBC with differential and urinalysis.

3. Participants/parents(s)/legal guardians(s) who are able to comply with the study visit schedule and are willing and able to complete the protocol-specified assessments.

4. Participants whose parent(s)/legal guardian(s) provide written consent to participate in the study.

Exclusion Criteria

1. Participants with known non-neurogenic conditions (identified on history or on examination) that may cause genitourinary problems (e.g., bladder fistula, bladder exstrophy).

2. Participants with clinically significant medical problems or other organ abnormality or pathology (e.g. medically uncontrolled cardiovascular, pulmonary, gastrointestinal, renal, endocrine, neurological, autoimmune, hematological, urological, psychiatric disorders, significantly reduced hepatic function, or renal impairment) for whom, in the opinion of the investigator, administration of oxybutynin would present undue risk.

3. Participants who have undergone bladder augmentation surgery.

4. Participants taking any medications other than oxybutynin chloride affecting bladder contractility (e.g., imipramine, pseudoephedrine, tolterodine, hyoscyamine, flavoxate hydrochloride).

5. Participants with any of the following gastrointestinal problems:
    - partial or complete GI obstruction
    - GI motility, such as paralytic ileus, intestinal atony, chronic and severe constipation (more than 3 days without bowel movement)

- Ulcerative colitis, megacolon

6. Participants who have taken an investigation drug within a period of 1 month prior to study entry.

7. Participants with known allergy or hypersensitivity to oxybutynin chloride or components of the syrup.

8. Participants who are currently taking antibiotics which interact with CYP3A metabolism such as antifungals, erythromycin, ceftizoxime or other cephalosporins.

9. Patients with known untreated narrow-angle glaucoma or untreated narrow anterior chamber angles.

14.3.2 Demographics and Baseline Disease Characteristics

Three US sites and one site in the Netherlands each enrolled 1 or more patients. There was a total of 19 patients screened and 16 enrolled (US sites enrolled 6 and the Netherlands site enrolled 10). Baseline demographic characteristics for these 16 patients are summarized in Table 29. The majority of the patients in the trial were male (68.8%) and Caucasian (75%). The second largest ethnic group was comprised of Hispanic patients. Individual ages ranged from 1 to 5 years. Median treatment group weight was 16.0 kg while individual weights ranged from 11 to 20 kg. In all enrolled patients, 50.0% of patients reported seven or more bowel movements per week, 25.0% reported no specific bowel regimen, and 68.7 % reported a history of fecal impaction with it occurring "rarely" in half of the patients who reported a history of fecal impaction.

Table 29 Study C-2000-043-00Baseline Demographics

	Enrolled patients (n=16)
Males	11
Females	5
Race/Ethnicity (n)	
Caucasian	12
African American	1
Hispanic	3
Asian	0
Other	0
Age	
1 yr	1
2 yr	5
3 yr	3
4 yr	4
5 yr	2
Median (range)	3 yr (1 – 5 yrs)
Weight	
Median (range)	16.0 kg (11 to 20 kg)

Source: Derived from Tables 12.1.2-1 on pg. 53.12/303

14.3.3 Withdrawals, compliance, and protocol violations

No patient discontinued early.

1 Page(s) Withheld

Medical Review (9/6/02)

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

14.4 Efficacy

14.4.1 Key Efficacy Assessments

Key measurement for efficacy assessments were the pharmacokinetic measurements taken after a minimum of two weeks of treatment with Ditropan syrup and the urodynamic measurements collected at baseline and at end of study treatment. The urodynamic evaluation included changes over time in maximal bladder capacity, detrusor and intravesical pressure at maximal bladder capacity, and presence of uninhibited detrusor contractions > 15 cm H_2O.

b(4)

Study C-2000-042-00 it is drawn at 12 hours. Since the PK results from the two studies are being pooled, there will be less data for the [ ] 12 hours time points. b(4)

14.4.3 Primary Efficacy Endpoint Analysis

The primary efficacy (Pharmacodynamic) measurements were all from the urodynamic evaluations done at baseline (visit 2) when the patient had not taken oxybutynin for 3 to 7 days, and again at the end of the study (Visit 3) when the patient had been on a consistent dosage and dosing regimen of Ditropan syrup for at least 2 weeks. The efficacy measurements were:

- Maximal cystometric capacity
- Abdominal (rectal) pressure
- Intravesical pressure
- Presence/absence of uninhibited contractions greater than 15 cm H_2O

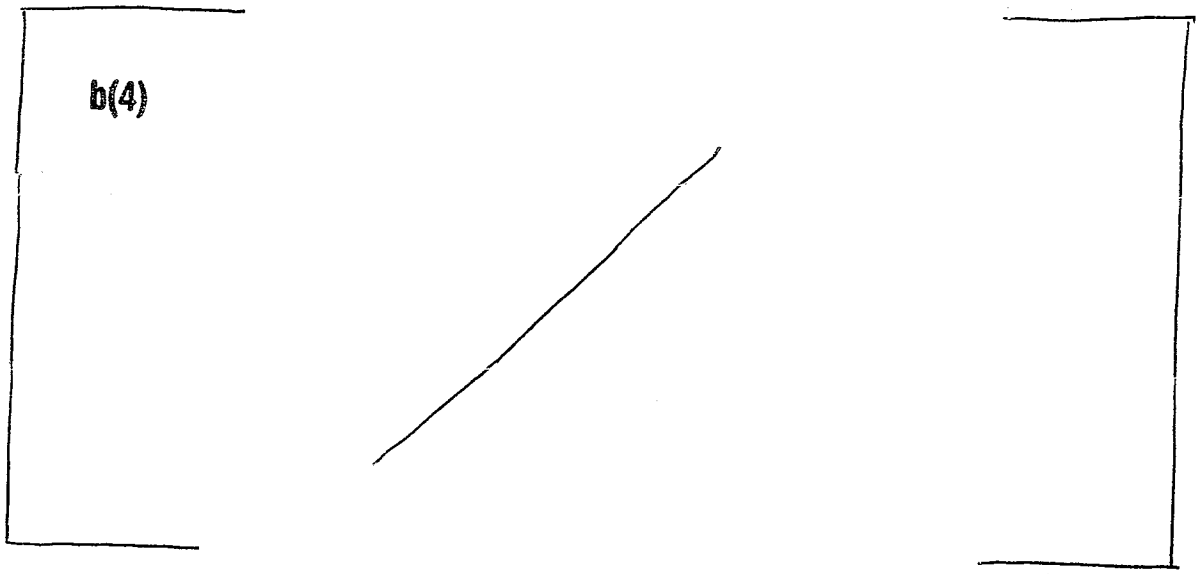
These measurements as presented in Tables 13.2.4-1 and 13.2.4-2 on pg. 53.15/1-7 and in Tables 12.1.8.1-6 through 12.1.8.1-10 on pg 53.3/26-30 were reviewed and are summarized in Table 30. Mean maximal cystometric capacity increased in 13/16 (81.3%) patients. There were no clinically relevant changes from baseline seen in mean detrusor or intravesical pressures at maximal cystometric capacity. At baseline, 11/16 patients (68.8%) demonstrated uninhibited detrusor contractions $\geq$15 cm H_2O; after 2 weeks of treatment with Ditropan syrup, 2/16 patients (12.5%) demonstrated uninhibited detrusor contractions. The two patients with continued uninhibited contractions demonstrated improvement with increased bladder capacity before the onset of uninhibited contractions and lower detrusor pressure at maximal cystometric capacity.

Table 30 Pharmacodynamic (Efficacy) Results Summary

	Change from Baseline to End of Study		
Urodynamic Variable	**N**	**Mean (SEM)**	**Range**
Maximal cystometric capacity (mL)	16	+71.5 (21.99)	-29 to +265
Detrusor pressure (cm H_2O)	15	+0.6 (4,79)	-21 to +50
Intravesical pressure (cm H_2O)	15	+0.9 (5.81)	[ ] b(4)

Source: pg. 53.12/219

b(4)



2 Page(s) Withheld

Medical Review (9/6/02)

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

14.5 Safety

14.5.1 Safety Measurements

All participants who received at least one dose of study medication were to be included in the summaries and listings of safety data. Premature termination, adverse events, vital signs, concomitant medications, and laboratory data were also to be summarized. The COSTART IV Thesaurus was to be used to map adverse event verbatim to body system and preferred term.

The following safety measurements were evaluated:

- Reports of adverse events (by participant, parent, or guardian)
- Laboratory assessment (hematology, serum chemistries, and urinalysis): at screening and study termination
- Physical examination and EKG: at screening and at end of Week 2 or early termination visit
- Vital signs (blood pressure and heart rate): at all clinic visits.
- Concomitant medications

14.5.2 Extent of exposure

Patients took Ditropan syrup for periods that ranged from 13 to 28 days. No patient had their daily dosage of Ditropan syrup adjusted by the study investigator during the study.

14.5.3 Serious adverse events

Deaths: there were no deaths
Premature termination due to safety reasons: no patients terminated prematurely form the study because of safety reasons.
Serious adverse events: there were no serious adverse events

14.5.4 Frequent adverse events

Adverse events that occurred after the patient started study medication (Visit 2) and within 3 days after the end of study medication were reported. At least one adverse event was reported by 13 (81.3%) of the patients (Appendix 13.2.6-1 on pg. 53.15/48-52. Most adverse events were reported by only one patient. The most frequent adverse events were urinary tract infections, vasodilation, constipation, diarrhea, ecchymosis, and otitis media. Table 34 presents the adverse events occurring in ≥10% of patients. All adverse events were rated as mild or moderate in severity. Treatment related adverse events were reported by a total of six patients and were all rated as mild: vasodilation (2 patients), abnormal stools (1 patient), constipation (2 patients), diarrhea (1 patients), eructation (1 patient), and pruritus (1 patient).

Table 34 Adverse Events Reported by ≥10% of Patients

	Number of Patients (%) (n=16)
Urinary tract infections	3 (18.8%)
Vasodilation	2 (12.5)
Constipation	2 (12.5)
Diarrhea	2 (12.5)
Ecchymosis	2 (12.5)
Otitis media	2 (12.5)

Source: Table I on pg. 53.12/292

One anticholinergic adverse event was reported: constipation.

Medical Reviewer's comment:

1) **It was unusual for an anticholinergic drug that none of the enrolled patients reported dry mouth as an adverse event. This may be due to young ages of the patients and their limited communication abilities making it difficult for them to report a dry mouth.**

14.5.5 Laboratory Values

The serum chemistry, hematology, and urinalysis test results were reviewed (Appendix 13.2.9-1 and 13.2.9-2 on pg. 53.15/62-151. Three clinically significant changes in the laboratory values were noted, two for the LDH values (normal 470-900) and one for the potassium value (normal 3.8-5). Patient 1003 had a normal LDH value at screening (652 U/L) and an elevated LDH (1037 U/L) at end of treatment. Patient 1007 had a normal LDH value (697 U/L) and a normal potassium (4.6) both at screening and an elevated LDH (1978 U/L) and an elevated potassium (6.5) both at end of treatment.

14.5.6 Concomitant Medications

The most common concomitant medications initiated during treatment (Appendix 13.2.7-1 on pg. 53.15/54) were antibiotics (3 of 7 medications). The most common concomitant medication initiated prior to dosing was Dridase. Dridase is a European tradename for oxybutynin and it was administered to 10 patients at the Netherlands site prior to enrollment. The Dridase was stopped at least 3 days prior to enrollment. Two patients took prohibited concomitant medications during treatment: Patient 1008 was treated with topical miconazole and Patient 2002 was treated with erythromycin. Both these patients began treatment with these concomitant medications prior to study enrollment.

14.5.7 Vital Signs

The heart rate and blood pressure values by visit (Table 12.1.6-5 on pg. 53.13/33 and Table 12.1.6-6 on pg. 53.13/34) were reviewed. For the heart rate and blood pressure values, no clinically significant change in mean or median or range of values was noted.

14.5.8 Reviewer's assessment of efficacy and safety

In Study **C-2000-043-00,** short-term treatment with Ditropan syrup for detrusor hyperreflexia in 16 pediatric patients with spina bifida aged 1 to 5 years was associated with an improvement (i.e. increase) in the maximal cystometric capacity but no improvement (i.e. decrease) in the mean detrusor or intravesical pressures at maximal cystometric capacity.

A statistically significant change in the mean maximal cystometric capacity (p=0.0054) from baseline (104 mL) to end of study (175 mL) was demonstrated. A statistically significantly change in the number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 (p=0.0039) from baseline (n=11) to end of study (n=2) was also demonstrated. No significant change from baseline in mean detrusor pressure at maximal cystometric capacity or intravesical pressure at maximal cystometric capacity was noted.

No new and unlabeled safety issues were identified.

[ ] b(4)

[ ] No clear dose-response or concentration-response relationships between the total daily dose administered of Ditropan syrup and the pharmacodynamic results in pediatric patients with spina bifida were identified. [ ]

[ ] b(4)

[b(4)] In addition, only one patient in the study was aged 1 year.

15 APPENDIX C: CRITICAL ANALYSIS

The sponsor submitted one report [pg. 53.15/186-406 and 53.16/1-399] to meet the two critical analyses requirements listed in the Written Request dated November 30, 2000.

The report was entitled "Critical Analysis of the Use of Oxybutynin Chloride in Adult and Pediatric Patients with Detrusor Hyperreflexia due to Neurogenic Conditions". It contained 29 pages of text supported by 63 references, two tables entitled "Table 1: Controlled Studies with Ditropan Tablets (NDA 17-577)" and "Table 2: Uncontrolled Studies with Ditropan Tablets or Syrup (NDA 17-577, 18-211)", and one Appendix entitled "Rationale for the Duration of Treatment for Efficacy Measurements in the Pivotal Clinical Studies for OROS® (Oxybutynin Chloride)".

The literature quoted in the Critical Analysis [pg. 53.15/194-5] advocates the use of antimuscarinic therapy in children when high detrusor filling pressures (i.e. >40 cm H_20), high pressure detrusor contractions (i.e. >90-100cm H_20), or uninhibited detrusor contractions are present (Kasabian et al 1992, Goessl et al 2000, and Baskin et al 1990). An association between detrusor storage pressures exceeding 40 cm H_20 with upper urinary tract deterioration has been reported (McGuire et al 1981, Flood et al 1994). The use of antimuscarinic therapy in combination with clean intermittent catheterizations in children with myelomeningocele and neurogenic bladder has been shown to prevent upper urinary tract deterioration (Joseph et al 1989, Geraniotis et al 1988, Flood et al 1994, Edelstein et al 1995) and to decrease incontinence by diminishing leakage of urine between catheterizations (Geraniotic et al 1988).

b(4)

The Kasabian reference [pg. 53.16/197-199] specifically discussed the prophylactic value of clean intermittent catheterization (CIC) and anticholinergic medication in 26 of 71 consecutive newborns with myelodysplasia versus conservative treatment in 56 of 106 consecutive newborns with myelodysplasia. The follow-up period ranged from 6 months to 5 years with a mean of 2.74 years. Oxybutynin therapy was started when bladder hypertonicity (filling pressures exceeding 40 cm H_20) or high-pressure contractions (greater than 90 to 100 cm H_20) occurred at a dose of 1.0 ml per year of age after age 1 year administered twice daily and proportionately less for infants younger than age 1 year. The average age at which CIC was begun in the 26 children was 12.5 months, however 6 neonates did not develop dyssynergia until age 1 or 2 years. The Kasabian reference offers an explanation regarding why the clinical study C-2000-042-00 did not demonstrate a decrease in detrusor pressures. Only 6 of the 16 subjects enrolled in C-2000-042-00 demonstrated >40 cm H_20 intravesical or detrusor pressure at maximal capacity at baseline [Appendix 13.2.4-1 pg. 53.15/1-5]. With so few subjects being eligible for oxybutynin therapy based on their baseline intravesical or detrusor pressure at maximal capacity, it would not be expected that any significant change in intravesical or detrusor pressure at maximal capacity with treatment would be demonstrated in C-2000-042-00. The Baskin reference [pg. 53.15/370-372] reported that the use of both CIC and anticholinergic therapy (oxybutynin at a dose of 0.1 mg/kg tid) initiated at ages 1-30 days in 35 infants diagnosed with detrusor hypertonia and followed for 20 to 60 months was effective in preventing urinary tract deterioration. The Baskin reference also reported that constipation was a common side effect, but was effectively managed with alterations in diet or bowel program. The Edelstein reference [pg. 53.16/102-106] reported on 69 children with myelodysplasia on ICC and only those with high bladder filling or high voiding pressures were also treated with anticholinergic medication.

It is interesting to the reviewer that the Geraniotis reference [pg. 53.16/118] supports the use of CIC alone in 24 infants and young children aged 7 to 39 months with myelomeningocele and neurogenic bladder dysfunction to prevent urinary tract deterioration.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brenda Gierhart
9/6/02 02:26:29 PM
MEDICAL OFFICER

Mark S. Hirsch
9/6/02 02:58:09 PM
MEDICAL OFFICER
I concur.

MEMORANDUM

To:	**NDA 17-577**
Through:	**Mark Hirsch, MD** **Acting Urology Team Leader, HFD-580**
From:	**Brenda S. Gierhart, MD** **Medical Officer, HFD-580**
Date:	**August 9, 2000**
Re:	**Submission SLR-032: NDA Supplement for Labeling** **Ditropan® (oxybutynin chloride) Tablets** **Alza Corporation** **Submitted September 10, 1999** **Received September 13, 1999**

Current submission:
Sponsor is submitting changes to the approved product labeling for Ditropan® (oxybutynin chloride) Tablets to the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **OVERDOSAGE** sections. These changes are based upon a) language in the approved product labeling for Ditropan® XL (oxybutynin chloride) Extended Release Tablets; b) two literature reports to support the revised language concerning metabolism and potential drug-drug interactions; and c) adverse events reported for the immediate-release formulation of oxybutynin chloride used in three clinical trials for the Ditropan® XL. The current label edition date for Ditropan® (oxybutynin chloride) Syrup is January, 1998. The current label edition date for Ditropan® XL is December, 1998.

Reviewer's comments:

1) **The proposed changes to the CONTRAINDICATIONS section are identical to the current wording of the same section in the approved Ditropan® XL label.**
   - [redacted]
   - [redacted]
   - It substitutes the contraindication "in patients with urinary retention [redacted] in patients who are at risk for this condition" for the following: [redacted]
   - It substitutes the contraindication "[redacted] uncontrolled narrow-angle glaucoma and in patients who are at risk for this condition" for the following: [redacted]

   b(4)

   Some elements of the approved label have been modified and relocated to the **PRECAUTIONS** section, under the *Urinary Retention* and *Gastrointestinal Disorders* subsections.

   All of the proposed changes to the CONTRAINDICATIONS section are acceptable with the exception of the misspelling of retention (retnetion) in the first sentence of the section submitted in Section 2: Strikeout/Underlined.

2) **The proposed WARNINGS section deletion is identical to the deleted WARNINGS section in the approved Ditropan® XL label.**

Some elements of the approved **WARNINGS** section have been modified and relocated to the **PRECAUTIONS** section, under **Information for Patients** and *Gastrointestinal Disorders* subsections.

The proposed change of deleting the WARNINGS section is acceptable.

3) **The proposed changes in the General subsection of the PRECAUTIONS section regarding patients with hepatic or renal impairment, *Urinary Retention*, *Gastrointestinal disorders*, and Information for Patients are identical to the approved Ditropan® XL label with the exception that the Ditropan® XL has references to its nonabsorbable shell and Sponsor proposes underlining General as submitted in Section 2: Strikeout/Underlined.**

Three sentences are deleted from the **PRECAUTIONS** section of the approved Ditropan® label:

> Ditropan® (oxybutynin chloride) should be used with caution in the elderly and in all patients with autonomic neuropathy, hepatic or renal disease. Ditropan® may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, and prostatic hypertrophy. Administration of Ditropan® to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

The proposed changes in the General subsection of the PRECAUTIONS section regarding patients with hepatic or renal impairment, *Urinary Retention*, *Gastrointestinal disorders*, and Information for Patients are acceptable, except for the following:

- **Delete the proposed underlining the subsection title General. None of the subsection titles in the PRECAUTIONS section should be underlined.**
- **In the proposed General subsection of the PRECAUTIONS section, add a new second sentence:**

  Ditropan® may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension,[ ]prostatic hypertrophy. b(4)
- **In the proposed *Gastrointestinal disorders* subsection of the PRECAUTIONS section, add a new second sentence:**

  Administration of Ditropan® to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

4) **The first two sentences of the proposed Drug Interactions subsection addition to the PRECAUTIONS section are identical to the first two sentence of the Drug Interactions subsection in the approved Ditropan® XL label.**

The first two sentence of the subsection addition are reasonable and will provide consistency with the approved Ditropan® XL label.

The first two sentences in the proposed changes in the Drug Interactions subsection addition to the PRECAUTIONS section are acceptable

5) **The third, fourth, and fifth sentences of the proposed Drug Interactions subsection addition to the PRECAUTIONS section differ from the approved Ditropan® XL label. In addition, Biopharmaceutics Review suggests adding a sixth sentence to this subsection:**

> **Caution should be used when such drugs are co-administered.**

The third, fourth, and fifth sentences of the subsection addition are substantiated by two references provided by the Sponsor and are reasonable. The Biopharmaceutics Review proposed sixth sentence is also reasonable.

The Sponsor proposed third, fourth, and fifth sentences and the Biopharmaceutics Review proposed sixth sentence (i.e. "Caution should be used when such drugs are co-administered.") to the PRECAUTIONS section Drug Interactions subsection addition are acceptable. Recommend the Ditropan® XL Drug Interactions subsection of the PRECAUTIONS section replace the current third and fourth sentences with the proposed third, fourth, fifth, and sixth sentences.

6) **The proposed changes in the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the PRECAUTIONS section give additional details regarding the 24-month rat study.**

The **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection of the **PRECAUTIONS** section in the Ditropan® XL approved label contains the identical first and second sentences to the proposed changes.

The proposed changes in the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the PRECAUTIONS section giving additional details regarding the 24-month rat study are acceptable. None of the subsection titles in the PRECAUTIONS section should be underlined.

7) **The proposed underlining of the subsection titles Pregnancy, Nursing Mothers, and Pediatric Use is unacceptable. None of the subsection titles in the PRECAUTIONS section should be underlined.**

8) **The proposed changes to the ADVERSE REACTIONS section deletes decreased sweating, replaces amblyopia with blurred vision, replaces decreased lacrimation with dry eyes, and adds dry skin, abdominal pain, diarrhea, flatulence, [ ] [ ], headache, and dry nasal and sinus mucous. The proposed changes do not alter:** b(4)

- [ ]
- [ ]

The **ADVERSE REACTIONS** section of the Ditropan® XL approved label is divided into two subsections: **Adverse Events with Ditropan® XL** and **Adverse Events with Oxybutynin Chloride**.

The **Adverse Events with Ditropan® XL** subsection:
- clearly identifies the safety information was provided for patients from three controlled clinical studies and one open label study.
- list the number of patients in the safety information
- provides the safety information in Table 2 entitled Incidence (5) of Adverse Events Reported by ≥5% of Patients Using Ditropan® XL (5-30 mg/day)
- discusses the discontinuation rate for adverse events and lists the most frequent adverse event causing early discontinuation
- lists the adverse events reported by 2 to <5% of patients using Ditropan® XL (5-30 mg/day) in all studies by categories General, Cardiovascular, Digestive, Musculoskeletal, Nervous, Respiratory, Skin, and Urogenital.

The **Adverse Events with Oxybutynin Chloride** subsection:
- contains the single sentence:

  Other adverse events [ ] tachycardia, hallucinations, cycloplegia, mydriasis, impotence, and suppression of [ ] b(4)

The proposed changes to the ADVERSE REACTIONS section are not acceptable. Recommend replacing the ADVERSE REACTIONS section with similar formatting to the ADVERSE REACTIONS Ditropan® XL section. Propose changing ADVERSE REACTIONS section to:

ADVERSE REACTIONS:
The safety and efficacy of Ditropan® (oxybutynin chloride) was evaluated in a total of 199 patients in three clinical trials with Ditropan® XL (Table 1). These participants were treated with 5-20 mg/day for up to 6 weeks. [ ] b(4)

Table 1
Incidence (%) of Adverse Events Reported by / 5% of Patients Using Ditropan® (5-20 mg/day) b(4)

Body System	Adverse Event	Ditropan® (5-20 mg/day) (n=199)
General	Abdominal pain	6.5%
	Headache	6.0%
Digestive	Dry mouth	71.4%
	Constipation	12.6%
	Nausea	10.1%
	Dyspepsia	7.0%
	Diarrhea	5.0%
Nervous	Dizziness	15.6%
	Somnolence	12.6%
Special senses	Blurred vision	[ ]%
	[ ]	[ ]%
Urogenital	Urination impaired	10.6%
	Post void residuals increase	5.0%
	Urinary tract infection	5.0%

b(4)

The most common adverse events reported by patients receiving 5-20 mg/day Ditropan® were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

In addition, the following adverse events were reported by 2 to <5% of patients using Ditropan® (5-20 mg/day) in [ ] studies. *General:* asthenia, dry nasal and sinus mucous membranes; *Cardiovascular:* palpitation; *Metabolic and Nutritional System:* peripheral edema; *Nervous System:* insomnia, nervousness, confusion; *Skin:* dry skin; *Special Senses:* dry eyes, taste perversion. b(4)

Other adverse events [ ] tachycardia, hallucinations, cycloplegia, mydriasis, impotence, suppression of lactation, vasodilatation, rash, decreased gastrointestinal motility, flatulence, [ ] decreased sweating. b(4)

9) **The proposed changes to the OVERDOSAGE section delete several symptoms associated with overdose and detailed therapy recommendations for overdose.**

The proposed changes to the **OVERDOSAGE** section are identical to the corresponding section in the Ditropan® XL label, except Ditropan® XL has the additional first and second sentences in the section:

> The continuous release of oxybutynin from Ditropan® XL should be considered in the treatment of overdosage. Patients should be monitored for at least 24 hours.

The proposed changes eliminate specific examples of [ ] excitation and other symptoms of oxybutynin overdosage. b(4)

The proposed changes to the OVERDOSAGE section are acceptable except for the following:

- **In the proposed third sentence of the OVERDOSAGE section after the phrase "[ ] excitation" add:** b(4)
  (e.g. restlessness, tremor, irritability, convulsions, delirium, hallucinations)
- **In the proposed OVERDOSAGE section, add a new fourth sentence:**
  Other symptoms may include hypotension or hypertension, respiratory failure, paralysis and coma.
- **Begin a new paragraph with the proposed third sentence in the OVERDOSAGE section.**

Recommendation:

The Sponsor should be sent a regulatory letter containing the following comments:

1) All of the proposed changes to the **CONTRAINDICATIONS** section are acceptable with the exception of the misspelling of retention (retnetion) in the first sentence of the section submitted in Section 2: Strikeout/Underlined.

2) The proposed change of deleting the **WARNINGS** section is acceptable.

3) The proposed changes in the General subsection of the **PRECAUTIONS** section regarding patients with hepatic or renal impairment, *Urinary Retention*, *Gastrointestinal disorders*, and **Information for Patients** are acceptable, except for the following:
   - Delete the proposed underlining the subsection title General. None of the subsection titles in the **PRECAUTIONS** section should be underlined.
   - In the proposed **General** subsection of the **PRECAUTIONS** section, add a new second sentence:
     Ditropan® may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension [ ] b(4)
     prostatic hypertrophy.
   - In the proposed *Gastrointestinal disorders* subsection of the **PRECAUTIONS** section, add a new second sentence:
     Administration of Ditropan® to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

4) The proposed first and second sentences of the proposed Drug Interactions subsection addition to the **PRECAUTIONS** section are acceptable.

5) The Sponsor proposed third, fourth, and fifth sentences and the Biopharmaceutics Review proposed sixth sentence (i.e. "Caution should be used when such drugs are co-administered.") to the PRECAUTIONS section Drug Interactions subsection addition are acceptable. Recommend the Ditropan® XL Drug Interactions subsection of the PRECAUTIONS section replace the current third and fourth sentences with the proposed third, fourth, fifth, and sixth sentences.

6) The proposed changes in the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection of the **PRECAUTIONS** section giving additional details regarding the 24-month rat study are acceptable. None of the subsection titles in the **PRECAUTIONS** section should be underlined.

7) The proposed underlining of the subsection titles **Pregnancy, Nursing Mothers**, and **Pediatric Use** is unacceptable. None of the subsection titles in the **PRECAUTIONS** section should be underlined.

8) The proposed changes to the **ADVERSE REACTIONS** section are not acceptable. Recommend replacing the **ADVERSE REACTIONS** section with similar formatting to the **ADVERSE REACTIONS** Ditropan® XL section. Propose changing **ADVERSE REACTIONS** section to:

ADVERSE REACTIONS:
The safety and efficacy of Ditropan® (oxybutynin chloride) was evaluated in a total of 199 patients in three clinical trials with Ditropan® XL (Table 1). These participants were treated with 5-20 mg/day for up to 6 weeks.[ ] b(4)

Table 1
Incidence (%) of Adverse Events Reported by / 5% of Patients Using Ditropan® (5-20 mg/day) b(4)

Body System	Adverse Event	Ditropan® (5-20 mg/day) (n=199)
General	Abdominal pain	6.5%
	Headache	6.0%
Digestive	Dry mouth	71.4%
	Constipation	12.6%
	Nausea	10.1%
	Dyspepsia	7.0%
	Diarrhea	5.0%
Nervous	Dizziness	15.6%
	Somnolence	12.6%
Special senses	Blurred vision	[ ]%
	[ ]	[ ]% b(4)
Urogenital	Urination impaired	10.6%
	Post void residuals increase	5.0%
	Urinary tract infection	5.0%

The most common adverse events reported by patients receiving 5-20 mg/day Ditropan® were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

In addition, the following adverse events were reported by 2 to <5% of patients using Ditropan® (5-20 mg/day) in all studies. *General:* asthenia, dry nasal and sinus mucous membranes; *Cardiovascular:* palpitation; *Metabolic and Nutritional System:* peripheral edema; *Nervous System:* insomnia, nervousness, confusion; *Skin:* dry skin; *Special Senses:* dry eyes, taste perversion.

Other adverse events[ ] tachycardia, hallucinations, b(4)
cycloplegia, mydriasis, impotence, suppression of lactation, vasodilatation, rash, decreased gastrointestinal motility, flatulence[ ]decreased sweating.

9) The proposed changes to the **OVERDOSAGE** section are acceptable except for the following:
   - In the proposed third sentence of the OVERDOSAGE section after the phrase "[ ]excitation" b(4) add:
     (e.g. restlessness, tremor, irritability, convulsions, delirium, hallucinations)
   - In the proposed OVERDOSAGE section, add a new fourth sentence:
     Other symptoms may include hypotension or hypertension, respiratory failure, paralysis and coma.
   - Begin a new paragraph with the proposed third sentence in the OVERDOSAGE section.

cc: Original NDA 17-577
HFD-580 Division File
S. Allen, D. Shames, M. Hirsch, B. Gierhart, K. Colangelo, HFD-580

To:	NDA 20-897
From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
Through:	Mark Hirsch, MD Team Leader, HFD-580
Date:	January 23, 2001
Re:	**SE1-009** Ditropan XL® (oxybutynin chloride) ALZA Corporation MO Review of Submitted Pediatric Study Reports and Critical Analyses Compared to Written Request Requirements Correspondence Date: December 7, 2001 Date Received: December 7, 2001

Current submission:
A Written Request (WR) letter dated November 30, 2000 asked ALZA Corporation to perform two pediatric studies with oxybutynin chloride and to prepare two critical analyses. The sponsor now responds to the WR by submitting one final study report, C-2000-043-00 (Study #1 in the Written Request), one interim study report, C-2000-042-01 (Study #2 in the Written Request), and two critical analyses in the 43-volume submission **SE1-009**. The purpose of this review is to determine whether ALZA's submission SE1-009 "fairly responds" to the WR by comparing the pediatric study reports and critical analyses submitted in SE1-009 with the requirements listed in the WR. The Division of Reproductive and Urologic Drug Products (DRUDP) will present the findings of this review to the Pediatric Exclusivity Board on February 1, 2002.

Reviewer's comment:

1) **The following is each line from the section of the oxybutynin Written Request that contains the requirements for the requested two studies and two critical analyses. After each line is a shaded box which contains any pertinent reviewer's comments, the location in SE1-009 where the requirement is met, and a notation regarding whether this requirement was met in SE1-009. The notation Y is used for "yes", N for "no, and N/A for "not applicable". An item is marked N/A when it is not a requirement in the Written Request. It is noted that ALZA provided a listing entitled "Annotated Written Request" outlining where they believed each requirement was met in Vol. 1 Section 1.3 on pages 53.1/14-22.**

Study #1: [This study is Protocol C-2000-043-00. Final study report is on pages 53.12/215-300. Final protocol is on pages 53.13/148-206 and it was never amended.] Y

Type of study: N/A

Pharmacokinetic (PK) and pharmacodynamic (PD [urodynamic]) study [Title of Protocol C-2000-043-00 is "The Pharmacokinetics and Pharmacodynamic Effects of Oxybutynin Chloride (Ditropan® Syrup) in the Treatment of Detrusor Hyperreflexia due to Neurogenic Conditions in Children Aged 1 to 5 years" per page 53.12/215 and page 53.13/149] Y

Objectives: N/A

To evaluate the pharmacokinetic profiles of Ditropan (oxybutynin chloride) syrup in pediatric patients with detrusor hyperreflexia due to neurogenic conditions on stable daily doses of oxybutynin chloride. [See pages 53.2/8-9, 53.12/217, 53.12/243 and 53.13/155] Y

To evaluate oxybutynin dose-effect (urodynamic) and concentration-effect (urodynamic) [redacted] of Ditropan syrup in pediatric patients with detrusor hyperreflexia due to neurogenic conditions. [Sponsor clearly met the requirement of having as an objective "to evaluate oxybutynin dose-effect (urodynamic) and concentration-effect (urodynamic)" [redacted] of Ditropan syrup in pediatric patients with detrusor hyperreflexia due to neurogenic conditions". Instead, the sponsor listed the following objective "to examine whether children on oxybutynin chloride require drug therapy based on comparison of urodynamic outcome at the end of study relative to baseline". However, the sponsor concluded that no clear dose-response or concentration-response relationships in terms of urodynamic effect could be established [redacted] The reviewer believes the sponsor fairly met this requirement. See pages 53.2/8-9, 53.12/217, 53.12/243, 53.12/297, and 53.13/155] Y b(4) b(4)

Indication: N/A

Detrusor hyperreflexia due to neurogenic conditions [See pages 53.12/215, 53.12/247, and 53.13/158] Y

Study design: N/A

Repeated dose, multiple-dose level, minimum 2-week duration, PK and PD study. [See pages 53.12/245-246 and 53.13/160-161] Y

For patients receiving oxybutynin chloride, the baseline urodynamic evaluation will be performed after a 3-7 day washout period off medication. [See pages 53.12/245-246 and 53.13/160-161] Y Urodynamic evaluation will be repeated after a minimum of 2 weeks of treatment with oxybutynin. [See pages 53.12/246 and 53.13/161] Y

Age group in which study will be performed: N/A

Ages one to five years [See pages 53.12/247 and 53.13/158] Y

Number of patients to be studied: N/A

Enroll approximately 15 patients to have at least eight patients for describing PK/PD profile. [16 patients enrolled, 16 patients completed the study [redacted] See pages 53.12/267-271, 53.12/301-302, 53.13/1, 53.13/157, and 53.14/301-314] Y b(4)

Study endpoints: N/A

Appropriate urodynamic evaluation: [See pages 53.12/256-257, 53.12/305-312 and 53.13/188-189] Y this may include maximal bladder capacity, intravesical pressure at

maximal bladder capacity, and presence of uninhibited detrusor contractions. N/A since it states that they "may" be included, however all three were included.

PK: appropriate stereospecific analysis of drug and metabolite plasma profiles; the sampling should be adequate to characterize the complete PK profile in this age group [

b(4)

]

Dose(in mg per kg)-effect (urodynamic) and concentration-effect (urodynamic) [The change in urodynamic effect (maximal bladder capacity and detrusor pressure at maximal bladder capacity) from baseline to end of Ditropan syrup therapy were evaluated as a function of the total daily dose per kilogram body weight and as a function of the average R-oxybutynin concentration C_{avg} at the same dose as end of study urodynamic measurement. See pages 53.12/288-290, 53.12/313-327, and 53.13/181] Y

Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular and laboratory parameters [Safety evaluations included vital signs (systolic/diastolic blood pressure and heart rate) at Visit 1 (Screening), Visit 2 (Baseline) and Visit 3 (End of treatment), standard laboratory parameters (urinalysis, serum chemistry, hematology) at Visits 1 and 3, EKG at Visits 1 and 3, urodynamic studies at Visits 1 and 3, and collection of adverse events at Visits 2 and 3. See pages 53.12/257-261, 53.12/291-296, 53.13/24-34, and 53.13/167-176] Y

Safety: Number of patients terminated prematurely [No patient terminated prematurely. See page 53.12/302] Y

Drug information: N/A

The drug product to be used in this study is the following commercially available formulation: Ditropan (oxybutynin chloride) Syrup, 5 mg/5 mL. [All patients received Ditropan syrup 5 mg/mL from one lot of the product per pages 53.12/249 and 53.13/282] Y A total daily dose of 5–15 mg will be administered orally divided into two or three doses. [The protocol stipulated a total daily dose of 5-15 mg administered orally divided into two or three doses. [

b(4)

]

Drug specific safety concerns: N/A

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents. [It was stated in the protocol (on page 53.13/171) that there would be monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents. The final study report (on page 53.12/258) stated this monitoring was done. Safety data and adverse event results are summarized on pages 53.12/290-296. The adverse event data tables are located on page 53.13/24-32] Y

Statistical information: N/A

PK: Descriptive stereospecific analysis to include reporting of AUC, C_{max}, and C_{min} for drug and metabolite. [See tables on pages 53.13/1-23; also pages 53.12/261-63 and 53.13/180-181] Y

Urodynamic: Urodynamic measurements to be tabulated as a function of dose (mg/kg). [See page 53.13/41 for Figure 12.2.2-2 labeled "Change from Baseline in Urodynamic variables versus Total Daily Dose (mg/kg)". Also see pages 53.12/263-4 and 53.13/181] Y Baseline measurements will be contrasted with on treatment measurements. [See pages 53.12/263-4 and 53.13/178-179] Y

Safety: Safety measurements are to be tabulated. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data. [See tables on pages 53.13/24-34. All participants who received at least one dose of study medication were included in the safety data summaries and listings. See pages 53.12/264 and 53.13/179-180] Y

Labeling that may result from the study: [See pages 53.1/36-89] Y

Appropriate changes to the label to incorporate the study results will be made. N/A

Format of reports to be submitted: N/A

A final study report will be submitted. [See pages 53.1/6-9, 53.2/8-9, and 53.12.215-300] Y We recommend that you follow the July 1996 ICH (E3) guideline for structure and content of clinical study report. N/A The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation. [See pages 53.1/6-9, 53.2/8-9, and 53.12.215-300]Y

Timeframe for submitting reports of the study: N/A

Report of the above study must be submitted to the Agency on or before December 15, 2002. [See 53.1/Cover letter] Y Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request. N/A

Study #2: [This study is Protocol C-2000-042-01. Interim study report is on pages 53.2/10-129. Final protocol is on pages 53.5/7-114 and Amendment #1 dated 12/19/00 is on page 53.5/1-6] Y

Type of study: N/A

Safety and dose-response study [Title of Protocol C-2000-042-01 is "The Safety and Tolerability of Oxybutynin Chloride (Ditropan XL®, Ditropan® Syrup or Ditropan®

Tablets) in the Treatment of Detrusor Hyperreflexia due to Neurogenic Conditions in Children Aged 6 to 15 years" per page 53.2/10 and page 53.5/31] Y

Objectives: N/A

To document the safety and tolerability of Ditropan (oxybutynin chloride) Syrup, Ditropan (oxybutynin chloride) Tablets, and/or Ditropan XL (oxybutynin chloride) extended-release tablets in pediatric patients with detrusor hyperreflexia due to neurogenic conditions on stable daily doses of oxybutynin chloride. [See pages 53.2/8-9, 53.2/12, 53.2/48, and 53.5/40] Y

To evaluate oxybutynin dose-effect (urodynamic) and concentration-effect (urodynamic) in order to establish safe and effective oxybutynin dosage regimens in pediatric patients with detrusor hyperreflexia due to neurogenic conditions. [The secondary objectives in this protocol were "to evaluate oxybutynin dose-effect (urodynamic) and concentration-effect (urodynamic) of Ditropan XL® extended-release tablets and Ditropan® tablets/syrup to establish safe and effective dosage regimens in the study population", however they only included the pharmacodynamic data in table format on pages 53.2/198-222 and 53.2/243-267. The final study report does not interpret the pharmacodynamic data except to state on page 53.2/114 that "in general there does not seem to be any significant relationship between effect and either C_{avg} or dose (mg/kg)". [ ] b(4) [ ] The reviewer believes the sponsor did not fairly meet this requirement. Also see pages 53.2/8-9] N

Indication: N/A

Detrusor hyperreflexia due to neurogenic conditions [See pages 53.2/10, 53.2/52, and 53.5/44] Y

Study design: N/A

24-week, open label, multiple-dose level, safety, dose response study [See pages 53.2/48-51and 53.5/46-47] Y There will be a PK/PD substudy. [See pages 53.2/48-51and 53.5/46-47] Y

For patients receiving oxybutynin chloride, the baseline urodynamic evaluation will be performed after a 3-7 day washout period off medication. [See pages 53.2/49 and 53.5/47] Y Urodynamic evaluation will be repeated at the Week 12 Visit. [See pages 53.2/49 and 53.5/47] Y For patients who withdraw prior to Week 12 Visit, an attempt will be made to repeat urodynamic evaluation while patient is still on the study dose of oxybutynin and before patient withdrawal. [See pages 53.2/49 and 53.5/72] Y

Age group in which study will be performed: N/A

Ages six to fifteen years [110 of the enrolled patients were aged 6 to 15 years. Per page 53.2/78, 5 of the 116 enrolled patients were less than age 6 at the time of enrollment and one was over age 15. These six patients were protocol deviations. Also see pages 53.2/10, 53.2/52, 53.2/132, and 53.5/44] Y

Number of patients to be studied: N/A

Enroll approximately 140 patients with approximately equal numbers of patients between the six to ten and eleven to fifteen age groups, to ensure a total of approximately 50 patients finishing 24 weeks of treatment with oxybutynin. [Overall 116 patients were enrolled; of

which 6 were not aged six to fifteen years and were major protocol violators. The reviewer is not willing to accept that 110 patients is approximately 140 patients, since the missing 30 patients represent 21% of the anticipated 140 patients. Of the 110 enrolled patients aged 6-16 years, 67 were aged 6-10 (61%) and 43 were aged 11-15 (39%). The reviewer accepts this as approximately equal numbers of patients between the six to ten and eleven to fifteen age groups. The sponsor divided the 116 enrolled patients into two cohorts, which was not planned in the Protocol or in Amendment #1. In the interim study report submitted in SE1-009, the sponsor only submitted complete safety and efficacy data on the Initial Cohort, which consisted of 60 patients who were enrolled as of May 24, 2001 and either completed 24 weeks of treatment by November 7, 2001 or discontinued from the study prematurely. In the Initial Cohort per the listing of exposure to study medication and termination reasons on pages 53.7/217-228, 53 patients completed 24-weeks or more of treatment with oxybutynin. Also see pages 53.2/13 and 53.2/74-76] N The PK subgroup will include a minimum of 32 patients with approximately 8 patients and a minimum of 5 patients on the syrup formulation, approximately 8 patients and a minimum of 5 patients on the tablet formulation, and approximately 8 patients and a minimum of 5 patients on the extended release formulation. [PK data was obtained on 42 patients: 12 on syrup, 11 on tablets, and 19 on XL. See pages 53.2/75, 53.2/115, 53.3/166, and 53.3/168.] Y

Study endpoints: N/A

Primary endpoint: volume of void. [See pages 53.2/13, 53.2/62, 53.5/71, 53.2/98, 53.7/242-356, and 53.8/1-126] Y *Other endpoints:* appropriate urodynamic evaluations, which may include maximal bladder capacity, intravesical pressure at maximal bladder capacity, and presence of uninhibited detrusor contractions. [See pages 53.2/79, 53.5/73, 53.5/92 and 53.8/78-126] Y In addition, we are requesting an assessment of occurrence of accidents/leakage episodes. [See page 53.2/62, 53.2/101, 53.5/72, 53.7/242-356, and 53.8/1-126] Y

PK: appropriate stereospecific analysis of drug and metabolite plasma profiles; the sampling should be adequate to characterize the complete PK profile in this age group [See pages 53.2/63-66, 53.2/113-127, 53.5/60-62, and 53.8/133-272] Y

Dose(in mg per kg)-effect (urodynamic) and concentration-effect (urodynamic) [The sponsor concluded on page 53.2/114 that in general there does not seem to be any significant relationship between effect and either C_{avg} or dose (mg/kg). Also see pages 53.2/8-9, 53.2/71, 53.2/113-114, 53.2/198-222 and 53.2/243-267, 53.5/75] Y

Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular and laboratory parameters [See pages 53.2/58-62, 53.2/80-98, 53.4/75-196, 53.4/245-249] Y

Safety: Number of patients terminated prematurely [Of the 60 patients in the Initial Cohort, 1.7% or one subject (#101) terminated prematurely due to personal reason-see page 53.2/131 and 53.7/133. The sponsor stated on page 53.2/82 that none of the Initial Cohort patients terminated prematurely from the study because of safety reasons. Also see pages 53.2/54-55] Y

Drug information: N/A

The drug products to be used in this study are the following commercially available formulations: Ditropan (oxybutynin chloride) Syrup, 5 mg/5 mL; Ditropan (oxybutynin

chloride) Tablets, 5 mg; or Ditropan XL (oxybutynin chloride) Tablets, 10 mg and 15 mg. [Ditropan XL® 5 mg tablets were administered in this study. See pages 53.2/55-57] N

For Ditropan (oxybutynin chloride) Syrup 5 mg/5 mL and for Ditropan (oxybutynin chloride) Tablets 5 mg, a total daily dose of 10 mg or 15 mg will be administered orally divided into two or three doses. For Ditropan XL (oxybutynin chloride) Tablets 10 mg and 15 mg, a total daily dose of 10 mg or 15 mg will be administered orally in one dose. [Per pages 53.7/116-132, 27 of the 116 enrolled patient (which included the 5 of the 60 Initial Cohort patients) were not dosing with a total daily dose of 10 or 15 mg oxybutynin at enrollment and were entrance criteria violators. Per page 53.3/9, 20 of the 116 enrolled patients were dosing with <10 mg or >15 mg total daily dose of oxybutynin. Six patients received oxybutynin syrup divided into four doses per day (#401 on page 53.7/230, #904 on page 53.7/236, #1003 on page 53.7/236, #1701 on page 53.7/237, #1703 on page 53.7/238, and #2602 on page 53.7/239) and were protocol deviations. Three patients (#104 on page 53.7/229, #605 on page 53.7/231, #620 on page 53.7/233, #1401 on page 53.7/237, interrupted study drug during the trial and were protocol deviations. Two patients (#707 per page 53.7/234 and #2001 on page 53.7/238) received Ditropan XL 5 mg once daily, with 5-mg tablets. One patient (#3607) dosed twice a day with Ditropan XL for a total daily dose of 10 mg with 5-mg tablets per page 53.7/241. One patient (#1701) was on a total daily dose of 7.5 mg intravesical immediate release oxybutynin tablets upon enrollment and during the study per pages 53.7/145, 53.7/224 and 53.7/237. Also see pages 53.2/55-57, 53.2/72 and 53.7/229-241.] N

Drug specific safety concerns: N/A

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents (e.g. constipation, dry mouth). [See page 53.2/85-86] Y Patients unable to swallow the Ditropan®XL Tablets whole should be placed on Ditropan® Syrup or Ditropan® Tablets because chewing, dividing, or crushing the Ditropan® XL Tablets could be unsafe. [See page 53.2/54] Y

Statistical information: N/A

PK: For each of the two age subgroups, for each of the two dose levels (10 and 15 mg), and for each dosage form, descriptive stereospecific analysis are to be performed to include reporting of AUC, C_{max}, and C_{min} for drug and metabolite. [See pages 53.2/70-71, 53.2/113-127, 53.5/60-62, and 53.8/133-272] Y

Urodynamic: Urodynamic measurements are to be tabulated and contrasted from baseline to end of study, and the measurements will be categorized and grouped according to total daily dose, dosage form, and age subgroup. [See pages 53.2/8-9, 53.2/71, 53.2/198-222 and 53.2/243-267, 53.5/75] Y Changes in void volume over time are to be described in a similar manner. [See pages 53.2/98-103 and 53.2/268-294] Y

Safety: Safety measurements are to be tabulated. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data. [See pages 53.2/58-62, 53.2/80-98, 53.4/75-195, 53.4/245-249] Y

Labeling that may result from the study: N/A

Appropriate changes to the label to incorporate the study results will be made. [See pages 53.1/36-89] Y

Format of reports to be submitted: N/A

A final study report will be submitted. [Protocol C-2000-042-01 is ongoing. The reviewer considers that the sponsor has submitted an incomplete study report since it contains the complete efficacy and safety data only on the 60 subjects in the Initial Cohort. The reviewer considers that the sponsor has not fairly responded to the requirement for a final study report to be submitted. See pages 53.2/10-129] N We recommend that you follow the July 1996 ICH (E3) guideline for structure and content of clinical study report. N/A The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation. [The Pharmacodynamic data was not fully interpreted in the submitted final study report. See pages 53.2/10-129] N

Time frame for submitting reports of the study: N/A

Report of the above study must be submitted to the Agency on or before December 15, 2002. [See Cover Letter 53.1] Y Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request. N/A

Critical Analyses: N/A

Provide a critical analysis of urodynamic data in adults with detrusor hyperreflexia due to neurogenic conditions treated with oxybutynin chloride. [See pages 53.15/186-406 and 53.16/1-399] Y This will be submitted with the final study reports. [See pages 53.15/186-406 and 53.16/1-399] Y The analysis will review clinical trial data and the published literature and will describe the dose-effect (urodynamic) of oxybutynin. [See pages 53.15/186-406 and 53.16/1-399] Y

Provide a critical analysis of oxybutynin usage in pediatric patients with emphasis on its safety profile, PK, PD, and efficacy. [See pages 53.15/186-406 and 53.16/1-399] Y This will be submitted with the final study reports. [The two critical analyses were combined into one report. See pages 53.15/186-406 and 53.16/1-399] Y

Recommendation:

It should be conveyed to the Pediatric Exclusivity Board that the requirements listed in the Written Request dated November 30, 2000 appear to be all met for Study #1 (Protocol C-2000-043-00), however they do not appear to be met for Study #2 (Protocol C-2000-042-01).

The deficiencies in Study #2 (Protocol C-2000-042-01) identified at this point include:

1) Incomplete final study report
2) Inadequate interpretation of the pharmacodynamic data.
3) Insufficient enrollment (116 patients with six patients <6 or >15 years of age)
4) Insufficient number of patients (N=34) who completed the requested 24-weeks of treatment with the requested oxybutynin total daily doses, tablet doses, and frequency of administration during entire treatment period (see unshaded patients listed in Attachment #1 entitled "Table #1: Study C-2000-042-01 Data for 53 patients in Initial Cohort who completed 24-weeks of oxybutynin treatment")

cc: Original NDA 20-897

HFD-580: V. Raczkowski, S. Allen, D. Shames, M. Hirsch, B. Gierhart, E. Farinas, and T. Crescenzi

Appears This Way
On Original

Attachment #1:
Table #1: **Study C-2000-042-01** Data for 53 patients in Initial Cohort who completed 24-weeks of oxybutynin treatment[1]

Patient number	Aged <6 or >15	Stopped treatment during 24 week period	Only treated with requested 10-15 mg total daily dose	Only treated with oxybutynin at requested frequency of administration	Only treated with requested tablet doses
102	N	Y-7 days	Y	Y	Y
104	N	Y-11 days	Y	Y	Y
105	N	N	Y	Y	Y
302	N	N	Y	Y	Y
401*	Y-Age 4	N	Y	N-Increased to QID[2] for 17 days	Y
501	N	N	Y	Y	Y
502	N	N	Y	Y	Y
601*	Y-Age 5	N	Y	Y	Y
602	N	N	Y	Y	Y
603	N	N	Y	Y	Y
604	N	N	N-Increased to 20 mg at Week 14	Y	Y
606	N	N	Y	Y	Y
607	N	N	Y	Y	Y
608	N	N	Y	Y	Y
610	N	N	Y	Y	Y
612	N	N	N-Increased to 20 mg at Week 16	Y	Y
613	N	N	Y	Y	Y
614	N	N	N-Increased to 20 mg at Week 15	Y	Y
615	N	N	Y	Y	Y
616	N	N	Y	Y	Y
617	N	N	Y	Y	Y
618	N	N	N-Increased to 20 mg at Week 12	Y	Y
620	N	Y- 2 days	Y	Y	Y

[1] Data was compiled from the following four Appendix in Volume 53.7:

- Appendix 13.2.1-1 entitled "Listing of Entrance Criteria Violations (Screened Patients)" on page 53.7/116-133
- Appendix 13.2.1-3 entitled "Listing of Protocol Deviations (Enrolled Patients)" on page 53.7/134-150
- Appendix 13.2.3-1 entitled "Listing of Exposure to Study Medication and Termination Reasons (Enrolled Patients)" on page 53.7/217-228
- Appendix 13.2.3-2 entitled "Listing of Initial Dosing Regimen and Dose Adjustments after Enrollment (Enrolled Patients)" on page 53.7/229-241

[2] QID is used for administration of treatment four times a day
*Major protocol violation

Patient number	Aged <6 or >15	Stopped treatment during 24 week period	Only treated with requested 10-15 mg total daily dose	Only treated with oxybutynin at requested frequency of administration	Only treated with requested tablet doses
622*	Y-age 5	N	Y	Y	Y
701	N	N	Y	Y	Y
702	N	N	Y	Y	Y
704	N	N	Y	Y	Y
705	N	N	Y	Y	Y
706	N	N	Y	Y	Y
801	N	N	Y	Y	Y
802*	N	N	N-22.5 mg/day	Y	Y
803	N	N	Y	Y	Y
804	N	N	Y	Y	Y
805	N	N	Y	Y	Y
806	N	N	Y	Y	Y
807	N	N	Y	Y	Y
808	N	N	Y	Y	Y
809	N	N	Y	Y	Y
901	N	N	Y	Y	Y
902	N	N	Y	Y	Y
903	N	N	Y	Y	Y
904*	N	N	N-30 mg	N-QID	Y
1001	N	Y-one day	Y	Y	Y
1002	N	Y-1.5 days	Y	Y	Y
1201	N	N	Y	Y	Y
1202*	Y-Age 16	N	Y	Y	Y
1502	N	N	Y	Y	Y
1503*	N	N	N-5 mg/day	Y	N-Ditropan XL 5 mg
1701*	N	N	N-7.5 mg/day intravesical for 22 days	N-QID for 23 weeks	Y
1702	N	N	Y	Y	Y
1703	N	N	Y	N-QID	Y
1704	N	N	Y	Y	Y
1705*	N	N	N-7.5 mg/day	Y	Y

QID is used for administration of treatment four times a day
*Major protocol violation

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brenda Gierhart
2/1/02 02:41:57 PM
MEDICAL OFFICER

Mark S. Hirsch
2/3/02 10:11:12 AM
MEDICAL OFFICER
1) Please see my memo dated 24 January 2001.
2) Please note that shaded areas of Dr. Gierhart's memo may not transmit properly to filing system for technical reasons.

Medical Officer's Filing Memo

To:	Dan Shames, MD Acting Director, HFD-580
Through:	Mark Hirsch, MD Team Leader, HFD-580
From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
Date:	February 4, 2002
Re:	NDA 20-897 SE1-009 Ditropan XL® (oxybutynin chloride) NDA 18-211 SE1-016 Ditropan® Syrup (oxybutynin chloride) NDA 17-577 SE1-033 Ditropan® Tablet (oxybutynin chloride) ALZA Corporation Correspondence Date: December 7, 2001 Date Received: December 7, 2001

Current submission:
A Written Request (WR) letter dated November 30, 2000 asked ALZA Corporation to perform two pediatric studies with oxybutynin chloride and to prepare two critical analyses. In the current 43-volume submission **SE1-009**, the sponsor has responded to the WR by submitting one final study report, C-2000-043-00 (Study #1 in the Written Request, a pharmacokinetic and pharmacodynamic study in 15 patients), one interim study report, C-2000-042-01 (Study #2 in the Written Request, a safety and dose-response study currently ongoing in 116 patients), and two critical analyses. The filing meeting for NDA 20-897: SE1-009 is scheduled for February 4, 2002.

The pertinent issue is whether SE1-009 should be accepted for filing. There are two major issues relevant to this filing decision.

1) Since Study report C-2000-042-01 is an interim report, final complete data sets were not submitted. Per the sponsor, C-2000-042-01 is still ongoing and enrollment closed November 2, 2001. By my review of the enrolled patients listing, the last patient enrolled on October 25, 2001 and should complete the study on April 11, 2002, since it is a 24-week trial. The sponsor has interpreted the interim efficacy data as having no clear dose-response or concentration-response relationship in terms of urodynamic effect [ ] b(4)
[ ] Based upon this new information, the sponsor proposed minimal changes to the label.

Reviewer's comment:
It is clear that Study Report C-2000-042-01 is an interim study report. Thus all data relevant to administration of Ditropan in children aged 6-15 may not become available to the Division. While this may limit the review, the reviewer still believes that the clinical

information already submitted may yield important clinical findings which could support labeling. Thus on a clinical basis, this part of the submission supports filing.

2) b(4)

b(4)

Recommendation:

1) Recommend accepting NDA 20-897 SE1-009 for filing.
2) The following comments should be conveyed to the Sponsor:
   - Clarify if the study report for C-2000-042-01 is an interim study report.
   - If the study report for C-2000-042-01 is an interim study report, provide the projected completion date for the study, and your plans for any additional submissions of data, either in interim or final report format.

cc: Original NDA 20-897
HFD-580: S. Allen, D. Shames, M. Hirsch, B. Gierhart, and E. Farinas

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ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brenda Gierhart
2/4/02 03:19:35 PM
MEDICAL OFFICER

Mark S. Hirsch
2/5/02 11:41:47 AM
MEDICAL OFFICER
I concur.

Daniel A. Shames
2/5/02 03:51:25 PM
MEDICAL OFFICER

Medical Officer's Filing Memo

To:	Dan Shames, MD Acting Director, HFD-580
Through:	Mark Hirsch, MD Team Leader, HFD-580
From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
Date:	February 4, 2002
Re:	NDA 20-897 SE1-009 Ditropan XL® (oxybutynin chloride) NDA 18-211 SE1-016 Ditropan® Syrup (oxybutynin chloride) NDA 17-577 SE1-033 Ditropan® Tablet (oxybutynin chloride) ALZA Corporation Correspondence Date: December 7, 2001 Date Received: December 7, 2001

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A Written Request (WR) letter dated November 30, 2000 asked ALZA Corporation to perform two pediatric studies with oxybutynin chloride and to prepare two critical analyses. In the current 43-volume submission **SE1-009**, the sponsor has responded to the WR by submitting one final study report, C-2000-043-00 (Study #1 in the Written Request, a pharmacokinetic and pharmacodynamic study in 15 patients), one interim study report, C-2000-042-01 (Study #2 in the Written Request, a safety and dose-response study currently ongoing in 116 patients), and two critical analyses. The filing meeting for NDA 20-897: SE1-009 is scheduled for February 4, 2002.

The pertinent issue is whether SE1-009 should be accepted for filing. There are two major issues relevant to this filing decision.

1) Since Study report C-2000-042-01 is an interim report, final complete data sets were not submitted. Per the sponsor, C-2000-042-01 is still ongoing and enrollment closed November 2, 2001. By my review of the enrolled patients listing, the last patient enrolled on October 25, 2001 and should complete the study on April 11, 2002, since it is a 24-week trial. The sponsor has interpreted the interim efficacy data as having no clear dose-response or concentration-response relationship in terms of urodynamic effect [ ] [ ] Based upon this new information, the sponsor proposed minimal changes to the label. b(4)

Reviewer's comment:
It is clear that Study Report C-2000-042-01 is an interim study report. Thus all data relevant to administration of Ditropan in children aged 6-15 may not become available to the Division. While this may limit the review, the reviewer still believes that the clinical

information already submitted may yield important clinical findings which could support labeling. Thus on a clinical basis, this part of the submission supports filing.

2) b(4)

b(4)

Recommendation:

1) Recommend accepting NDA 20-897 SE1-009 for filing.
2) The following comments should be conveyed to the Sponsor:
   - Clarify if the study report for C-2000-042-01 is an interim study report.
   - If the study report for C-2000-042-01 is an interim study report, provide the projected completion date for the study, and your plans for any additional submissions of data, either in interim or final report format.

cc: Original NDA 20-897
HFD-580: S. Allen, D. Shames, M. Hirsch, B. Gierhart, and E. Farinas

APPEARS THIS WAY
ON ORIGINAL

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/s/

Brenda Gierhart
2/11/02 04:54:54 PM
MEDICAL OFFICER

Mark S. Hirsch
2/14/02 01:21:54 PM
MEDICAL OFFICER

NDA 20-987 SE8-009

Medical Team Leader's Memorandum

Date submitted: December 7, 2001
Date received: December 7, 2001
Memo completed: January 24, 2001

Drug: Ditropan XL® (oxybutnin chloride)
Doses available: 5 mg, 10 mg and 15 mg
Sponsor: ALZA Corporation

I. Regulatory background:
Ditropan (oxybutnin chloride) is an approved drug for the treatment of urinary incontinence. It has been marketed for over a decade, with vast clinical exposure in both adults and children.

Ditropan XL is a novel, once-daily formulation of Ditropan. Drug product is encased in a special shell, through which a single hole has been laser-drilled. As the tablet proceeds down the gut, drug is osmotically pumped out of the hole. Thus, Ditropan is delivered continuously for one full day. Ditropan XL was approved on December 16, 1998.

On October 6, 2000, sponsor submitted a Proposed Pediatric Study Request. On November 30, 2000, ODE 3 issued sponsor a Written Request (WR) letter, stating that

> "To obtain needed pediatric information on oxybutynin chloride, the Food and Drug Administration is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act) that you submit information from the following two studies and two critical analyses."

The WR letter described two individual studies. The first study ("Study #1") was intended to evaluate the pharmacokinetic profile of Ditropan syrup in pediatric patients aged 1 to 5 years with detrusor hyperreflexia. In addition, the study was meant to evaluate dose-effect and concentration-effect (using pharmacodynamic endpoints) for Ditropan syrup in these patients.

The second study (Study #2) was intended to document the safety and tolerability of Ditropan Syrup, Ditropan Tablets, or Ditropan XL in pediatric patients aged six to fifteen years with detrusor hyperreflexia. In addition, the sponsor was asked to evaluate dose-effect and concentration effect in order to establish safe and effective oxybutynin dosage regimens in these patients.

On December 7, 2001, the sponsor submitted the results from two trials that they believe meet the terms of the Written Request.

II. Primary medical officer's review:
Since this submission was received on December 7, 2001, the Division was required to forward "a completed package" to the Exclusivity Board by January 21, 2001. This package should include the following:

1. Pediatric Exclusivity Determination Checklist
2. Cover letter from submission
3. Written Request and any Amendments

4. Summary/synopsis of studies submitted
5. Annotated Written Request (if included in application)
6. Proposed labeling.

The Division requested and was granted presentation time at the February 1, 2001 meeting of the Exclusivity Board.

The primary medical officer, Dr. Gierhart, reviewed SE1-008 on its face, for purposes of completing the Pediatric Exclusivity Determination Checklist and for presenting to the Pediatric Exclusivity Board (draft review dated December 20, 2001). For this type of review, the Division is asked to provide an opinion on whether the submitted studies respond "fairly" to the terms of the WR. As Dr. Galson's memorandum of September 19, 2001 states, "If the Division believes that all terms have not been met and that the submission does not "fairly respond" (sic) to the WR as a whole, it must explain that finding in writing. This memorandum can be prepared either before, or no later than 1 week after following the Board meeting. That memorandum should document, among other things, relevant prior contacts with the sponsors that potentially bear on the sufficiency of the studies or their responsiveness to the WR."

III. Major issues from the MO draft review:

1. In her draft review dated December 20, 2001, Dr. Gierhart concluded that all WR terms for "Study #1" were met in the final study report for Protocol C-2000-043-00 (children aged 1 to 5 years).

2. Dr. Gierhart concluded that the information provided for "Study #2" in the final study report for Protocol C-2000-042-01 (children aged sic to fifteen) did not respond "fairly" to the terms of Written Request. This decision was based on the following:

   a. **The final study report was "incomplete".** – The WR specified a final study report.

   b. **There was "inadequate interpretation" of the pharmacodynamic data.** – The WR specified that urodynamic measurements (PD data) would be tabulated and contrasted from baseline to end of study, and these measurements would be categorized and grouped according to the total daily dose, dosage form, and age subgroup. Of relevance, the secondary objective of the trial was to evaluate oxybutynin dose-effect (using urodynamic measurements) and concentration-effect (using urodynamic measurements) of Ditropan XL extended-release tablets and Ditropan tablets/syrup to establish safe and effective dosage regimens in the study population.

   c. **There was "insufficient" enrollment (116 patients with six patients <6 or >15 years of age).** – The WR specified that "approximately 140 patients" would be enrolled to ensure a total of approximately 50 patients finishing 24 weeks of treatment with oxybutynin.

   d. **There was "insufficient" number of patients (N=34) who completed the requested 24 weeks of treatment with the requested oxybutynin daily doses, tablet doses, and frequency of administration during the entire treatment period.** – The WR specified that a total of "approximately 50 patients" would finish 24 weeks of treatment with oxybutynin.

3. Dr. Gierhart concluded that the answer to the final question on the "Pediatric Exclusivity Determination Checklist" ("Did the studies fairly respond to the Written Request?") was "No".

4. Dr. Gierhart also concluded that the answer to Question #5 on the Checklist ("If there was no written agreement, were the studies conducted in accord with good scientific principles?") was "No".

IV. Medical team leader's comments:

1. The issue of an "incomplete" versus "final" study report for Study# 2.

The cover page for Protocol C-2000-042 describes this report as a "Pediatric Study Report". While the word "final" does not appear on the report, the study dates are listed as:

First patient treated – 16 February 2001
Last patient completed – 7 November 2001

In this report, the sponsor has divided the enrolled population into two groups:

1. an *Initial Cohort* population – consisting of a subgroup of 60 patients enrolled between 16 February 2001 and 25 May 2001.
2. an *All Enrolled Patients* population. – consisting of 116 patients enrolled between 16 February 2001 and 2 November 2001.

The number of patients to be studied in this trial under the terms of the WR was "enroll approximately 140 patients...to ensure a total of approximately 50 patients finishing 24 weeks of treatment with oxybutynin."

My impression, therefore, is that the sponsor conducted an interim analysis using a data cut-off date of November 7, 2001, at which time there were 49 patients with at least 24 weeks of exposure "ensured". Based upon this data cut-off, the sponsor then wrote a report that analyzes efficacy and safety separately for the Initial Cohort group and the All Enrolled group.

While this apparently "arbitrary" safety cut-off date and separation of study population troubles the primary MO, I am not disturbed. First, the WR emphasizes that the sponsor should ensure that approximately 50 patients finish 24 weeks of treatment. This stipulation implies that FDA is particularly interested in the results from that cohort (e.g. for long-term safety data). Second, the sponsor does report all information on all enrolled patients up to the safety cut-off date. In fact, there is per-protocol pharmacodynamic data (urodynamics) for 78 individuals at Week 12.

In summary, while this is not a true "final report", and while it does not adhere literally to the "Format of study report to be submitted" section of the WR, it adheres to the spirit of WR.

In sum, I believe that this report fairly responds to the "format" element of the WR.

2. The issue of "inadequate interpretation" of the pharmacodynamic data.

The WR specified that urodynamic measurements (PD data) would be tabulated and contrasted from baseline to end of study, and these measurements would be categorized and grouped

according to the total daily dose, dosage form, and age subgroup. This was done in the submission.

Of relevence, the secondary objective of the trial was to evaluate oxybutynin dose-effect (using urodynamic measurements) and concentration-effect (using urodynamic measurements) of Ditropan XL extended-release tablets and Ditropan tablets/syrup with the intent of establishling safe and effective dosage regimens in the study population.

The sponsor did analyze change-from-baseline in urodynamic parameters (PD) as a function of average concentration and dose (Figures 12.2.3-6). These did not demonstrate any real relationships between PD effect and either dose or concentration. The sponsor argues that "this was an expected outcome because, in general, patients were on a stable efficacious dose." I agree with the sponsor.

In sum, I believe this report responds fairly to the "objectives" element of the WR.

3. The issue of "insufficient" enrollment (116 patients with six patients <6 or >15 years of age).

The WR stipulates that approximately 140 patients should be enrolled to ensure that approximately 50 patients finish 24 weeks of treatment. The study actually enrolled 116 patients. Of these, 6 patients were outside the stipulated age range of five years to fifteen years (one was 4 years old, four were 5 years old, and one was 16 years old).

I believe that in the context of the information to be gained from this trial, all six children who were just outside the stipulated age range should not be excluded from consideration in the determination of exclusivity.

In addition, I believe that the WR identifies "ensuring approximately 50 patients finish 24 weeks of treatment" as a major reason for selecting 140 patients for enrollment. Approximately 50 patients did complete 24 weeks of treatment. Thus, enrollment of 116 patients rather than 140 patients did not preclude this outcome. Further, I do not believe that enrolling 116 patients rather than 140 substantially limited the information or conclusions from this trial.

In sum, I believe the report responds fairly to the "numbers of patients" element of the WR.

4. **The issue of "insufficient" number of patients completing the requested 24 weeks of treatment.**

The sponsor believes that 49 patients completed at least 24 weeks of treatment on oxybutynin at the requested doses, formulations and regimens. Dr. Gierhart believes only 34 patients fit this criteria.

I have reviewed Dr. Gierhart's reasons for excluding these patients. These include wrong age (N=3), wrong total daily dose (N=9), stopped treatment briefly during the 24 weeks (N= 5), wrong frequency of daily dosing (N=4), and wrong formulation (N=1). Some patients had more than one reason for exclusion.

The wrong age category excluded children of ages 4, 5 and 16 years. The pre-specified age range = 5 to 15 years.

The wrong total daily dose category excluded 6 patients who required increase of total daily dose to 20 mg, 22.5 mg and 30 mg per day, 2 patients who took less than the required total daily dose (5 mg and 7.5 mg per day), and one patient who received intravesical oxybutynin. The pre-specified total daily dose = 10 mg or 15 mg.

The wrong frequency category included 4 patients using four times daily dosing. The pre-specified frequency of dosing = two or three daily doses.

The wrong formulation category included one patient who received Ditropan XL 5 mg tablets.

Overall, I believe that these minor differences from the WR are not meaningful. I still agree with sponsor that approximately 50 patients finished 24 weeks of therapy with the proscribed drugs, dosages, and formulations.

Thus, I believe the sponsor has responded fairly to the "Drug information" section of the WR.

V. Medical team leader's conclusion:

1. The studies submitted appear to fairly respond to the Written Request as a whole.
2. The studies appear to have been conducted in accord with good scientific principles.

VI. Supervisory medical officer's recommendation:

1. I recommend that the Division present the divergent views of the medical officer and medical team leader to the Exclusivity Board at its next meeting on February 1, 2002.

2. I recommend that both the medical officer and medical team leader's draft memos be forwarded to the Board in the meeting package.

Mark S. Hirsch
Medical Team Leader, Urology
Division of Reproductive and Urologic Drug Products
Arch NDA 20-897
Cc: HFD-580/Div File
HFD-580/DShames/BGierhart/EFarinas

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/s/

Mark S. Hirsch
2/3/02 10:16:56 AM
MEDICAL OFFICER

Daniel A. Shames
2/5/02 01:40:08 PM
MEDICAL OFFICER

NDA 20-987 **SE8**-009

Medical Team Leader's Memorandum

Date submitted: December 7, 2001
Date received: December 7, 2001
Memo completed: January 24, 2001

Drug: Ditropan XL® (oxybutnin chloride)
Doses available: 5 mg, 10 mg and 15 mg
Sponsor: ALZA Corporation

I. Regulatory background:
Ditropan (oxybutnin chloride) is an approved drug for the treatment of urinary incontinence. It has been marketed for over a decade, with vast clinical exposure in both adults and children.

Ditropan XL is a novel, once-daily formulation of Ditropan. Drug product is encased in a special shell, through which a single hole has been laser-drilled. As the tablet proceeds down the gut, drug is osmotically pumped out of the hole. Thus, Ditropan is delivered continuously for one full day. Ditropan XL was approved on December 16, 1998.

On October 6, 2000, sponsor submitted a Proposed Pediatric Study Request. On November 30, 2000, ODE 3 issued sponsor a Written Request (WR) letter, stating that

> "To obtain needed pediatric information on oxybutynin chloride, the Food and Drug Administration is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act) that you submit information from the following two studies and two critical analyses."

The WR letter described two individual studies. The first study ("Study #1") was intended to evaluate the pharmacokinetic profile of Ditropan syrup in pediatric patients aged 1 to 5 years with detrusor hyperreflexia. In addition, the study was meant to evaluate dose-effect and concentration-effect (using pharmacodynamic endpoints) for Ditropan syrup in these patients.

The second study (Study #2) was intended to document the safety and tolerability of Ditropan Syrup, Ditropan Tablets, or Ditropan XL in pediatric patients aged six to fifteen years with detrusor hyperreflexia. In addition, the sponsor was asked to evaluate dose-effect and concentration effect in order to establish safe and effective oxybutynin dosage regimens in these patients.

On December 7, 2001, the sponsor submitted the results from two trials that they believe meet the terms of the Written Request.

II. Primary medical officer's review:
Since this submission was received on December 7, 2001, the Division was required to forward "a completed package" to the Exclusivity Board by January 21, 2001. This package should include the following:

1. Pediatric Exclusivity Determination Checklist
2. Cover letter from submission
3. Written Request and any Amendments

4. Summary/synopsis of studies submitted
5. Annotated Written Request (if included in application)
6. Proposed labeling.

The Division requested and was granted presentation time at the February 1, 2001 meeting of the Exclusivity Board.

The primary medical officer, Dr. Gierhart, reviewed SE1-008 on its face, for purposes of completing the Pediatric Exclusivity Determination Checklist and for presenting to the Pediatric Exclusivity Board (draft review dated December 20, 2001). For this type of review, the Division is asked to provide an opinion on whether the submitted studies respond "fairly" to the terms of the WR. As Dr. Galson's memorandum of September 19, 2001 states, "If the Division believes that all terms have not been met and that the submission does not "fairly respond" (sic) to the WR as a whole, it must explain that finding in writing. This memorandum can be prepared either before, or no later than 1 week after following the Board meeting. That memorandum should document, among other things, relevant prior contacts with the sponsors that potentially bear on the sufficiency of the studies or their responsiveness to the WR."

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2. Dr. Gierhart concluded that the information provided for "Study #2" in the final study report for Protocol C-2000-042-01 (children aged sic to fifteen) did not respond "fairly" to the terms of Written Request. This decision was based on the following:

   a. **The final study report was "incomplete".** – The WR specified a final study report.

   b. **There was "inadequate interpretation" of the pharmacodynamic data.** – The WR specified that urodynamic measurements (PD data) would be tabulated and contrasted from baseline to end of study, and these measurements would be categorized and grouped according to the total daily dose, dosage form, and age subgroup. Of relevance, the secondary objective of the trial was to evaluate oxybutynin dose-effect (using urodynamic measurements) and concentration-effect (using urodynamic measurements) of Ditropan XL extended-release tablets and Ditropan tablets/syrup to establish safe and effective dosage regimens in the study population.

   c. **There was "insufficient" enrollment (116 patients with six patients <6 or >15 years of age).** – The WR specified that "approximately 140 patients" would be enrolled to ensure a total of approximately 50 patients finishing 24 weeks of treatment with oxybutynin.

   d. **There was "insufficient" number of patients (N=34) who completed the requested 24 weeks of treatment with the requested oxybutynin daily doses, tablet doses, and frequency of administration during the entire treatment period.** – The WR specified that a total of "approximately 50 patients" would finish 24 weeks of treatment with oxybutynin.

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4. Dr. Gierhart also concluded that the answer to Question #5 on the Checklist ("If there was no written agreement, were the studies conducted in accord with good scientific principles?") was "No".

IV. Medical team leader's comments:

1. The issue of an "incomplete" versus "final" study report for Study# 2.

The cover page for Protocol C-2000-042 describes this report as a "Pediatric Study Report". While the word "final" does not appear on the report, the study dates are listed as:

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In sum, I believe that this report fairly responds to the "format" element of the WR.

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according to the total daily dose, dosage form, and age subgroup. This was done in the submission.

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I believe that in the context of the information to be gained from this trial, all six children who were just outside the stipulated age range should not be excluded from consideration in the determination of exclusivity.

In addition, I believe that the WR identifies "ensuring approximately 50 patients finish 24 weeks of treatment" as a major reason for selecting 140 patients for enrollment. Approximately 50 patients did complete 24 weeks of treatment. Thus, enrollment of 116 patients rather than 140 patients did not preclude this outcome. Further, I do not believe that enrolling 116 patients rather than 140 substantially limited the information or conclusions from this trial.

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The wrong frequency category included 4 patients using four times daily dosing. The pre-specified frequency of dosing = two or three daily doses.

The wrong formulation category included one patient who received Ditropan XL 5 mg tablets.

Overall, I believe that these minor differences from the WR are not meaningful. I still agree with sponsor that approximately 50 patients finished 24 weeks of therapy with the proscribed drugs, dosages, and formulations.

Thus, I believe the sponsor has responded fairly to the "Drug information" section of the WR.

V. Medical team leader's conclusion:

1. The studies submitted appear to fairly respond to the Written Request as a whole.
2. The studies appear to have been conducted in accord with good scientific principles.

VI. Supervisory medical officer's recommendation:

1. I recommend that the Division present the divergent views of the medical officer and medical team leader to the Exclusivity Board at its next meeting on February 1, 2002.

2. I recommend that both the medical officer and medical team leader's draft memos be forwarded to the Board in the meeting package.

Mark S. Hirsch
Medical Team Leader, Urology
Division of Reproductive and Urologic Drug Products
Arch NDA 20-897
Cc: HFD-580/Div File
HFD-580/DShames/BGierhart/EFarinas

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/s/

Mark S. Hirsch
4/9/03 01:43:12 PM
MEDICAL OFFICER

Daniel A. Shames
4/9/03 03:02:45 PM
MEDICAL OFFICER

MEMORANDUM

To:	NDA 20-897 Ditropan XL® (oxybutynin chloride) Extended Release Tablets
Through:	Mark Hirsch, MD Urology Team Leader, HFD-580
From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
Date:	March 21, 2003
Re:	NDA 20-897 SLR-010 Submitted July 2, 2002 Received July 3, 2002 NDA 20-897 Amendment to SLR-010 (BL) Submitted: December 23, 2002 Received: December 26, 2002
Sponsor:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Background:
The current labeling for Ditropan XL® (oxybutynin chloride) Extended Release Tablets is dated July 2002. On July 2, 2002 in **SLR-010**, the sponsor submitted revised draft labeling for Ditropan XL® (oxybutynin chloride) Extended Release Tablets, specifically changing the *Drug Interactions* subsection of the **PRECAUTIONS** section. By error, this submission was returned to the document room to be filed in the archival NDA after an acknowledgement letter was sent to the sponsor by the Division on July 17, 2002. The supplement had not been reviewed by the Division. The supplement was discovered in the main document room in NDA 20-897 Volume A57.1 and will now be evaluated in addition to the recent Amendment to SLR-010 (BL) that was submitted on December 23, 2002.

<u>July 2, 2002 SLR-010 Submission:</u>
Background
The sponsor was sent a regulatory letter to **NDA 20-897** on **May 8, 2001** requesting specific changes to the Ditropan XL *Drug Interactions* subsection of the **PRECAUTIONS** section regarding pharmacokinetic studies with patients concomitantly receiving cytochrome P450 enzyme inhibitors such as ketoconazole. In particular, the letter requested the current third and fourth sentences of the *Drug Interactions* subsection in the **PRECAUTIONS** section of the Ditropan XL labeling be deleted and replaced with the following four sentences:

> "Mean oxybutynin chloride plasma concentrations were approximately [ ] fold higher when DITROPAN / was administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents, (eg, itraconazole and miconazole) or macrolide antibiotics (eg, erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (ie, C_{mzx} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered."

b(4)

This request inadvertently crossed with the sponsor submitting a revised Pharmacokinetic final study report **I-98-005** entitled "Pharmacokinetic evaluation of OROS® (oxybutynin chloride) and IR oxybutynin administered alone and in the presence of Ketoconazole" to **IND 48,930** on [ ] in Serial No. [ ] after they discovered a calculation error in the original Clinical Pharmacology and Biopharmaceutics studies leading to an overestimation of oxybutynin and the primary metabolite by 2-fold. It was the recommendation of the Clinical Pharmacology and Biopharmaceutics Reviewer in his review of IND 48,930 Serial No.[ ] dated [ ] that the sponsor should make suitable alterations in the labeling based on these corrected calculated values of the drug and metabolite. This comment was conveyed to the sponsor in a regulatory letter to IND 48,930 dated November 6, 2001. b(4)

Current Submission

Due to this correction of the calculation error, the sponsor submitted in **SLR 010** revised labeling of the above Division's proposed 4 sentences to the Drug Interactions subsection of the PRECAUTIONS section of the Ditropan XL labeling. Specifically, the sponsor changed the [ ] fold higher" to only a "2 fold higher" in the first sentence, changed [ ] to "DITROPAN XL" in the first sentence, and made minor editorial changes throughout the label as follows: b(4)

- all capital letters are now used for the product name
- the addition of the **www.DITROPANXL.com** web site to the sentence following **Rx only** which currently reads "For more information call 1-888-395-1232"
- the addition of the name and logo of the new distributor, Ortho-Mc-Neil Pharmaceutical, Inc.
- deleting the number "00096531" which currently is the next to the last line in the labeling
- changing the Edition from "07/99" to "07/02"

These changes were implemented in 3Q02. The submission was reviewed.

Reviewer's comment:

1) **All the changes to the labeling proposed in SLR-010 are acceptable to the reviewer.**

December 23, 2002 Amendment to SLR-010 (BL) Submission:

As an amendment to NDA 20-897 SLR-010, the sponsor now submits revised changes to the approved product labeling for Ditropan® (oxybutynin chloride) Tablets to the **CONTRAINDICATIONS, PRECAUTIONS**, and **ADVERSE REACTIONS** sections in addition to minor editing changes throughout the labeling. The Amendment to SLR-010 (BL) is the labeling change that the sponsor stated in a letter dated October 16, 2002 that they intended to submit to be considered in the labeling review for S-009. The submission was reviewed.

Reviewer's comments:

1) **In the Amendment to SLR-010 submission, the additional minor editing changes throughout the label were all acceptable to the reviewer and were as follows:**
   - using all capital letters for the product name
   - b(4)
   - deleting the registered trademark "®" symbol from the current labeling except after in the title and in the first time the word DITROPAN XL occurs on each page of the labeling
   - adding the www.DITROPANXL.com web site to the sentence following Rx only which currently reads "For more information call 1-888-395-1232"
   - deleting "distributed, and marketed" from the sentence which currently reads "Manufactured distributed, and marketed by" in the **HOW SUPPLIED** section
   - deleting "Marketed" which currently appears next to the ALZA logo in the **HOW SUPPLIED** section

- changing the sentence "by UCB Pharma, Inc., Smyrna, GA 30080" to "Distributed and Marketed by Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ 08869"in the **HOW SUPPLIED** section
- adding the Ortho-McNeil Pharmaceutical, Inc. Logo to the **HOW SUPPLIED** section
- changing the final part number from "00096531" to "00096532" as the next to the last line of the labeling
- changing the Edition from "07/99 7/02" to "12/02" as the last line of the labeling

2) **In the Amendment to SLR-010 submission, the sponsor proposed one change to the CONTRAINDICATIONS section as follows, which is acceptable to the reviewer:**
   - The sponsor added the phrase "and other severe decreased gastrointestinal motility conditions" to the first sentence after the phrase "gastric retention".

3) **In the Amendment to SLR-010 submission, the sponsor added a [ ] before the phrase "in patients with hepatic or renal impairment and added the phrase** in patients with myasthenia gravis due to the risk of symptom aggravation" **as the last line of the General subsection of the PRECAUTIONS section. Adding the phrase is acceptable to the reviewer; however, the reviewer finds it [ ] the two phrases combined into one sentence.** b(4)

4) **In the Amendment to SLR-010 submission, the sponsor deleted the words "and myasthenia gravis" from the second sentence in the Gastrointestinal Disorders subsection of the PRECAUTIONS section. This is acceptable to the reviewer since it was added to the General subsection of the PRECAUTIONS section.**

5) [b(4)]

6) **In the Amendment to SLR-010 submission, the sponsor added a new second sentence to the second paragraph of the Drug Interactions subsection of the PRECAUTIONS section, which is acceptable to the reviewer, as follows:** "This may be of concern for drugs with a narrow therapeutic index."

7) **In the Amendment to SLR-010 submission, the sponsor deleted the current third and fourth paragraphs of the Drug Interactions subsection of the PRECAUTIONS section and added a new third paragraph to the same subsection as follows:**

> "Mean oxybutynin chloride plasma concentrations were approximately 2 fold higher when DITROPAN XL was administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents, (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C_{mzx} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered."

These changes are acceptable to the reviewer.

8) **In the Amendment to SLR-010 submission, the sponsor adds a new final paragraph to the Adverse Events with DITROPAN XL subsection of the ADVERSE REACTIONS section as follows: "Additional** rare adverse events reported from worldwide post-marketing experience with [ ] include: peripheral edema, cardiac arrythmia, tachycardia, hallucinations, convulsions, and impotence." **The sponsor also adds the words** "other" **and** "formulations" **and deletes the words** "tachycardia, hallucinations, and impotence" **from the only sentence in the subsection Adverse Events with Oxybutynin Chloride in the ADVERSE REACTIONS section and proposes the sentence to now read as follows:** "Other adverse events have been reported with other oxybutynin chloride [ ] cycloplegia, mydriasis, and suppression of lactation. **These changes are not acceptable to the reviewer since the first subsection is specifically for adverse events with Ditropan XL, the word** "arrythmias" **was misspelled, and the phrasing should be similar for the two sentences . The reviewer recommends deleting the phrase "oxybutynin chloride" and adding the word "DITROPAN XL" to the new [ ] sentence of the Adverse Events with DITROPAN XL subsection in the ADVERSE REACTIONS section, changing** "arrthmias" **to** "arrhythmias", **and changing the only sentence in the subsection Adverse Events with Oxybutynin to the following:** "Additional adverse events reported with [ ] [ ] formulations include: cyclоplegia, mydriasis, and suppression of lactation." b(4)

Recommendation:
Recommend sending the labeling in Appendix A to the sponsor as part of the labeling process for NDA 20-897 Supplement No. 009 (the pediatric efficacy supplement). If possible, the reviewer considers it appropriate to resolve pediatric efficacy Supplement No. 009 and SLR 010 at the same time.

cc: DFS re: NDA 20-897 SLR 010 and Amendment to SLR 010 (BL)
HFD-580: D. Shames, M. Hirsch, B. Gierhart, and J. King

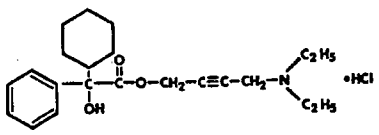
Appendix A:

DITROPAN XL®
(oxybutynin chloride)
Extended Release Tablets

DESCRIPTION
DITROPAN XL® (oxybutynin chloride) is an antispasmodic, anticholinergic agent. Each DITROPAN XL Extended Release Tablet contains 5 mg, 10 mg or 15 mg of oxybutynin chloride USP, formulated as a once-a-day controlled-release tablet for oral administration. Oxybutynin chloride is administered as a racemate of R- and S- enantiomers.

Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \bullet HCl$.

Its structural formula is:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alkalis.

DITROPAN XL also contains the following inert ingredients: cellulose acetate, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, synthetic iron oxides, titanium dioxide, polysorbate 80, sodium chloride, and butylated hydroxytoluene.

System Components and Performance
DITROPAN XL uses osmotic pressure to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice in the semipermeable membrane on the drug-layer side of the tablet. In an aqueous environment, such as the gastrointestinal tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and the push layer to expand. This expansion pushes the suspended drug out through the orifice. The semipermeable membrane controls the rate at which water permeates into the tablet core, which in turn controls the rate of drug delivery. The controlled rate of drug delivery into the gastrointestinal lumen is thus independent of pH or gastrointestinal motility. The function of DITROPAN XL depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract. Since the osmotic gradient remains constant, drug delivery remains essentially constant. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY
Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Antimuscarinic activity resides predominantly in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in in vitro studies.

Pharmacokinetics
Absorption
Following the first dose of DITROPAN XL® (oxybutynin chloride), oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter steady concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with oxybutynin.

The relative bioavailabilities of R- and S-oxybutynin from DITROPAN XL are 156% and 187%, respectively, compared with oxybutynin. The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 1. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape; Figure 1 shows the profile for R-oxybutynin.

Table 1
Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters
Following a Single Dose of DITROPAN XL 10 mg (n=43)

Parameters (units)	R-Oxybutynin		S-Oxybutynin	
C_{max} (ng/mL)	1.0	(0.6)	1.8	(1.0)
T_{max} (h)	12.7	(5.4)	11.8	(5.3)
$t_{1/2}$ (h)	13.2	(6.2)	12.4	(6.1)
$AUC_{(0-48)}$ (ng·h/mL)	18.4	(10.3)	34.2	(16.9)
AUC_{inf} (ng·h/mL)	21.3	(12.2)	39.5	(21.2)

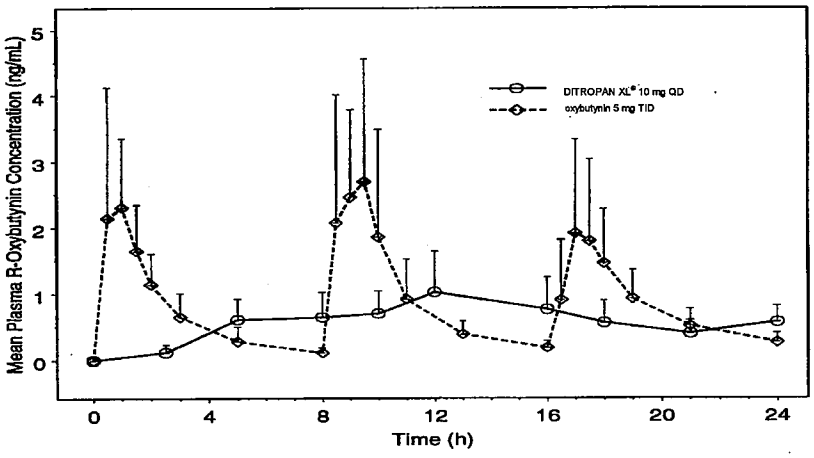


Figure 1. *Mean R-oxybutynin plasma concentrations following a single dose of DITROPAN XL 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment).*

Steady-state oxybutynin plasma concentrations are achieved by Day 3 of repeated DITROPAN XL®(oxybutynin chloride) dosing, with no observed drug accumulation or change in oxybutynin and desethyloxybutynin pharmacokinetic parameters.

Reviewer's comment:

1) **Additional pediatric pharmacokinetics labeling is currently under review under the NDA 20-897 pediatric efficacy Supplement No. 009.**

Food Effects

The rate and extent of absorption and metabolism of oxybutynin are similar under fed and fasted conditions.

Distribution

Plasma concentrations of oxybutynin decline biexponentially following intravenous or oral administration. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin chloride.

Metabolism

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active. Following DITROPAN XL administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin.

Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

Dose Proportionality
Pharmacokinetic parameters of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of 5-20 mg of DITROPAN XL are dose proportional.

Special Populations
Geriatric: The pharmacokinetics of DITROPAN XL were similar in all patients studied (up to 78 years of age).

Pediatric: The pharmacokinetics of DITROPAN XL® (oxybutynin chloride) were not evaluated in individuals younger than 18 years of age. See **PRECAUTIONS:** Pediatric Use.
Reviewer's comment:
1) **Specific labeling for this Pediatric section is currently under review under the NDA 20-897 pediatric efficacy Supplement No. 009.**

Gender: There are no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following administration of DITROPAN XL.

Race: Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of DITROPAN XL.

Renal Insufficiency: There is no experience with the use of DITROPAN XL in patients with renal insufficiency.

Hepatic Insufficiency: There is no experience with the use of DITROPAN XL in patients with hepatic insufficiency.

Drug-Drug Interactions: See **PRECAUTIONS:** Drug Interactions.

Clinical Studies
DITROPAN XL was evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (89.0%) and female (91.9%) with a mean age of 59 years (range, 18 to 98 years). Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge) as evidenced by ≥ 6 urge incontinence episodes per week and ≥ 10 micturitions per day. Study 1 was a forced dose escalation design, whereas the other studies used a dose adjustment design in which each patient's final dose was adjusted to a balance between improvement of incontinence symptoms and tolerability of side effects. Controlled studies included patients known to be responsive to oxybutynin or other anticholinergic medications, and these patients were maintained on a final dose for up to 2 weeks.

The efficacy results for the three controlled trials are presented in the following tables and figures.

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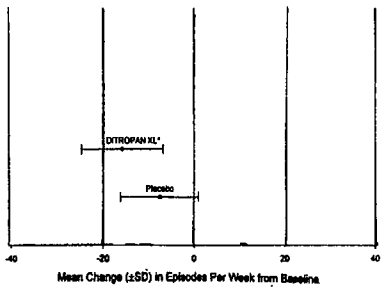
Number of Urge Urinary Incontinence Episodes Per Week

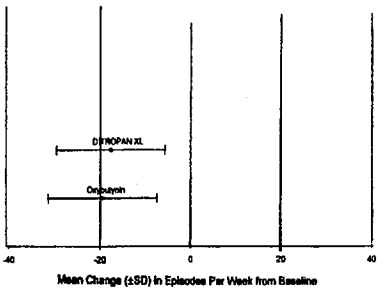
Study 1	N	DITROPAN® XL	N	Placebo
Mean Baseline	34	15.9	16	20.9
Mean (SD) Change from Baseline†	34	-15.8 (8.9)	16	-7.6 (8.6)
95% Confidence Interval for Difference (DITROPAN® XL – Placebo)		(-13.6, -2.8)*		

* The difference between DITROPAN® XL and placebo was statistically significant.
† Covariate adjusted mean with missing observations set to baseline values



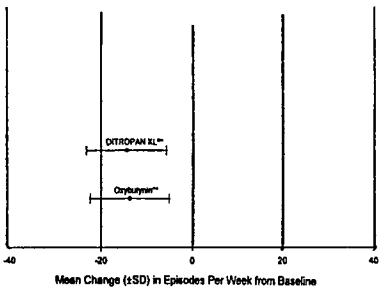
Study 2	N	DITROPAN® XL	N	oxybutynin
Mean Baseline	53	27.6	52	23.0
Mean (SD) Change from Baseline†	53	-17.6 (11.9)	52	-19.4 (11.9)
95% Confidence Interval for Difference (DITROPAN® XL – oxybutynin)		(-2.8, 6.5)		

† Covariate adjusted mean with missing observations set to baseline values



Study 3	N	DITROPAN® XL	N	oxybutynin
Mean Baseline	111	18.9	115	19.5
Mean (SD) Change from Baseline†	111	-14.5 (8.7)	115	-13.8 (8.6)
95% Confidence Interval for Difference (DITROPAN® XL – oxybutynin)		(-3.0, 1.6)**		

** The difference between DITROPAN® XL and oxybutynin fulfilled the criteria for comparable efficacy.
† Covariate adjusted mean with missing observations set to baseline values



INDICATIONS AND USAGE

DITROPAN XL® (oxybutynin chloride) is a once-daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Reviewer's comment:

1) **A new indication is currently under review under the NDA 20-897 pediatric efficacy Supplement No. 009.**

CONTRAINDICATIONS

DITROPAN XL is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

DITROPAN XL is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

General

DITROPAN XL should be used with caution in patients with hepatic or renal impairment and in patients with myasthenia gravis due to the risk of symptom aggravation.

Urinary Retention:

DITROPAN XL should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

Gastrointestinal Disorders:

DITROPAN XL should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

DITROPAN XL, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal atony.

DITROPAN XL should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

As with any other nondeformable material, caution should be used when administering DITROPAN XL to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations.

Information for Patients

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Patients should be informed that DITROPAN XL® (oxybutynin chloride) should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush tablets. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Drug Interactions
The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 2 fold higher when DITROPAN XL was administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility
A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25 and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems.

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility.

Pregnancy: Teratogenic Effects
Pregnancy Category B
Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN XL administration to women who are or who may become pregnant has not been established. Therefore, DITROPAN XL should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers
It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DITROPAN XL® (oxybutynin chloride) is administered to a nursing woman.

Pediatric Use

The safety and efficacy of DITROPAN XL in pediatric patients have not been established.

Reviewer's comment:

1) **Additional labeling for pediatric use is currently under review under the NDA 20-897 pediatric efficacy Supplement No. 009.**

Geriatric Use

The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar (See **CLINICAL PHARMACOLOGY, Pharmacokinetics,** ***Special Populations***: *Gender*).

ADVERSE REACTIONS

Adverse Events with DITROPAN XL

The safety and efficacy of DITROPAN XL was evaluated in a total of 580 participants who received DITROPAN XL in clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5-30 mg/day for up to 4.5 months. Safety information is provided for 429 patients from three controlled clinical studies and one open label study (Table 2). The adverse events are reported regardless of causality.

Table 2
Incidence (%) of Adverse Events Reported by ≥ 5% of Patients Using DITROPAN XL (5-30 mg/day)

Body System	Adverse Event	DITROPAN XL 5-30 mg/day (n=429)
General	headache	9.8
	asthenia	6.8
	pain	6.8
Digestive	dry mouth	60.8
	constipation	13.1
	diarrhea	9.1
	nausea	8.9
	dyspepsia	6.8
Nervous	somnolence	11.9
	dizziness	6.3
Respiratory	rhinitis	5.6
Special senses	blurred vision	7.7
	dry eyes	6.1
Urogenital	urinary tract infection	5.1

The most common adverse events reported by patients receiving 5-30 mg/day DITROPAN XL were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

The discontinuation rate for all adverse events was 6.8%. The most frequent adverse event causing early discontinuation of study medication was nausea (1.9%), while discontinuation due to dry mouth was 1.2%.

In addition, the following adverse events were reported by 2 to < 5% of patients using DITROPAN XL® (oxybutynin chloride) (5-30 mg/day) in all studies. *General:* abdominal pain, dry nasal and sinus mucous membranes, accidental injury, back pain, flu syndrome; *Cardiovascular:* hypertension, palpitation, vasodilatation; *Digestive:* flatulence, gastroesophageal reflux; *Musculoskeletal:* arthritis; *Nervous:* insomnia, nervousness, confusion; *Respiratory:* upper respiratory tract infection, cough, sinusitis, bronchitis, pharyngitis; *Skin:* dry skin, rash; *Urogenital:* impaired urination (hesitancy), increased post void residual volume, urinary retention, cystitis.

Additional rare adverse events reported from worldwide post-marketing experience with DITROPAN XL include: peripheral edema, cardiac arrhythmia, tachycardia, hallucinations, convulsions, and impotence.

Adverse Events with Oxybutynin Chloride
Additional adverse events reported with other [ ] formulations include: cyclopegia, mydriasis, and suppression of lactation. **b(4)**

OVERDOSAGE
The continuous release of oxybutynin from DITROPAN XL® (oxybutynin chloride) should be considered in the treatment of overdosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

Overdosage with oxybutynin has been associated with anticholinergic effects including CNS excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention.

Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13 year old boy who experienced memory loss, and a 34 year old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

DOSAGE AND ADMINISTRATION.

DITROPAN XL must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

DITROPAN XL may be administered with or without food.

Adults: The recommended starting dose of DITROPAN XL is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.
Reviewer's comment:
1) **Additional labeling for dosage and administration in children is currently under review under the NDA 20-897 pediatric efficacy Supplement No. 009.**

HOW SUPPLIED
DITROPAN XL Extended Release Tablets are available in three dosage strengths, 5 mg (pale yellow), 10 mg (pink) and 15 mg (gray) and are imprinted with
"5 XL", "10 XL" or "15 XL". DITROPAN XL Extended Release Tablets are supplied in bottles of 100 tablets.

5 mg	100 count bottleNDC 17314-8500-1
10 mg	100 count bottleNDC 17314-8501-1
15 mg	100 count bottleNDC 17314-8502-1

Storage
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and humidity.

Rx only

For more information call 1-888-395-1232 or visit www.DITROPANXL.com

Manufactured by
ALZA Corporation, Mountain View, CA 94043.

An ALZA OROS®
Technology Product

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Distributed and Marketed by
Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ 08869.

Placeholder for Ortho-McNeil Pharmaceutical, Inc. Logo

00096532

Edition: 12/02

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/s/

Brenda Gierhart
3/21/03 04:51:07 PM
MEDICAL OFFICER

Mark S. Hirsch
3/24/03 09:05:45 AM
MEDICAL OFFICER
I concur.

MEMORANDUM

To:	NDA 17-577 Ditropan® (oxybutynin chloride) Tablets NDA 18-211 Ditropan® (oxybutynin chloride) Syrup
Through:	Mark Hirsch, MD Urology Team Leader, HFD-580
From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
Date:	March 21, 2003
Re:	NDA 17-577 Amendment to SLR-032 (BL) NDA 18-211 Amendment to SLR-014 (BL) Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Submitted: December 23, 2002 Received: December 26, 2002

Background:
The current labeling for Ditropan® (oxybutynin chloride) Tablets and Syrup is dated January 1998. On September 10, 1999 in **SLR-032**, the sponsor submitted changes to the approved product labeling for Ditropan® (oxybutynin chloride) Tablets to the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **OVERDOSAGE** sections. These changes were based upon a) language in the approved product labeling for Ditropan® XL (oxybutynin chloride) Extended Release Tablets; b) two literature reports to support the revised language concerning metabolism and potential drug-drug interactions; and c) adverse events reported for the immediate-release formulation of oxybutynin chloride used in three clinical trials for the Ditropan® XL. The submission was reviewed (see Medical Officer Memorandum dated August 9, 2000) and the sponsor was sent a regulatory letter with revised labeling on April 6, 2001. The sponsor did not accept the revised labeling. The current labeling for Ditropan® XL is dated July 2002.

Current submission:
As identical amendments to NDA 17-577 SLR-032 and to NDA 180211 SLR-014, the sponsor now submits revised changes to the approved product labeling for Ditropan® (oxybutynin chloride) Tablets to the **CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS** and **OVERDOSAGE** sections in addition to minor editing changes throughout the labeling. The submission was reviewed.

Reviewer's comments:

1) **In the current submission, the additional minor editing changes throughout the label were all acceptable to the reviewer and were as follows:**
   - deleting "(oxybutynin chloride)" except for the first time the product is mentioned on each page of the labeling. In the current approved labeling the phrase "®(oxybutynin chloride)" follows the word DITROPAN the first time the word DITROPAN appears in each section of the labeling.

- deleting the registered trademark "®" symbol from the current labeling except after in the title and in the first time the word DITROPAN occurs in the **DESCRIPTION** section
- adding "(oxybutynin chloride)" to follow the word DITROPAN the first time the word DITROPAN appears in the labeling in the **DESCRIPTION** section
- adding "®(oxybutynin chloride)" to follow the word DITROPAN in the **INDICATIONS AND USAGE** section
- adding " (oxybutynin chloride)" to follow the word DITROPAN® in the Drug Interactions subsection of the **PRECAUTIONS** section
- adding "®(oxybutynin chloride)" to follow the word DITROPAN in the Pediatric Use subsection of the **PRECAUTIONS** section
- adding the word "syrup" to both sentences in the Syrup "Pediatric patients over 5 years of age" subsection of the **DOSASGE AND ADMINISTRATION** section
- adding "®(oxybutynin chloride)" to follows the word DITROPAN when it first appears in the **HOW SUPPLIED** section
- deleting information regarding 1000 ct. bottles and Unit Dose Identifications Paks of 100 tablets from the HOW SUPPLIED section since they will no longer be available.
- changing the manufacturer from Hoechst Marion Roussel, Inc., Kansas City, MO 64137 to Aventis Pharmaceuticals, Inc., Kansas City, MO 64137 in the **HOW SUPPLIED** section following the words "Manufactured by..."
- changing the sentence in the **HOW SUPPLIED** section from "Distributed by ALZA Corporation, Mountain View, CA 941043" to "Distributed and Marketed by Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ 08869"
- adding the Ortho-McNeil Pharmaceutical, Inc. Logo to the **HOW SUPPLIED** section
- changing the edition from 01/98 to 12/02 at the end of the labeling
- changing the final part number from 50016519 to 50017115 at the end of the labeling

2) **In the current submission, the misspelling of** "retention" **in the first sentence of the CONTRAINDICATIONS section was corrected, as requested by the Division in the 4/6/01 regulatory letter. In the current submission, the sponsor proposed changes to the CONTRAINDICATIONS section are identical to the labeling acceptable to the Division as stated in the 4/6/01 regulatory letter with the following addition, which is acceptable to the reviewer:**
   - The sponsor added the phrase "and other severe decreased gastrointestinal motility conditions" to the first sentence after the phrase "gastric retention".

3) **In the current submission, the underlining of the subsections titles in the PRECAUTIONS section was deleted, as requested by the Division in the 4/6/01 regulatory letter.**

4) **In the current submission, the sponsor added the phrase /** in patients with myasthenia gravis due to the risk of symptom aggravation" **as the last line of the General subsection of the PRECAUTIONS section. This is acceptable to the reviewer; however the reviewer finds it** [redacted] b(4)

5) **In the current submission, the sponsor deleted the words** "and myasthenia gravis" **from the second sentence in the Gastrointestinal Disorders subsection of the PRECAUTIONS section. This is acceptable to the reviewer since it was added to the General subsection of the PRECAUTIONS section.**

6) **In the 4/6/02 regulatory letter, the [ ] from the General subsection of the PRECAUTIONS section as follows:** b(4)

"Ditropan® may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, [ ] prostatic hypertrophy." b(4)

In the current labeling, this sentence is the second sentence of the General subsection of the PRECAUTIONS section. [ ]

b(4)

[ ] The sponsor limited their search for cardiac effects from 1998 to June 21, 2002,which was inappropriate since Ditropan has been used for decades. The sponsor limited their search to the ALZA medical safety database, which was inappropriate since the safety base began in 1998 and Ditropan has been used for decades. The reviewer recommends adding the sentence as stated in the 4/6/02 regulatory letter.

7) **In the 4/6/02 regulatory letter, the [ ] from** b(4)
General subsection of the PRECAUTIONS section as follows:

"Administration of Ditropan® to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease. "

In the current labeling, this sentence is the third sentence of the General subsection of the PRECAUTIONS section. [ ]

b(4)

[ ] continues to recommend adding the sentence as stated in the 4/6/02 regulatory letter.

8) **In the current submission, all changes in the Information for Patients subsection of the PRECAUTIONS section are identical to those agreed to by the Division in the 4/6/01 regulatory letter.**

9) **In the current submission, the sponsor accepted the new sixth sentence added to the Drug Interactions subsection of the PRECAUTIONS section (i.e.** "Caution should be used when such drugs are co-administered.") **as proposed in the 4/6/01 regulatory letter and the remainder of the Drug Interactions subsection is identical to the language agreed to by the Division in the 4/6/01 regulatory letter with the following exceptions:**

- Changes the word "that" to "which" in the first sentence
- [ ] b(4)
- Adds the new third sentence "This may be of concern for drugs with a narrow therapeutic index."
- Changes "eg" to "e.g." and "ie" to "i.e." in the next to last sentence

The above changes to the Drug Interactions subsection are all acceptable to the reviewer

[ ] b(4)

10) **In the current submission, all changes in the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the PRECAUTIONS section are identical to those agreed to by the Division in the 4/6/01 regulatory letter.**

11) **In the current submission, the sponsor adds a new Geriatric Use subsection to the PRECAUTIONS section as follows:**

"Clinical studies of DITROPAN did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses [ ] elderly and younger patients. / general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy." b(4)

The sponsor did not provide references to support the second sentence; therefore, the reviewer recommends accepting the first and third sentences of the new Geriatric Use subsection and changing the second sentence to add that a lower initial starting dose of 2.5 mg given 2 or 3 times a day has been recommended for the frail elderly due to a prolonged elimination half-life from 2 to 3 hours to 5 hours.[1,2,3]

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[1] Hughes KM et al. Measurement of oxybutynin and its *N*-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. *Xenobiotica.* 1992; 22 (7): 859-869.

[2] Ouslander J et al. Pharmacokinetics and Clinical Effects of Oxybutynin in Geriatric Patients. *J. Urol.* 1988; 140: 47-50

[3] Yarker Y et al. Oxybutynin: A review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapeutic Use in Detrusor Instability. *Drugs & Aging.* 1995; 6 (3): 243-262.

12) The current submission accepts the changes to the ADVERSE REACTIONS section as proposed by the Division in the 4/6/01 regulatory letter with the following exceptions:

- The number of clinical trials was 3 in the 4/6/01 regulatory letter and the current submission [ ] The sponsor agrees to include the data from Clinical trial 95-049 and 97-020 [ ]
- The number of subjects was 199 patients in the 4/6/01 regulatory letter and the current submission [ ] in the first sentence and in Table #1.
- [ ] b(4)
- The current submission changes the phrase in the first sentence "with Ditropan XL" to "comparing DITROPAN [ ] DITROPAN XL".
- Since the [ ] in the current submission, the actual incidence of adverse events was changed in Table #1.
- [ ]
- The current submission adds the adverse events "convulsions, urinary retention" and [ ] "flatulence" from the list of other adverse events that have been reported with oxybutynin.

[b(4)]

[ ] **Until additional details are submitted, the reviewer recommends changing the Adverse Event section as stated in the 4/6/02 regulatory letter.**

13) In the 4/6/02 regulatory letter, the sponsor was asked to add [ ] the phrase into the proposed third sentence "(e.g., restlessness, tremor, irritability, convulsions, delirium, hallucinations)" **which occurs immediately after the phrase** "[ ] excitation", **add a new fourth sentence** "Other symptoms may include hypotension or hypertension, respiratory failure, paralysis and coma" **and begin a new paragraph with the proposed third sentence. In the current label, the phrase** "(e.g., restlessness, tremor, irritability, convulsions, delirium, hallucinations)"**and the symptoms of** "hypotension or hypertension, respiratory failure, paralysis and coma" **are in the second sentence in the OVERDOSAGE section.** [ ]

[b(4)]

[ ] **recommends incorporating the same three changes to the OVERDOSAGE section as listed in the 4/6/02 regulatory letter.**

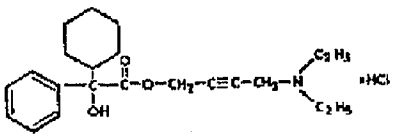
Recommendation:
Recommend sending the labeling in Appendix A to the sponsor as part of the labeling process for pediatric efficacy supplements NDA 17-577 Supplement No. 033 and NDA 18-211 Supplement No. 016. If possible, the reviewer believes it appropriate to resolve these two SLRs and the pediatric efficacy supplements at the same time.

cc: DFS re: NDA 17-577 SLR032
HFD-580: D. Shames, M. Hirsch, B. Gierhart, and J. King

Appendix A:

DITROPAN®
(oxybutynin chloride)
Tablets and Syrup

DESCRIPTION
Each scored biconvex, engraved blue DITROPAN® (oxybutynin chloride) Tablet contains 5 mg of oxybutynin chloride. Each 5 mL of DITROPAN Syrup contains 5 mg of oxybutynin chloride. Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \bullet HCl$. The structural formula appears below:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alkalis.
DITROPAN Tablets
Also contains: calcium stearate, FD&C Blue #1 Lake, lactose, and microcrystalline cellulose.
DITROPAN Syrup
Also contains: citric acid, FD&C Green #3, glycerin, methylparaben, flavor, sodium citrate, sorbitol, sucrose, and water.
DITROPAN Tablets and Syrup are for oral administration.
Therapeutic Category: Antispasmodic, anticholinergic.

CLINICAL PHARMACOLOGY
Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. DITROPAN exhibits only one fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that DITROPAN increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the

detrusor muscle, and delays the initial desire to void. DITROPAN thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Reviewer's comment:

1) **Additional clinical pharmacology and pharmacokinetic information in adults and in children is intended for this section and is currently under review under the NDA 17-577 pediatric efficacy Supplement No. 033 and NDA 18-211 pediatric efficacy Supplement No. 016.**

INDICATIONS AND USAGE

DITROPAN ® (oxybutynin chloride) is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria).

CONTRAINDICATIONS

DITROPAN is contraindicated in patients with urinary retention, gastric retention, and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk of these conditions.

DITROPAN is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

General

b(4)

Urinary Retention:

DITROPAN should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (See **CONTRAINDICATIONS**).

Gastrointestinal Disorders:

DITROPAN should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Administration of Ditropan® to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

DITROPAN, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, and intestinal atony.

DITROPAN should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

Information for Patients

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Drug Interactions
The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 3-4 fold higher when DITROPAN® (oxybutynin chloride) was administered with ketoconazole, a potent CYP3A4 inhibitor.

Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility
A 24-month study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum human exposure, based on surface area.

[ ] showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae* and *Salmonella typhimurium* test systems. b(4)

[ ] in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility.

Pregnancy
Category B. Reproduction studies in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN administered to women who are or who may become pregnant has not been established. Therefore, DITROPAN should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

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

Pediatric Use
The safety and efficacy of DITROPAN ® (oxybutynin chloride) administration have been demonstrated for pediatric patients 5 years of age and older (see DOSAGE AND ADMINISTRATION). [redacted] b(4)

Geriatric Use
Clinical studies of DITROPAN did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between healthy elderly and younger patients; however, a lower initial starting dose of 2.5 mg given 2 or 3 times a day has been recommended for the frail elderly due to a prolongation of the elimination half-life from 2-3 hours to 5 hours.[4,5,6] In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
The safety and efficacy of Ditropan® (oxybutynin chloride) was evaluated in a total of 199 patients in three clinical trials comparing DITROPAN with DITROPAN XL (Table 1). These participants were treated with 5-20 mg/day for up to 6 weeks. [redacted] b(4)

Table 1
Incidence (%) of Adverse Events Reported by / 5% of Patients Using DITROPAN (5-20 mg/day) b(4)

Body System	Adverse Event	DITROPAN (5-20 mg/day) (n=199)
General	Abdominal pain	6.5%
	Headache	6.0%
Digestive	Dry mouth	71.4%
	Constipation	12.6%
	Nausea	10.1%
	Dyspepsia	7.0%
	Diarrhea	5.0%
Nervous	Dizziness	15.6%
	Somnolence	12.6%
Special senses	Blurred vision	[redacted]%
	[redacted]	[redacted]%

b(4)

[4] Hughes KM et al. Measurement of oxybutynin and its *N*-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. *Xenobiotica.* 1992; 22 (7): 859-869.
[5] Ouslander J et al. Pharmacokinetics and Clinical Effects of Oxybutynin in Geriatric Patients. *J. Urol.* 1988; 140: 47-50
[6] Yarker Y et al. Oxybutynin: A review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapeutic Use in Detrusor Instability. *Drugs & Aging.* 1995; 6 (3): 243-262.

Urogenital	Urination impaired	10.6%
	Post void residuals increase	5.0%
	Urinary tract infection	5.0%

The most common adverse events reported by patients receiving DITROPAN 5-20 mg/day were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

In addition, the following adverse events were reported by 2 to <5% of patients using DITROPAN (5-20 mg/day) in all studies. *General:* asthenia, dry nasal and sinus mucous membranes; *Cardiovascular:* palpitation; *Metabolic and Nutritional System:* peripheral edema; *Nervous System:* insomnia, nervousness, confusion; *Skin:* dry skin; *Special Senses:* dry eyes, taste perversion.

Other adverse events that have been reported include: tachycardia, hallucinations, cycloplegia, mydriasis, impotence, suppression of lactation, vasodilatation, rash, decreased gastrointestinal motility, flatulence, [ ] decreased sweating. b(4)

OVERDOSAGE
Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

Overdosage with oxybutynin has been associated with anticholinergic effects including central nervous system excitation (e.g., restlessness, tremor, irritability, convulsions, delirium, hallucinations), flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Other symptoms may include hypotension or hypertension, respiratory failure, paralysis and coma.

Ingestion of 100mg oxybutynin chloride in association with alcohol has been reported in a 13 year old boy who experienced memory loss, and a 34 year old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

DOSAGE AND ADMINISTRATION
Tablets
Adults: The usual dose is one 5-mg tablet two to three times a day. The maximum recommended dose is one 5-mg tablet four times a day. A lower starting dose of 2.5 mg two or three times a day is recommended for the frail elderly.
Pediatric patients over 5 years of age: The usual dose is one 5-mg tablet two times a day. The maximum recommended dose is one 5-mg tablet three times a day.

Syrup
Adults: The usual dose is one teaspoon (5 mg/5 mL) syrup two to three times a day. The maximum recommended dose is one teaspoon (5 mg/5 mL) syrup four times a day.
Pediatric patients over 5 years of age: The usual dose is one teaspoon (5 mg/5 mL) syrup two times a day. The maximum recommended dose is one teaspoon (5 mg/5mL) syrup three times a day.

HOW SUPPLIED

DITROPAN ® (oxybutynin chloride) Tablets are supplied in bottles of 100 tablets (NDC 17314-9200-1) Blue scored tablets (5 mg) are engraved with DITROPAN on one side with 92 and 00, separated by a horizontal score, on the other side.

DITROPAN Syrup (5 mg/5 mL) is supplied in bottles of 16 fluid ounces (473 mL) (NDC 17314-9201-4).

Pharmacist: Dispense in tight, light-resistant container as defined in the USP.

Store at controlled room temperature (59-86°F).

Rx ONLY

Manufactured by Aventis Pharmaceuticals Inc., Kansas City, MO 64137

Distributed and Marketed by Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ 08869

Placeholder for Ortho-McNeil Pharmaceutical, Inc. Logo

Edition: 03/03

50017115

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/s/

Brenda Gierhart
3/21/03 04:47:04 PM
MEDICAL OFFICER

Mark S. Hirsch
3/24/03 09:02:08 AM
MEDICAL OFFICER
I concur.

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of Response to Approvable Letter

NDAs	20-897: SE-8 Supplement No. 009 17-577: SE-8 Supplement No. 033 18-211: SE-8 Supplement No. 016
NDA Owner	ALZA Corporation 1900 Charleston Road P.O. Box 7210 Mountain View, CA 94039-7210
Regulatory Submissions	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. 1125 Trenton-Harbourton Road Titusville, New Jersey 08560-0200 Phone: (609) 730-3357 Fax: (609) 730-3091
Drug names	NDA 20-897: Ditropan XL (oxybutynin chloride) extended release tablets NDA 17-577: Ditropan (oxybutynin chloride) tablet NDA 18-211: Ditropan (oxybutynin chloride) syrup
Drug Class	Muscarinic receptor antagonist
Approved Indications	NDA 20-897: "Ditropan XL is a once-daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency." NDA 17-577 and NDA 18-211: "Ditropan is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e. urgency, frequency, urinary leakage, urge incontinence, dysuria)."
Route of Administration	Oral
Dosage Form/Strengths	NDA 20-897: 5 mg, 10 mg, and 15 mg extended release tablets NDA 17-577: 5 mg immediate release tablet NDA 18-211: immediate release syrup (5 mg/5mL)
Dosing Regimens	NDA 20-897 Ditropan XL The recommended starting dose of Ditropan XL is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals. NDA 17-577 Ditropan tablets *Adults*: The usual dose is one 5-mg tablet two to three times a day. The maximum recommended dose is one 5-mg tablet four times a day. *Children over 5 years of age*: The usual dose is one 5-mg tablet two times a day. The maximum recommended dose is one 5-mg tablet three times a day. NDA 18-211 Ditropan syrup *Adults*: The usual dose is one teaspoon (5 mg/5 mL) syrup two to three times a day. The maximum recommended dose is one teaspoon (5 mg/5mL) four times a day. *Children over 5 years of age*: The usual dose is one teaspoon (5 mg/5 mL) two times a day. The maximum recommended dose is one teaspoon (5 mg/5 mL) three times a day.
Dates	
Submitted	October 16, 2002
CDER stamp date	October 17, 2002
PDUFA date	April 17, 2003

Related NDAs	None
Related INDs	[redacted] IND 48,930 Ditropan XL (Johnson and Johnson) b(4)
Medical Reviewer	Brenda S. Gierhart, MD
Date Review Completed	March 21, 2003

TABLE OF CONTENTS

EXECUTIVE SUMMARY

1 RECOMMENDATIONS

1.1 Recommendation Regarding Approval

1.1.1 Approvability

It is recommended that the efficacy supplements for NDA 20-897 (SE8-009), NDA 17-577 (SE8-033) and NDA 18-211 (SE8-015) and their respective Amendments receive an approvable action since satisfactory labeling negotiations with the sponsor have not been concluded to date.

1.1.2 Basis for Recommendation Regarding Approvability (Risk/Benefit Analysis)

There was no change in the risk/benefit analysis contained in my Medical Officer's Review of NDA Efficacy Supplements NDA 20-897 (SE8-009), NDA 17-577 (SE8-033) and NDA 18-211 (SE8-015) dated August 30, 2002 after review of the sponsor's Response to Approvable Letter.

1.2 Specific Recommendations to the Sponsor

If the labeling in APPENDIX B and C is not acceptable to the sponsor, sponsor should provide appropriately revised drug labeling in particular regarding:

a) **CLINICAL PHARMACOLOGY** Sections of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.

b) **PRECAUTIONS** Section, **Pediatric Use.** Subsection of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.

c) **DOSAGE AND ADMINISTRATION** Sections of the Ditropan Tablets and Syrup Physician Insert and the Ditropan XL Physician Insert.

d) **INDICATIONS AND USES** Section of the Ditropan XL Physician Insert.

2 SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

2.1.1 Drug

Oxybutynin chloride is an antispasmodic, anticholinergic medication first approved as immediate release tablets in 1975. It is currently available from the sponsor in three different formulations: Ditropan tablets (5 mg immediate release tablets), Ditropan Syrup (5 mg/5mL supplied in 16 fluid ounce bottles), and Ditropan XL (5, 10, and 15 mg extended release tablets). Ditropan syrup was approved on November 29, 1979. Ditropan XL was approved on December 16, 1998.

2.1.2 Clinical Program

The sponsor submitted identical SE8 efficacy supplements (i.e. labeling supplement with clinical data) to NDA 20-897 (S-009), NDA 17-577 (S-033), and NDA 18-211(S-016) on December 7, 2001. These three efficacy supplements included an interim study report for C-2000-042-01 and a final study report for C-2000-043-00. On July 29, 2002, the sponsor submitted the final study report for C-2000-042-01 in 21 volumes of new clinical data. It was determined that the new clinical data included in the final study report for C-2000-042-01 was submitted too late in the original 10-month review cycle to be adequately reviewed. Therefore, only the data submitted in the interim report for C-2000-042-01 was reviewed during the first review cycle [see Medical Officer's Review of NDA Efficacy Supplements NDA 20-897 (SE8-009), NDA 17-577 (SE8-033) and NDA 18-211 (SE8-015) dated August 30, 2002].

On October 7, 2002, an approvable letter was sent to the sponsor regarding these three NDA supplements. The letter advised the sponsor that they could incorporate the 21-volume submission dated July 29, 2002 by specific reference as part of their response to the deficiencies cited in the letter. The letter also requested that the sponsor submit a highlighted or marked-up copy of the most recently approved package inserts showing all proposed labeling changes.

The sponsor submitted a Response to Approvable Letter on October 16, 2002 consisting of a one-page letter that requested the Division reference the complete submission package of July 29, 2002 containing the final study report for C-2000-042-01 for review. The letter also stated that the sponsor intended to submit a labeling supplement that would highlight outstanding labeling changes to be considered in the labeling negotiations for the referenced supplements.

A clean and marked copy of the most recently approved Ditropan Tablet and Syrup package insert with the sponsor's proposed draft labeling was submitted on December 23, 2002 to NDA 17-577 in SLR 032 (BL) regarding Ditropan Tablets and to NDA 18-211 in SLR 014 (BL) regarding Ditropan syrup. In the Ditropan tablets and syrup proposed labeling, the sponsor proposed additions to the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**, and **OVERDOSAGE** sections.

A clean and marked copy of the most recently approved Ditropan XL package insert with the sponsor's proposed draft labeling was submitted to NDA 20-897 on December 23, 2002 as SLR 010 (BL). For Ditropan XL, the SLR 010 proposed changes were additions only to the **CONTRAINDICATIONS, PRECAUTIONS**, and **ADVERSE REACTIONS** sections.

The reviewer noted that the sponsor did not include any pediatric claims regarding the submitted clinical trial data from Study C-2000-042-01 and Study C-2000-043-00 in the three SLR Amendments dated December 23, 2002. The sponsor was contacted and they stated that the proposed labeling in the December 23, 2002 submissions replaced the proposed labeling previously submitted on December 7, 2001. On March 11, 2003, the sponsor stated that an error had been made and that the proposed labeling in the three SLR Amendments in the December 23, 2002 submissions were in addition to the previously submitted December 7, 2001 proposed labeling changes. However, the latest proposed labeling submitted to the electronic document room on March 17, 2003 only contained the sponsor's proposed labeling as was submitted on December 7, 2001.

On March 3, 2003, the reviewer noted that Appendix 13.1.9 through 13.2.5 appeared to be missing from the July 29, 2002 Final Study Report for C-2000-042-01. The sponsor was contacted and concurred that the missing Appendix were listed in the Table of Contents but were not included in the final report. On March 14, 2003, the sponsor submitted to NDA 20-897 in an Amendment to Supplement 009 (BM: Minor Amendment-Clinical) the missing Appendix as Volumes 22 through 27 of the Final Study Report for C-2000-042-01. The vast majority of information in the Appendix submitted in Volume 22-27 had previously been submitted in Volume 1-21 in other Appendix. The Assay Validation Report and Analytical Report in Appendix 13.1.9-1 in Volume 22 and Case Report Forms for Patients 304, 708, 709, 1601, and 2802 in Appendix 13.3.1 in Volumes 26 and 27 had not been previously submitted in Volumes 1-21.

Reviewer's comments:

1) **See Medical Officer Memorandum dated March 10, 2003 [to NDA 17-577 regarding Amendment to SLR-032 (BL) Ditropan Tablets and to NDA 18-211 regarding Amendment to SLR-014 (BL) Ditropan Syrup] for specific comments regarding the sponsor proposed labeling changes submitted on December 23, 2002 for Ditropan Tablets and Syrup. The sponsor requested that these changes be included in the pediatric labeling negotiations; therefore**

recommended labeling from these amendments has been incorporated into the Reviewer proposed labeling for Ditropan tablets and Ditropan syrup located in Appendix B.

2) **See Medical Officer Memorandum dated March 11, 2003 [to NDA 20-897 regarding SLR-010 dated July 2, 2002 and regarding amendment to SLR-010 (BL) dated December 23, 2002] for specific comments regarding the sponsor proposed labeling changes submitted on December 23, 2002 for Ditropan XL. The sponsor requested that these changes be included in the pediatric labeling negotiations; therefore recommended labeling from this supplement and amendment has been incorporated into the Reviewer proposed labeling for Ditropan XL located in Appendix C.**

2.1.3 Design of the Clinical Study

Study C-2000-042-01: See **Appendix A** for review of the C-2000-042-01 final study report and see Medical Officer's Review of NDA Efficacy Supplements NDA 20-897 (SE8-009), NDA 17-577 (SE8-033) and NDA 18-211 (SE8-015) dated August 30, 2002 for review of the C-2000-042-01 interim study report. Study **C-2000-042-01** was a multicenter, 24-week treatment duration, open label, multiple-dose level, dose-response and safety study of oxybutynin (administered either as Ditropan XL, Ditropan tablets, or Ditropan syrup) in 116 pediatric subjects diagnosed with detrusor hyperreflexia due to neurogenic conditions and aged 6 to 15 years. The dose-effect (urodynamic) and concentration-effect (urodynamic) of oxybutynin chloride were evaluated. A PK substudy was conducted in 42 patients at steady state: 12 on Ditropan syrup, 11 on Ditropan tablets, and 19 on Ditropan XL.

2.2 Efficacy

2.2.1 Efficacy Endpoints

The primary efficacy assessment in **C-2000-042-01** was the volume of urine collected per catheterization as recorded on the patient diaries. The change from baseline in the measured volume of urine per catheterization (averaged catheterized urine volume and first catheterization after morning awakening) was analyzed during treatment at Weeks 4, 12, and 24 (or early termination). Additional secondary efficacy parameters included:

- The percentage of episodes of leakage between catheterizations documented at baseline, Weeks 4, 12, and 24.
- Urodynamic measurement collected at baseline, Week 12, and Week 24 (or early termination). Of interest were changes over time in maximal bladder capacity, detrusor and intravesical pressure at maximal bladder capacity, and presence of uninhibited detrusor contractions > 15 cm H_2O.

The **Pharmacokinetic** data was analyzed for plasma R- and S- oxybutynin and the metabolite enantiomers, R- and S-desethyloxybutynin for C_{max}, T_{max}, C_{min}, T_{min}, K, $t_{1/2}$, AUC_{dose}, $AUC_{dosing\ regimen}$, and Clearance.

2.2.2 Efficacy Results

In Study **C-2000-042-01**, the primary efficacy assessment was the volume of urine collected per catheterization as recorded on the patient diaries. The change from baseline in the measured volume of urine per catheterization (averaged catheterized urine volume and first catheterization after morning awakening) was analyzed during treatment at Weeks 4, 12, and 24 (or early termination). The change from baseline to last visit in average urine volume per catheterization for the All Enrolled patients population (Table 1) was statistically significant ($p<0.0001$) and the changes were sustained over 24 weeks of treatment.

Table 1 Study C-2000-042-01 Change from baseline in average urine volume per catheterization[a] (All Enrolled patients)

	Baseline (n=116)	Week 4 (n=114)	Week 12 (n=114)	Week 24 (n=109)	Last Visit[b] (n=115)
Statistics					
n	116	114	114	109	115
Mean (SEM)	112.4 (6.57)	133.8 (5.88)	136.5 (5.94)	138.2 (6.05)	137.5 (6.07)
Median	104.5	121.5	124.3	133.3	133.3
Range	13 to 455	9 to 332	23 to 345	15 to 375	15 to 375
Change from Baseline[c]					
n		114	114	109	115
Mean (SEM)		21.6 (4.65)	26.0 (4.72)	25.5 (5.86)	25.7 (5.72)
Median		18.4	29.8	26.1	26.1
Range		-209 to 145	-163 to 148	-292 to 245	-292 to 245
p-value[d]		<0.0001	<0.0001	0.0023	<0.0001

Source: Table 12.1.4.1-1 in Volume 1 on page 127

[a] Average urine volume per catheterization = total volume on the diaries divided by the number of catheterizations

[b] Data included are from the last visit completed in the study after baseline

[c] Change from baseline is the value at the visit minus the value at baseline

[d] p-value was calculated using the paired t-test

In Study **C-2000-042-01** for the enrolled patients population, statistically significant changes in the mean detrusor pressure at maximal cystometric capacity ($p<0.001$) from baseline (42.9 cmH_20) to last visit (34.0 cmH_20), mean intravesical pressure at maximal cystometric capacity ($p=0.002$) from baseline (55.1 cmH_20) to last visit (47.4 cmH_20), and number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 ($p=<0.0001$) from baseline (n=66 or 56.9%) to end of study (n=30 or 26.3%) were also documented.

The pharmacokinetic results from a subset of subjects in Study **C-2000-042-01** were completely submitted with the interim study report [see Medical Officer's Review of NDA Efficacy Supplements NDA 20-897 (SE8-009), NDA 17-577 (SE8-033) and NDA 18-211 (SE8-015) dated August 30, 2002]. No clear relationship between the total daily dose (in mg) and the pharmacokinetic results was identified. After administering the same total daily dose of the same oxybutynin formulation, a fairly large range of values for C_{max} and $AUC_{(0-t)}$ for R-oxybutynin was noted. In an attempt to correct for differing body weights accounting for this large range of values, C_{max} and $AUC_{(0-t)}$ for R-oxybutynin was then further evaluated by the reviewer by total daily dose in mg/kg and by ranking the data by increasing total daily dose (in mg/kg) by each formulation. Again, no clear relationships were identified with the possible exception that Ditropan XL, C_{max} and $AUC_{(0-t)}$ for R-oxybutynin tended to increase as the total daily dose in mg/kg increased. The reviewer suspects that individual variations in metabolism and failure to be compliant with dose administration are responsible for the persisting wide range of values despite adjusting the total daily dose for body weight. The reader is referred to the clinical pharmacologist's review for additional information.

2.2.3 Other Efficacy Issues

Approximately 40% of the enrolled patients failed to adhere to Protocol C-2000-042-01 Inclusion/Exclusion criteria. Approximately 32% of the enrolled patients failed to adhere to study procedures during the conduct of Protocol C-2000-042-01. The reviewer understands that compliance

may be difficult to achieve in pediatric trials; however, the reviewer believes that these percentages of protocol violators and protocol deviators in C-2000-042-01 compromised the findings to some degree.

2.2.4 Proposed Label Claims

Reviewer proposed labeling for Ditropan tablets and Ditropan syrup is located in **Appendix B.**

Reviewer proposed labeling for Ditropan XL located in **Appendix C.**

The reviewer did not concur with many of the sponsor proposed labeling changes, as previously detailed in Medical Officer's Review of NDA Efficacy Supplements NDA 20-897 (SE8-009), NDA 17-577 (SE8-033) and NDA 18-211 (SE8-015) dated August 30, 2002. In addition to these comments, the reviewer believes that it is necessary to extensively update the Ditropan tablet and syrup CLINICAL PHARMACOLOGY section and in particular to incorporate adult pharmacokinetic (PK) data into the Ditropan labeling in order to interpret the pediatric PK data in Study C-2000-042-01 and Study C-2000-043-00. The Ditropan PK information proposed in the labeling was obtained from a review of the literature, the Clinical Pharmacology and Biopharmaceutics Review of NDA 20-897 dated December 15, 1998, and the archival NDA 20-897. NDA 20-897 for Ditropan XL contained Ditropan Tablet PK information as well as Ditropan XL PK data. Additional labeling was proposed by the clinical pharmacology team.

In addition, the sponsor requested that proposed labeling from NDA 17-577 Amendment to SLR-032 (BL) Ditropan Tablets and from NDA 18-211 Amendment to SLR-014 (BL) be included in the Ditropan Tablet and Syrup pediatric labeling negotiations. Therefore reviewer recommended labeling from these amendments has been incorporated into the proposed labeling for Ditropan tablets and Ditropan syrup located in Appendix B.

In addition, the sponsor requested that proposed labeling from NDA 20-897 SLR-010 and Amendment to SLR-010 (BL) be included in Ditropan XL pediatric labeling negotiations. Therefore reviewer recommended labeling from this supplement and amendment has been incorporated into the proposed labeling for Ditropan XL located in Appendix C.

2.3 Safety

No new and unlabeled safety issues were identified during this review.

3 APPENDIX A: CLINICAL TRIAL C-2000-042-01

3.1 Summary

Title: "The Safety and Tolerability of Oxybutynin Chloride (Ditropan XL, Ditropan Syrup or Ditropan Tablets) in the Treatment of Detrusor Hyperreflexia due to Neurogenic Conditions in Children Aged 6 to 15 years".

This appendix will detail differences in the C-2000-042-01 Final Study Report (Volumes 1-27) when compared to the previously reviewed interim study report. Refer to the Medical Officer's Review of NDA Efficacy Supplement dated August 30, 2002 for details of the C-2000-042-01interim study report.

3.1.1 Objectives

There were no changes from the interim report.

3.1.2 Overall Design

There were no changes from the interim report. The same 28 principal investigators (24 principal investigators enrolled patients) were listed in the interim report (Vol. 53.5/pg. 175-178) and in the final study report (Vol. 2 pg. 352-355). The reviewer believes that the sponsor was in error when they stated the following in the summary attached to the cover letter dated July 29, 2002 (pg. 3): "Since the submission of Supplement 009, two additional investigators were added and are included in the list of Investigators in Appendix." There were no changes to the protocol since the interim report.

3.2 Study Procedures and Conduct

3.2.1 Schedule of Study Assessments

There were no changes from the interim report.

3.2.2 Study Drugs

There were no changes from the interim report except in the extent of drug exposure and the number and ages of patients on each Ditropan formulation. The mean duration of drug exposure was 24.3 weeks (range 6 to 31 weeks). Most patients at enrollment received a total daily dose of oxybutynin chloride of 0.20-<0.40 mg/kg (45.7%) or 0.40-<0.60 mg/kg (34.5%). During the study, 30 patients received Ditropan syrup, 28 received Ditropan tablets, and 61 patients received Ditropan XL (note: these numbers add up to more than the 116 enrolled subjects due to three subjects changing formulations during the study). Of the 72 patients who were $\leq$ 10 years, 25 were on Ditropan syrup, 12 were on Ditropan tablets, and 35 were on Ditropan XL. Of the 44 patients who were > 10 years, 5 were on Ditropan syrup, 14 were on Ditropan tablets, and 25 were on Ditropan XL.

3.3 Patient Population

There were no changes in the Inclusion or Exclusion Criteria since the interim report

3.3.1 Demographics and Baseline Disease Characteristics

There was no change in the Demographics and Baseline Disease Characteristics from the interim report except that an error was corrected. The interim report stated that 55 males and 61 females were enrolled. The final study report stated that 56 males and 60 females were enrolled.

3.3.2 Withdrawals, compliance, and protocol violations

At the time of the interim report, two patients had discontinued early. At the end of the study, five patients (Vol. 12 pg. 161) had discontinued early as follows:

- Patient 101 (age 14/male) on Ditropan tablets 5 mg TID (15 mg total daily dose) discontinued after 12.7 weeks for personal reasons

- Patient 803 (age 8/female) on Ditropan syrup 5mg/5mL TID (15 mg total daily dose) was lost to follow-up after Week 12 visit; known to have been on 12.4 weeks of study medication
- Patient 1902 (age 11/male) on Ditropan tablets 5 mg TID (15 mg total daily dose) discontinued after 13.6 weeks for lack of efficacy
- Patient 2001 (age 13/female) on Ditropan XL 5 mg (5 mg total daily dose) was discontinued after 5.7 weeks for noncompliance; last visit completed was Baseline Visit
- Patient 2803 (age 5/male) on Ditropan XL 10 mg (10 mg total daily dose) discontinued after 12.3 weeks at the request of the IRB. The patient had been granted a waiver to enroll at 5 years of age and began treatment. Subsequently, the site notified the IRB of the child's enrollment. The IRB requested that the child discontinue due to their policy not to allow patients outside of the IRB-approved inclusion/exclusion criteria into a study.

One patient in the PK subgroup discontinued early (Patient 803-see above).

The reviewer noted 16 patients who were noncompliant with treatment (per Appendix 8.1.1.3 in Vol. 12 on pg. 162-194 and Appendix 8.1.3.2 in Vol. 12 on pg. 273-287):

- Patient 102-missed approximately one week of dose; dates unknown
- Patient 104-stopped treatment for 11 days due to AE
- Patient 605-discontinued medications for 4 days due to abdominal pain; increased dose to 20 mg
- Patient 611-changed formulation once after enrollment
- Patient 620-stopped treatment for 2 days due to AE
- Patient 709-changed formulation twice after enrollment
- Patient 1001-missed one day of dose at Visit 4, days are unknown
- Patient 1002-missed 3 doses equivalent of 1.5 days of study drug, dates unknown
- Patient 1401-interrupted treatment twice for total of 6 days due to AE; formulation changed twice after enrollment
- Patient 1503-missed several days from taking study drug due to incorrect drug dispensed at Visit 2
- Patient 2202-patient was non-complaint with study medication throughout participation in study and took on an average 4 doses per week
- Patient 2702-patient dosed with some of personal Ditropan supply in addition to study drug
- Patient 3001-missed 4 days due to adverse events
- Patient 3401-patient did not take study medication for four days while recording Visit 3 diaries
- Patient 3606-patient did not take study medication for 15 days because she "lost drug"

The reviewer noted that compliance could not be verified in at least 4 patients:

- Patients 101, 302, 502, 1001- used study medication was not returned

After enrollment, 22 patients (19.0%) had at least one change to their total daily dose: 22 patients had one dose increase, 2 patients had one dose decrease, and 7 patients had dose interruptions (in Vol. 1 on pg. 125).

The reviewer noted that a total of 50 entrance criteria **protocol violations** occurred in 47 (40%) of the 116 enrolled patients (Appendix 8.1.1.1 in Vol. 12 on pg. 144-160) as follows:

- Inclusion Criteria #1 (e.g. age 6 to 15 with detrusor hyperreflexia)-Incorrect age (6 patients: one was 4 years, three were 5 years, and one was 16 years)
- Inclusion Criteria #2 (e.g. total daily dose of oxybutynin 10-15 mg/day)-Patient on higher or lower dose of oxybutynin at screening than stipulated (28 patients)
- Inclusion Criteria #4 (e.g. general good health)-waiver granted (4 patients)
- Inclusion Criteria #7 (e.g. able to comply with schedule)-waiver granted to change schedule (7 patients)
- Exclusion Criteria #1 (e.g. has treatable condition that may cause incontinence)-waiver granted to enroll patient (1 patient)
- Exclusion Criteria #4 (e.g. is taking medication affecting bladder contractility)-waiver granted to allow prohibited medication (3 patients)

The reviewer noted that at least 226 **protocol deviations** occurred in 115 of the 116 enrolled patients (Appendix 8.1.1.3 in Vol. 12 on pg. 162-194; Appendix 8.1.3.1 in Vol. 12 on pg. 261-272; and Appendix 8.1.3.2 in Vol. 12 on pg. 273-287). Many of the deviations were minor scheduling problems: however, pertinent deviations included:

- 31 patients (26.7% of patients) did not receive 10 or 15 mg total daily dose Ditropan:
  - Patient 303-took 11.25 mg total daily dose Ditropan syrup
  - Patient 401-increased dose to 20 mg total daily dose Ditropan syrup for 17 days
  - Patient 403-took 7.5 mg total daily dose Ditropan syrup
  - Patient 604-increased dose to 20 mg total daily dose Ditropan XL at Week 14
  - Patient 605-increased dose to 20 mg total daily dose Ditropan XL at Week 13
  - Patient 612-increased dose to 20 mg total daily dose Ditropan XL at Week 16
  - Patient 614-increased dose to 20 mg total daily dose Ditropan XL at Week 16
  - Patient 618-increased dose to 20 mg total daily dose Ditropan XL at Week 12
  - Patient 707-took 5 mg total daily dose Ditropan XL
  - Patient 802-took 22.5 mg total daily dose Ditropan syrup
  - Patient 904-took 30 mg total daily dose Ditropan syrup
  - Patient 1003-took 12 mg total daily dose Ditropan syrup
  - Patient 1203-took 7.5 mg total daily dose Ditropan tablets
  - Patient 1503-took 5 mg total daily dose Ditropan XL
  - Patient 1701-took 7.5 mg total daily dose Ditropan tablets for 4 weeks
  - Patient 1704-took 10.5 mg total daily dose Ditropan syrup
  - Patient 1705-took 7.5 mg total daily dose Ditropan tablets
  - Patient 1706- took 7.5 mg total daily dose Ditropan tablets
  - Patient 2001-took 5 mg total daily dose Ditropan XL

- Patient 2202-took 5 mg total daily dose Ditropan syrup
- Patient 2601-took 12 mg total daily dose Ditropan syrup
- Patient 2602-took 20 mg total daily dose Ditropan syrup
- Patient 2603-took 5 mg total daily dose Ditropan XL for 12 weeks
- Patient 3302-took 9 mg total daily dose Ditropan syrup
- Patient 3401-took 11.25 mg total daily dose Ditropan syrup
- Patient 3402-took 5 mg total daily dose Ditropan XL
- Patient 3403-took 5 mg total daily dose Ditropan XL
- Patient 3404-took 7.5 mg total daily dose Ditropan XL
- Patient 3408-took 9 mg total daily dose Ditropan syrup
- Patient 3602-took 5 mg total daily dose Ditropan XL for 4 weeks
- Patient 3605-took 7.5 mg total daily dose Ditropan tablets

- 6 patient used dosing schedules not permitted in the protocol
  - Patient 401-increased dosing to QID for 17 days
  - Patient 904-took Ditropan syrup QID
  - Patient 1003-took Ditropan syrup QID
  - Patient 1701-took Ditropan tablets QID
  - Patient 1703-took Ditropan tablets QID
  - Patient 2602-took Ditropan syrup QID
- 3 patients changed formulation after enrollment (Patients 611, 709, and 1401)
- 2 patients took prohibited medication after enrollment (pseudoephedrine) (Patients 903, 1902)

Medical reviewer comments:

1) **No summary or analysis of compliance was found in the C-2000-042-01 final study report except for the following two statements:**
   - **The sponsor stated that a large number of pediatric patients took doses other than the stipulated 10 or 15 mg/day; however, they thought that these changes did not substantively affect the study findings (in Vol. 1 on pg. 57).**
   - **The sponsor stated (in Vol. 1 on pg. 61) that they did not believe that the protocol deviations affected the findings of the study.**
2) **The medical reviewer disagrees with the above sponsor statements. Approximately 40% of the enrolled patients failed to adhere to Protocol C-2000-042-01 Inclusion/Exclusion criteria. Approximately 32% of the enrolled patients failed to adhere to study procedures during the conduct of Protocol C-2000-042-01. The reviewer understands that compliance may be difficult to achieve in pediatric trials; however, the reviewer believes that these percentages of protocol violators and protocol deviators in C-2000-042-01 compromised the findings to some degree.**

3.4 Efficacy

3.4.1 Key Efficacy Assessments

There was no change from the interim report. Data from only one patient was excluded from the efficacy analyses: patient 1705 had an extra set of diaries completed for Visit 3 (Week 4) after resolution of a urinary tract infection. The original, protocol-specified diaries that were completed while the patient had the urinary tract infection were used in the analysis of diary data, and the extra diaries were not included in the analysis. No adjustments for covariates were made in the efficacy analyses. Dropouts were not replaced.

Reviewer's comment:

1) **The sponsor stated (in Vol. 1 on pg. 89) that no interim analyses were conducted. The reviewer disagrees since she considers the C-2000-042-01 study report submitted to NDA 20-987 in SE-8 Supplement No. 009 on December 7, 2001 to have been an interim report. It is acceptable to the reviewer that no adjustment was made due to the one interim analysis conducted since C-2000-042-01 was an open-label study with no control group.**

3.4.2 Pharmacokinetic Assessments

There was no change from the interim report.

3.4.3 Primary Efficacy Endpoint Analysis

As in the interim report, the primary efficacy assessment was the volume of urine collected per catheterization as recorded on the patient diaries. The change from baseline in the measured volume of urine per catheterization (averaged catheterized urine volume and first catheterization after morning awakening) was analyzed during treatment at Weeks 4, 12, and 24 (or early termination).

The change from baseline in average urine volume per catheterization for the All Enrolled patients is presented in Table 2. The data demonstrated statistically significant increases in average urine volume per catherization at all treatment time points (mean 134-138 mL) when compared to baseline (mean 112 mL). The change in urine volume per catheterization was not due to any significant change in the mean total number of catherizations per day, which was 4.7 at baseline, 4.5 at Week 4, 4.7 at Week 12, 4.6 at Week 24, and 4.7 at Last Visit. The number of catherizations per day ranged from 2 to 10 per day.

Table 2 Change from baseline in average urine volume per catheterization (All Enrolled patients)

	Baseline (n=116)	Week 4 (n=114)	Week 12 (n=114)	Week 24 (n=109)	Last Visit[a] (n=115)
Average Volume per Catheterization (mL)[b]					
<=50	19 (16.4%)	12 (10.5%)	7 (6.1%)	4 (3.7%)	6 (5.2%)
>50-100	36 (31.0%)	24 (21.1%)	23 (20.2%)	28 (25.7%)	29 (25.2%)
>100-150	37 (31.9%)	31 (27.2%)	46 (40.4%)	39 (35.8%)	41 (35.7%)
>150-200	17 (14.7%)	29 (25.4%)	25 (21.9%)	23 (21.1%)	23 (20.0%)
>200-250	2 (1.7%)	16 (14.0%)	5 (4.4%)	9 (8.3%)	9 (7.8%)
>250	5 (4.3%)	2 (1.8%)	8 (7.0%)	6 (5.5%)	7 (6.1%)
Statistics					
n	116	114	114	109	115

Mean (SEM)	112.4 (6.6)	133.8 (5.9)	136.5 (5.9)	138.2 (6.1)	137.5 (6.1)
Median	104.5	121.5	124.3	133.3	133.3
Range	13 to 455	9 to 332	23 to 345	15 to 375	15 to 375
Change from Baseline[c]					
n		114	114	109	115
Mean (SEM)		21.6 (4.7)	26.0 (4.7)	25.5 (5.9)	25.7 (5.7)
Median		18.4	29.8	26.1	26.1
Range		-209 to 145	-163 to 148	-292 to 245	-292 to 245
p-value[d]		<0.0001	<0.0001	<0.0001	<0.0001

Source: Table 12.1.4.1-1 in Vol. 1 on pg. 127

[a] Data included are from the last visit completed in the study after baseline

[b] Average Volume per catheterization = total volume on the diaries divided by the number of catheterization

[c] Change from baseline is the value at the visit minus the value at baseline

[d] p-value was calculated using the paired t-test

The change from baseline in urine volume after morning awakening for the All Enrolled patients is presented in Table 3. The data demonstrated statistically significant increases in urine volume after morning awakening at all treatment time points (mean 172-180 mL) when compared to baseline (mean 147 mL).

Table 3 Change from baseline in urine volume after morning awakening (All Enrolled patients)

	Baseline (n=116)	**Week 4 (n=114)**	**Week 12 (n=114)**	**Week 24 (n=109)**	**Last Visit[a] (n=115)**
Volume after morning awakening (mL)[b]					
<=50	10 (8.6%)	10 (8.8%)	8 (7.0%)	4 (3.7%)	5 (4.3%)
>50-100	29(25.0%)	13 (11.4%)	16 (14.0%)	20 (18.3%)	21 (18.3%)
>100-150	30 (25.9%)	31 (27.2%)	30 (26.3%)	20 (18.3%)	22 (19.1%)
>150-200	24 (20.7%)	19 (16.7%)	28 (24.6%)	28 (25.7%)	29 (25.2%)
>200-250	13 (11.2%)	21 (18.4%)	17 (14.9%)	16 (14.7%)	16 (13.9%)
>250	10 (8.6%)	20 (17.5%)	15 (13.2%)	21 (19.3%)	22 (19.1%)
Statistics					
n	116	114	114	109	115
Mean (SEM)	146.7 (8.1)	172.0 (8.0)	172.1 (8.8)	179.6 (8.9)	178.3 (8.69)
Median	135.0	160.0	160.0	172.5	170.0
Range	5 to 540	5 to 375	20 to 493	17 to 550	17 to 550
Change from Baseline[c]					
n		114	114	109	115
Mean (SEM)		25.1 (6.7)	26.4 (7.7)	33.0 (8.3)	32.1 (8.1)
Median		25.0	24.0	26.7	25.0
Range		-270 to 200	-195 to 280	-223 to 450	-223 to 450
p-value[d]		0.0003	0.0008	0.0001	0.0001

Source: Table 12.1.4.1-2 in Vol. 1 on pg. 128
[a] Data included are from the last visit completed in the study after baseline
[b] Volume after morning awakening = average of volumes of the first catheterizations after morning awakening on the diaries.
[c] Change from baseline is the value at the visit minus the value at baseline
[d] p-value was calculated using the paired t-test

3.4.4 Secondary (Supportive) Efficacy Analyses

Regarding the secondary efficacy parameter, the percentage of episodes of leakage between catheterizations documented at baseline, Weeks 4, 12, and 24 (or early termination), the All Enrolled patient data is presented in Table 4. The data demonstrated statistically significant increases in the percentage of catheterizations without a leaking accident at all treatment time points (mean 55-57 %) when compared to baseline (mean 36%).

Table 4 Change from baseline in percentage of catheterizations without a leaking accident (All Enrolled patients)

	Baseline (n=116)	Week 4 (n=114)	Week 12 (n=114)	Week 24 (n=109)	Last Visit[a] (n=115)
% of catheterizations without a leaking accident[b]					
<10	38 (32.8%)	15 (13.2%)	17 (14.9%)	18 (16.5%)	18 (15.7%)
10-<20	12 (10.3%)	7 (6.1%)	6 (5.3%)	6 (5.5%)	6 (5.2%)
20-<40	15 (12.9%)	21 (18.4%)	13 (11.4%)	13 (11.9%)	13 (11.3%)
40-<60	17 (14.7%)	11 (9.6%)	14 (12.3%)	14 (12.8%)	16 (13.9%)
60-<80	16 (13.8%)	25 (21.9%)	26 (22.8%)	23 (21.1%)	25 (21.7%)
80-<90	8 (6.9%)	11 (9.6%)	14 (12.3%)	12 (11.0%)	12 (10.4%)
>=90	10 (8.6%)	24 (21.1%)	24 (21.1%)	23 (21.1%)	25 (21.7%)
Statistics					
n	116	114	114	109	115
Mean (SEM)	36.0 (3.2)	55.2 (3.2)	57.3 (3.2)	55.5 (3.4)	56.5 (3.2)
Median	26.4	62.5	66.7	60.0	60.0
Range	0 to 100	0 to 100	0 to 100	0 to 100	0 to 100
Change from Baseline[c]					
n		114	114	109	115
Mean (SEM)		19.6 (3.2)	22.2 (3.0)	21.5 (3.3)	21.1 (3.2)
Median		16.7	16.1	14.3	15.4
Range		-100 to 100	-50 to 100	-100 to 100	-100 to 100
p-value[d]		<0.0001	<0.0001	<0.0001	<0.0001

Source: Table 12.1.4.1-3 in Vol. 1 on pg. 129
[a] Data included are from the last visit completed in the study after baseline
[b] Percentage of catheterizations without a leaking accident = number of time 'leaking accident since last catheterization' is checked 'No' on the diaries divided by the number of catheterizations.
[c] Change from baseline is the value at the visit minus the value at baseline
[d] p-value was calculated using the Wilcoxon match-pairs signed-ranks test

Regarding the secondary efficacy parameter, change from baseline in the number of catheterizations per day, All Enrolled patient data is presented in Table 5. The data demonstrated no statistically significant change in the number of catheterizations per day at all treatment time points (mean 4.5-4.7) when compared to baseline (mean 4.7).

Table 5 Change from baseline in the number of catheterizations per day (All Enrolled patients)

	Baseline (n=116)	Week 4 (n=114)	Week 12 (n=114)	Week 24 (n=109)	Last Visit[a] (n=115)
Number of catheterizations per day[b]					
<2	0	0	0	0	0
2-<4	10 (8.6%)	12 (10.5%)	8 (7.0%)	6 (5.5%)	6 (5.2%)
4-<6	80 (69.0%)	81 (71.1%)	79 (69.3%)	80 (73.4%)	83 (72.2%)
6-<8	23 (19.8%)	20 (17.5%)	23 (20.2%)	20 (18.3%)	23 (20.0%)
8-<10	2 (1.7%)	1 (0.9%)	4 (3.5%)	2 (1.8%)	2 (1.7%)
>=10	1 (0.9%)	0	0	1 (0.9%)	1 (0.9%)
Statistics					
n	116	114	114	109	115
Mean (SEM)	4.7 (0.11)	4.5 (0.09)	4.7 (0.10)	4.6 (0.10)	4.7 (0.10)
Median	4.5	4.2	4.5	4.3	4.5
Range	2 to 10	3 to 8	3 to 9	3 to 10	3 to 10
Change from Baseline[c]					
n		114	114	109	115
Mean (SEM)		0.3 (0.09)	0.1 (0.09)	0.1 (0.08)	0.1 (0.08)
Median		0.0	0.0	0.0	0.0
Range		-2 to 3	-5 to 4	-3 to 3	-3 to 3
p-value[d]		0.0039	0.2419	0.2815	0.2510

Source: Table 12.1.4.1-4 in Vol. 1 on pg. 130

[a] Data included are from the last visit completed in the study after baseline

[b] Number of catheterizations per day = Total number of catheterizations on the diaries divided by the number of diaries.

[c] Change from baseline is the value at baseline minus the value at the visit

[d] p-value was calculated using the paired t-test

Also evaluated were the urodynamic measurements (in particular changes over time in maximal bladder capacity, detrusor and intravesical pressure at maximal bladder capacity, and presence of uninhibited detrusor contractions > 15 cm H_2O) collected at baseline, Week 12, and Week 24 and Last Visit as presented in Tables 12.1.4.1-6 through 12.1.4.1-10 in Vol. 1 on pg. 132-136. The data demonstrated:

- statistically significant increases in maximum cystometric capacity at all treatment time points (mean 260-269 mL) when compared to baseline (mean 197 mL)
- statistically significant decreases in detrusor pressure at maximal bladder capacity at all treatment time point s(mean 32-34 cmH_20) when compared to baseline (mean 43 cmH_20)
- statistically significant decreases in intravesical pressure at maximal bladder capacity at all treatment time points (mean 44-47 cmH_20) when compared to baseline (mean 55 cmH_20)

- statistically significant increases in the number of patients with no uninhibited detrusor contractions at all treatment time points (range of 75 to 84 patients) when compared to baseline (50 patients)

Efficacy summaries provided by the sponsor by age group (Tables 12.1.4.2-1 through 12.1.4.2.9 in Vol. 1 on pg. 137-154), by total daily dose (mg) of Ditropan (Tables 12.1.4.3-1 through 12.1.4.3-9 in Vol. 1 on pg. 155-199), by total daily dose (mg) per kilogram body weight of Ditropan (Tables 12.1.4.4-1 through 12.1.4.4-9 in Vol. 1 on pg 200-244), and by formulation of Ditropan (Tables 12.1.4.5-1 through 1.2.1.4.5-9 in Vol. 1 on pg. 245-271) were also reviewed. Overall, there was no change from the previous efficacy conclusions based on the subgroup analyses. There was less of a decrease from baseline in intravesical pressure at maximum cystometric capacity in the age group >10 years than in the age group ≤ 10 years. There was more variability due to small numbers of patients in each group when the data was subdivided into 5 dosing groups by total daily dose and by total daily dose per kilogram body weight.

3.4.5 Pharmacokinetic Data Summary (PK Subgroup)

There were no changes from the interim report.

3.5 Safety

3.5.1 Safety Measurements

There were no changes from the interim report.

3.5.2 Extent of exposure

The duration of exposure is summarized in Table 6. The mean duration of exposure was 24.3 weeks (range 5.7 to 31.4 weeks). After enrollment, 22 patients (19.0%) had at least one change to their total daily dose: 22 patients had one dose increase, 2 patients had one dose decrease, and 7 patients had dose interruptions ranging from 2 to 15 days (in Vol. 1 on pg. 65 and 125). After enrollment, three patients changed their formulation.

Table 6 Duration of Treatment for Patients

Weeks on Treatment	Patients (n=116)
<20	5
20-<22	1
22-<24	19
24-<26	66
26-<28	19
>28	6

Compiled from Table G in Vol. 1 on pg. 64

3.5.3 Serious adverse events

Deaths: there were no deaths

Premature termination due to safety reasons: no patients terminated prematurely form the study because of safety reasons.

Serious adverse events: Fourteen patients reported a total of 17 serious adverse events: 1 prior to enrollment, 3 treated with Ditropan syrup, 2 treated with Ditropan tablets, and 7 treated with Ditropan XL (see Table 25). None of the serious adverse events were considered by the investigator to be related to study treatment.

Table 7 Serious Adverse Events by Treatment Group (All Enrolled Patients)

Patient #	Age (years)	Formulation	Total Daily Dose (mg)	Serious Adverse Event	Relationship to Treatment
2601	10	Prior to enrollment	N/A	Hospitalized: urinary tract infection	Not related
303	10	Ditropan syrup	11.25	Surgery: bilateral pelvic osteotomies (for correction of congenital bilateral hip dysplasia) and post-op urinary tract infection	Not related
1704*	11	Ditropan syrup	10.5	Hospitalized: evaluation of nocturnal hypoventilation [ ] and Surgery: release tethered cord [ ]	Not related
2201	8	Ditropan syrup	15	Hospitalized: pyelonephritis [ ] Surgery: ventriculoperitoneal shunt [ ]	Not related
1001*	12	Ditropan tablets	10	Surgery: elective exploration of ventriculoperitoneal shunt	Not related
1203*	7	Ditropan tablets	7.5	Surgery : release of tight right hip flexor	Not related
304	7	Ditropan XL	10	Surgery: bilateral Sta-Peg subtalar implants, mid foot, heel, and ankle tendon release	Not related
601*	5	Ditropan XL	10	Hospitalized: Pyelonephritis x 5 days	Not related
617*	10	Ditropan XL	10	Surgery: release of tethered cord	Not related
708	11	Ditropan XL	15	Surgery: revision of ventriculoperitoneal shunt	Not related
709	13	Ditropan XL	10	Surgery: revision of ventriculoperitoneal shunt	Not related
1201*	14	Ditropan XL	10	Surgery: replacement of nonfunctioning ventriculoperitoneal shunt	Not related
1401	11	Ditropan XL	10	Surgeries: release of tethered cord [ ] ventriculoperitoneal shunt revision [ ]	Not related
2802	10	Ditropan XL	10	Hospitalized for elective bilateral cast replacement	Not related

b(6)

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Source: Table 8.1.5.2 in Vol. 14 on pg. 120-125 and Table M in Vol. 1 on pg. 71

Medical Reviewer's comment:

1) **Narratives for the 17 serious adverse events (Attachment 12.3.1 in Vol. 2 on pg. 167-175) were reviewed. The two cases of pyelonephritis could be related to study drug if the larger volumes per void on treatment resulted in an increased tendency to reflux urine. However all patients**

were being catheterized multiple times each day, so the reviewer considers the two during treatment hospitalizations for pyelonephritis to be expected.

3.5.4 Frequent adverse events

At least one adverse event was reported by 100 (86.2%) of the All Enrolled patient group. The most frequent adverse events were urinary tract infections, headache, surgical procedure, constipation, and upper respiratory tract infection. The surgical procedures were all unrelated to study medications and due to the underlying disease of the patients. Table 14 presents the adverse events occurring in ≥5% in the All Enrolled patient group

Table 8 Adverse Events Reported by ≥5% of Total Patients in the All Enrolled Patient Group

	Ditropan Syrup (n=30)	Ditropan tablets (n=28)	Ditropan XL (n=611)	Total (n=116)
Urinary tract infections	17 (56.7%)	8 (28.6%)	32 (52.5%)	57 (49.1%)
Headache	3 (10.0%)	4 (14.3%)	4 (4.9%)	10 (8.6%)
Surgical procedure	2 (6.7%)	1 (3.6%)	7 (11.5%)	10 (8.6%)
Constipation	1 (3.3%)	2 (7.1%)	6 (9.8%)	9 (7.8%)
Upper respiratory tract infection	4 (13.3%)	2 (7.1%)	3 (4.9%)	9 (7.8%)
Pain	2 (6.7%)	1 (3.6%)	5 (8.2%)	8 (6.9%)
Diarrhea	0	2 (7.1%)	6 (9.8%)	8 (6.9%)
Otitis media	3 (10.0%)	2 (7.1%)	3 (4.9%)	8 (6.9%)
Pharyngitis	2 (6.7%)	3 (10.7%)	2 (3.3%)	7 (6.0%)
Rhinitis	1 (3.3%)	2 (7.1%)	3 (4.9%)	6 (5.2%)

Source: Table J in Vol. 1 on pg. 67

At least one adverse event **related to study medication** was reported by 21 (18.1%) patients. The most frequently reported adverse event felt by the investigator to be related to treatment was constipation (n=8, 6.9%). One patient (#601) in the Initial Cohort had a normal EKG at baseline (heart rate=91 bpm, PR interval=95 msec) and had first degree atrioventricular (AV) block (heart rate=180 bpm, PR interval=200 msec) at the end of the study. The EKG change was considered by the investigator to be related to study treatment. The sponsor reported (in Vol. 2 on pg. 175) that after data base lock, assessment of these EKG scans by an in-house medical expert determined that the baseline PR interval and the end-of-study heart rate were reported incorrectly. The correct values were 190 msec for the baseline PR interval and 82 bpm for the end-of-study heart rate. One severe adverse event felt to be related to study medication (more frequent urine leakage [urinary incontinence]) was reported. The one adverse event potentially related both to treatment and to patient age was constipation: eight of the 9 patients who reported constipation were in the younger age group (i.e. 10 years old or younger).

Anticholinergic adverse events were reported by 18 (15.5%) of the All Enrolled. Constipation (9 patients, 7.8%) and vomiting (4 patients, 3.4%) were the most frequently reported events. Other reported anticholinergic effects were asthenia, dry mouth, insomnia, nervousness, and somnolence in one patient each and dyspepsia in two patients.

Medical Reviewer's comment:

1) **It was highly unusual for an anticholinergic drug to have only 1 (0.9%) of the 116 All Enrolled patients report dry mouth as an adverse event.**

Because of adverse events, two patients had the dose of their study treatment decreased, five patients had doses interrupted, and one patient had the dose increased (in Vol. 1 on pg. 69)

3.5.5 Laboratory Values

For laboratory values, retest values were excluded from the summary tables. These values were included in the lab listings only. The serum chemistry, hematology, and urinalysis test results provided in Tables 12.1.6-12. 12.1.6-14 and 12.1.6-16 in Vol. 2 on pg. 102-107, 111-116 and 120-121 were reviewed. Shift tables were provided in Tables 12.1.6-13, 12.1.6-15, and 12.1.6-17 in Vol. on pg. 108-110, 117-119 and 122 were reviewed. No clinically significant changes in the laboratory values were noted. The individual laboratory abnormalities that required immediate notification of the investigator or were considered clinically significant and were recorded as an adverse event and were provided in Vol. 1 on pg. 764-75 were reviewed. None of the individual laboratory abnormalities warranted being disclosed in labeling.

3.5.6 Concomitant Medications

The concomitant medications listed in Table 12.1.6-9 on pg. 96-99 for the enrolled patients were reviewed. The five most common concomitant medication were antibiotics or acetaminophen: Amoxicillin (n=16, 14.3%), Suprax (n=14, 12.5%), Tylenol (n=12, 10.7%), Bactrim (n=11, 9.8%), and Augmentin (n=9, 8.0%). None of the concomitant medications warrant being discussed in labeling.

3.5.7 Vital Signs

The heart rate and blood pressure values by visit (Table 12.1.6-10 and Table 12.1.6-11 in Vol. 2 on pg. 100-101) for the enrolled patients were reviewed. For the heart rate values, no significant change in mean or median or range of values was noted. For blood pressure values, no significant change in mean or median systolic or diastolic blood pressure was noted.

3.5.8 Reviewer's assessment of efficacy and safety

In Study **C-2000-042-01,** administration of Ditropan tablets, Ditropan syrup, and Ditropan XL for a duration of up to 24 weeks was demonstrated to be effective and safe for the treatment of detrusor hyperreflexia in 116 pediatric patients with spina bifida 6 years of age and older.

For the enrolled patient population, statistically significant changes in the mean average volume of urine per catheterization ($p<0.001$) from baseline (112 mL) to last visit (138 mL), mean maximal cystometric capacity ($p<0.001$) from baseline (197 mL) to last visit (269 mL), mean detrusor pressure at maximal cystometric capacity ($p<0.001$) from baseline (42.9 cmH_20) to last visit (34.0 cmH_20), mean intravesical pressure at maximal cystometric capacity ($p=0.004$) from baseline (55.1 cmH_20) to last visit (47.4 cmH_20), and a decreased number of patient who demonstrated uninhibited detrusor contractions of at least 15 cm H_20 from baseline (n=66) to end of study (n=30) were documented.

No new or unlabeled safety issues were identified.

No clear relationship between the total daily dose (by mg or by mg/kg) administered of Ditropan tablets, Ditropan syrup, or Ditropan XL and the pharmacokinetic results in pediatric patients with spina bifida was identified.

No clear dose-response or concentration-response relationship between the total daily dose administered of Ditropan tablets, Ditropan syrup, or Ditropan XL and pharmacodynamic results in pediatric patients with spina bifida was identified. The reader is referred to additional comments relevant to the PK/PD relationship in the clinical pharmacologist's review.

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The reviewer understands that compliance may be difficult to achieve in pediatric trials; however, the reviewer believes that the percentage of protocol violators and significant protocol deviators in C-2000-042-01 compromised the findings to some degree.

17 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Brenda Gierhart
3/21/03 05:39:41 PM
MEDICAL OFFICER

Mark S. Hirsch
3/24/03 09:12:14 AM
MEDICAL OFFICER
I concur.

NDA 20-897 **SE8**-009
NDA 17-577 **SE8**-033
NDA 18-211 **SE8**-016

Medical Team Leader's Memo: Pediatric Efficacy Supplements

Submitted:

Original sNDA	December 7, 2001
Response to Approvable	October 16, 2002
Received:	
Original sNDA	December 7, 2001
Response to Approvable	October 17, 2002
Memo completed:	April 10, 2003

Sponsor: ALZA Corporation, Mountain View, CA
Sponsor for regulatory submissions: Johnson & Johnson Pharmaceutical R&D, Titusville, N.J.
Drugs: Ditropan XL extended release tablets (oxybutynin chloride)
Ditropan Tablets (oxybutynin chloride)
Ditropan Syrup (oxybutynin chloride)

Regarding: Pediatric clinical and clinical pharmacology data supporting new labeling

1. Executive summary:
The purpose of this memo is to provide the Division Director with my recommendation regarding regulatory action on these three efficacy supplements. I recommend **approval** of all three supplements. The sponsor has provided substantial new clinical efficacy and safety information to support a new pediatric indication for Ditropan XL. Further, additional clinical and clinical pharmacology information in children has been submitted to support new labeling in the corresponding sections of the Ditropan Tablets and Syrup label, two products already approved for use in children.

2. Scientific background:
Oxybutynin chloride has long been a mainstay in the treatment of urinary urgency, urinary frequency and urinary incontinence in both adults and children. It is an anticholinergic agent that relaxes bladder smooth muscle through both its antagonism of the parasympathetic nervous system and its direct bladder muscle relaxing action. This relaxation serves to enhance the storage function of the bladder by increasing maximum bladder capacity and by reducing the occurrence of involuntary bladder (or "detrusor") contractions (IDCs). Thereby, the symptoms of urgency, urge incontinence and frequency are lessened in patients suffering from this problem.

While a great deal of research has recently been focused on the problem of urinary incontinence in adults, the problem of incontinence in children is equally as significant but has not received as much attention. The youngest of children (those of age 5 years and less) learn and develop bladder control as the body matures and as training ensues. However, in some children maturation and training does not fully accomplish the goal of dryness.

Incontinence in children may be viewed as two broad categories: children with known neurological etiologies for their symptoms and children without known etiologies. In the group without known etiology there are a great number of children who experience episodes of nocturnal urine loss (enuresis) without a known etiology. In the vast majority of these children, nocturnal symptoms abate with time. This group is not the focus of these supplements. In

another group of children older than 5 years of age, there are also symptoms of daytime urgency, incontinence, and frequency without obvious neurological etiology. In the majority of this group (sometimes referred to as those with "overactive bladder", or "detrusor overactivity with no associated neurological condition"), the symptoms also abate with growth and maturation. Again, this is not the focus of these supplements.

The focus of these sNDAs is the group of children with urinary incontinence as a result of known neurological conditions. The majority of these children have congenital malformations of the spinal cord, conditions known generically as "spina bifida" or "myelomeningocele". In these children, neither maturation nor training fully relieves the urinary symptoms. Many of these children have an array of urinary symptomatology including both urinary incontinence and urinary retention. Some require chronic or intermittent bladder catheterization. Their problem with urinary incontinence, coupled with their other physiological dysfunctions and physical ailments, has a substantial impact on quality-of-life for both them and their caregivers. Additional therapies for the management of urinary incontinence would certainly be welcomed in this community. Such was the intent of these supplements; that is, to provide an additional therapy for these children (Ditropan XL tablets), and to further improve the understanding of the currently approved therapy (Ditropan Tablets [immediate-release] and Ditropan Syrup).

3. Regulatory history:

3.1. Rationale for the Written Request

The regulatory history of these 3 supplements has been nicely discussed by the primary medical officer, Dr. Gierhart, in her original NDA review (page 8-9) and her review of the complete response to approvable (page 4-5). In brief, Ditropan Tablets were approved for marketing in 1975, Ditropan Syrup was approved in 1979, and Ditropan XL was approved in 1998.

Ditropan Tablets and Syrup are approved for use in children and this use is widespread. Nevertheless, the label has never contained information relevant to pharmacokinetics, actual clinical effect, or the relationship between the two in children.

Ditropan XL is not approved for children. It is approved in adults for the treatment of "overactive bladder", a symptomatic condition encompassing symptoms of urinary urgency, frequency, or incontinence. The sponsor and the Division believed that Ditropan XL might offer a good alternative in children for whom both Ditropan Tablets and Syrup are already indicated (those with detrusor overactivity of neurological origin). Ditropan XL has the known benefit of once daily dosing and the potential benefits of a more consistent delivery of drug over 24 hours. However, no data was available for Ditropan XL to assure the Division of its safety, efficacy or pharmacokinetics in children.

Therefore, on November 30, 2000, the Office issued the sponsor a Written Request (WR) to conduct studies in children using Ditropan XL, Ditropan Tablets and Ditropan Syrup. The Division requested that two studies be conducted under the terms of the WR.

3.2 Studies in the Written Request

The first study (**C-2000-042-01**) was intended as a large efficacy, safety and pharmacokinetic evaluation in approximately 116 children with detrusor overactivity related to neurogenic conditions (e.g. spina bifida). This would be 24 weeks in duration, would include all three formulations and would assess efficacy using both clinical parameters (via voiding diary and catheterization schedules) and urodynamic parameters (maximum bladder capacity, detrusor pressures at maximum capacity, and voume at first involuntary detrusor contraction). In addition, sparse sampling for serum oxybuynin chloride concentrations would be used to derive

pharmacokinetic parameters for each formulation. Finally, safety would be assessed mainly by clinical adverse events, serum laboratories and EKGs. The hope was that the information from this study would support a new indication for Ditropan XL and new information in the Ditropan Tablets/Syrup label.

The second study (**C-2000-043-01**) was intended as a smaller pilot (or exploratory) study of Ditropan Syrup in children less than aged six with known myelomeningocele. The rationale in this case was that "prophylactic" anticholinergic treatment might improve long-term bladder function in these children. This type of treatment had been reported in the clinical literature and was being used by some practicing pediatric urologists. Therefore, the study was designed as a short (13 to 28 days) and small study (n=16). The efficacy parameters were from urodynamic studies (especially focusing on bladder pressures). [ ] [ ] [ ] [ ] [ ] At the very least, this effort might lead to additional research in this important area.

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3.3. Review of the supplements

On December 7, 2001, the sponsor submitted a 43-volume NDA supplement for each of these three NDAs. This document contained the majority of the data from Study 042 (an interim report) and the full report for Study 043. On February 1, 2002, at a meeting of the Pediatric Exclusivity Board, it was decided that despite the interim nature of the study report for Study 042, the materials the sponsor had submitted "fairly responded" to the exact specifications of the WR. A six-month extension of exclusivity on all remaining exclusivity and patents for all three formulations was granted.

On March 12, 2002, an amendment to these supplements was received. On July 29, 2002, an additional amendment was received. Because labeling negotiations had not been completed and because additional time was needed to review the large July 29 clinical amendment, the Division took an "approvable" regulatory action on October 7, 2002. On October 17, 2002, the sponsor submitted a regulatory letter re-submitting the July 29, 2002 amendment as a "Complete Response to Approvable" (as had been agreed upon with the Division). Both the original submission and the complete response underwent detailed review by Drs. Gierhart and Hirsch for the clinical team and by Drs Sun, Chatterjee and Parekh for the clinical pharmacology team.

In the next sections, I will present a very brief overview of the data derived from the trials, the conclusions drawn and the labeling found to be appropriate. The reader should be aware that both Dr. Gierhart and Dr. Chatterjee's reviews contain greater detail about the results of these trials. The reader is referred to these sources for more information.

4. Data from Study 042

4.1. Demographics and Disposition in Study 042

The total number of patients enrolled was 116 at a total of twenty-three U.S. sites and one site in the Netherlands. The inclusion/exclusion criteria called for children with "detrusor hyperreflexia due to neurogenic conditions (e.g. spina bifida)". These children all were previous users of oxybutynin chloride in conjunction with clean intermittent urethral catheterization (CIC). There were 56 males and 60 females. The median age was 10 years and ranged from 4 years to 16 years of age. Seventy-two patients were less than 10 years old and 44 were older than 10 years. The majority of children (64%) were Caucasian. Of the remainder, 20% were Hispanic and 15% were African-American. The median patient weight was 30.4 kg and ranged from 16 to 100 kg. Of

note, 32% of patients had a history of fecal impaction and 72% reported a history of fecal incontinence.

In terms of study drugs, mean duration of exposure to oxybutynin was 24.3 weeks (range 6 to 31 weeks). Sixty-one patients received Ditropan XL, 30 received Ditropan Syrup and 28 received Ditropan Tablets. (These numbers tally >116 because 3 patients switched formulation during the trial.) The doses taken during the trial for Ditropan XL were either 10 or 15 mg once daily. The total daily doses taken for Syrup were 5mg to 30mg, and for Tablets 5mg to 15mg, both in BID, TID or QID divided doses. The total daily oxybutynin dose on a mg/kg basis was either 0.20-<40 mg/kg (46%), or 0.40-<0.60mg/kg (34%) in the majority of patients.

Five patients out of 116 discontinued from study prematurely, none due to adverse reactions. A fair number of patients either missed doses or adjusted dosage schedules (in a strict sense, these were "non-compliers"), and a fair number took dosage regimens not exactly specified in the WR or protocol. I do not believe that these minor compliance issues preclude our deriving important information from this trial.

4.2. Clinical Efficacy and Urodynamic Results in Study 042
Clinical efficacy results demonstrated the benefit of oxybutynin on urine storage. Improvements were noted in the "all enrolled" group (N=116) in terms of increasing average urine volume per catheterization, increasing urine volume after morning awakening, and increasing percentage of catheterizations without a leaking accident. The exact figures for these endpoints may be found in Dr. Gierhart's March 21, 2003 review in Tables #2, #3 and #4. A summary of this data was translated to the appropriate product label as follows:

At total daily doses ranging from 5 mg to 15 mg, treatment with **Ditropan Tablets** was associated with an increase from baseline in mean urine volume per catheterization from 122 mL to 145 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 168 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 43% to 61%.

At total daily doses ranging from 5 mg to 30 mg, treatment with **Ditropan Syrup** was associated with an increase from baseline in mean urine volume per catheterization from 113 mL to 133 mL, an increase from baseline in mean urine volume after morning awakening from 143 mL to 165 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 63%.

Administration of **DITROPAN XL** 5 to 20 mg/day was associated with an increase from baseline in mean urine volume per catheterization from 108 mL to 136 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 189 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 51%.

Urodynamic results measured over time were consistent with these clinical results. These included: increases in maximum cystometric bladder capacity, decreases in detrusor pressure at maximal bladder capacity (a particularly welcome finding), and an increases in the percentage of patients with no inhibited detrusor contractions. These results were translated to the labels as follows:

Treatment with **Ditropan Tablets** was associated with an increase from baseline in maximum cystometric capacity from 230 mL to 279 mL, a decrease from baseline in

mean detrusor pressure at maximum cystometric capacity from 36 cm H_20 to 33 cm H_20, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_20) from 39% to 20%.

Treatment with **Ditropan Syrup** was associated with an increase from baseline in maximum cystometric capacity from 192 mL to 294 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 46 cm H_20 to 37 cm H_20, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_20) from 67% to 28%.

Administration of **DITROPAN XL** resulted in an increase from baseline in mean maximum cystometric capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 cm H_2O to 33 cm H_2O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_2O) from 60% to 28%.

4.3. Pharmacokinetic Results in Study 042

Forty-two patients out of the total 116 "all enrolled group" underwent sparse sampling for oxybutynin chloride serum concentrations. In this group, 19 were taking Ditropan XL, 11 were taking Ditropan Tablets, and 12 were taking Ditropan Syrup. The total daily dose was 10mg in 43% of these patients and 15mg in 41%. The total daily dose on a mg/kg basis was 0.20-<0.40 mg/kg in 50% and 0.40-<60mg/kg in 31% of these patients. Twenty-five children in the pK subgroup were <=10 years of age and 17 were older than 10 years. The medical officer was unable to determine any relationship between total daily dose or total daily dose in mg/kg and pharmacokinetic parameters. However, our clinical pharmacology were successful in using all the available data to derive some pK conclusions. Specifically, for Ditropan Tablets and Syrup, when all available data were normalized to a total dose of 5 mg BID or TID, the pK parameters at steady state were translated to the label as the Tables #1 and #2 and Figure #1 that follow:

Table 1. Mean (± SD) R- and S-oxybutynin and R- and S-desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 7.5 mg to 15 mg Total Daily Dose of Ditropan Tablets. All Available Data Normalized to An Equivalent of 5 mg BID or TID at Steady State.(N=11)

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}*(ng/mL)	6.1± 3.2	10.1 ± 7.5	55.4 ± 17.9	28.2 ± 10.0
T_{max} (hr)	1.0	1.0	2.0	2.0
AUC** (ng.hr/mL)	19.8 ± 7.4	28.4 ± 12.7	238.8 ± 77.6	119.5 ± 50.7

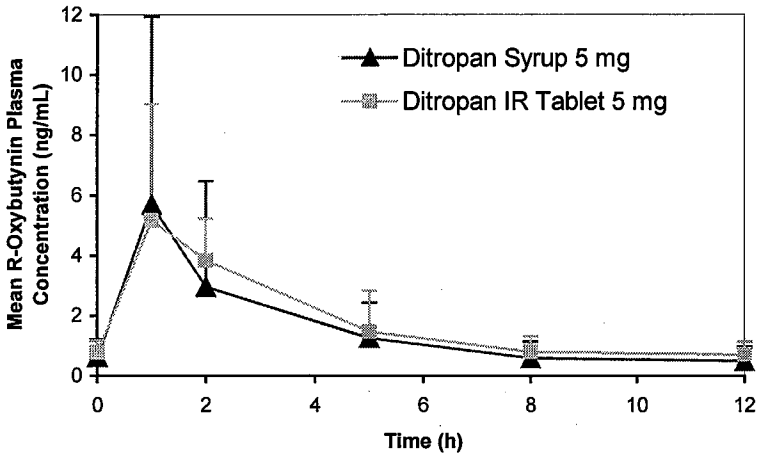
*Reflects C_{max} for pooled data **$AUC_{0\text{-end of dosing interval}}$

Table 2. Mean (± SD) R- and S-oxybutynin and R- and S-desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 5 mg to 22.5 mg Total Daily Dose of Ditropan Syrup. All Available Data Normalized to An Equivalent of 5 mg BID or TID at Steady State.(N=12)

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}* (ng/mL)	5.7 ± 6.2	7.3 ± 7.3	54.2 ± 34.0	27.8 ± 20.7
T_{max} (hr)	1.0	1.0	1.0	1.0
AUC** (ng.hr/mL)	16.3 ± 17.1	20.2 ± 20.8	209.1 ± 174.2	99.1 ± 87.5

*Reflects C_{max} for pooled data **$AUC_{0\text{-end of dosing interval}}$

Figure 1. *Mean steady-state (±SD) R-oxybutynin plasma concentrations following administration of total daily Ditropan dose of 5 mg to 30 mg (0.21 mg/kg to 0.77 mg/kg) in children 5-15 years of age. – Plot represents all available data normalized to the equivalent of Ditropan 5 mg BID or TID at steady state*

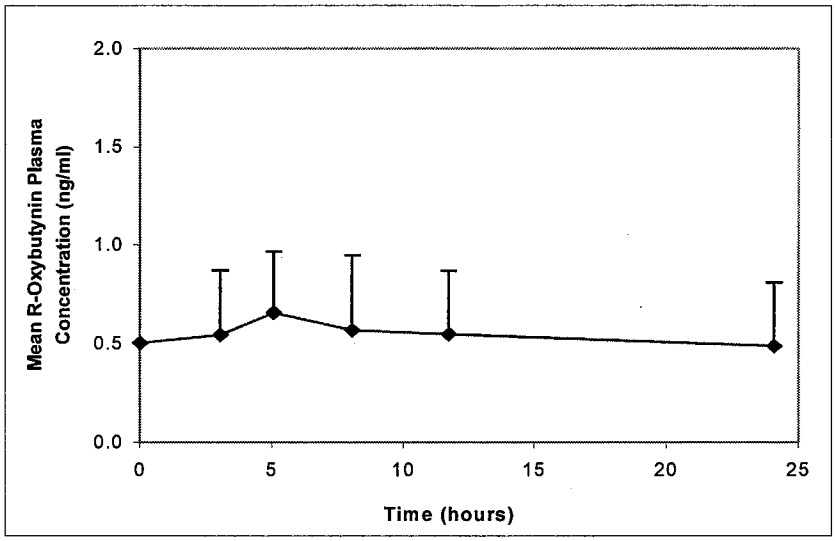


For Ditropan XL, the label reflects the following derived pharmacokinetic parameters in children:

Table 3. Mean R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5 to 20mg Ditropan XL Once Daily. All Available Data Normalized To An Equivalent of Ditropan XL 5 mg Once Daily. (N=19)

	R-Oxybutynin	S-Oxybutynin	R-Desethyloxybutynin	S-Desethyloxybutynin
C_{max} (ng/mL)	0.7 ± 0.4	1.2 ± 0.8	6.8 ± 3.5	3.8 ± 2.2
T_{max} (hr)	5.0	5.0	5.0	5.0
AUC (ng.hr/mL)	12.8 ± 7.0	23.7 ± 14.4	125.1 ± 66.7	73.6 ± 47.7

Figure 2. *Mean steady state (±SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg Ditropan XL once daily in children aged 5-15. - Plot represents all available data normalized to an equivalent of Ditropan XL 5 mg once daily*



For additional information relevant to this pharmacokinetic information, the reader is referred to Dr. Chatterjee's detailed review of these supplements.

Close examination of this data and the relationships between dose, pharmacokinetic (pK) parameters ,and pharmacodynamic (pD) parameters did not provide definitive evidence of direct correlation between dose and pK or between pk and pD. Nevertheless, this efficacy and pK data still supports a dosage and administration recommendation similar to that used in Study 042, but none more specific that that.

4.4 Safety Results from Study –042

In terms of exposure, 5 patients took drug for <20weeks, 1 patient took drug for 20-22 weeks, 19 patients took drug for 22-24 weeks, 66 patients took drug for 24-26 weeks, 19 patients took drug for 26-28 weeks and 6 took drug for >28 weeks.

There were no deaths and there were no premature discontinuations due to adverse events. Fourteen patients reported serious adverse events but none were judged as being related to treatment. Virtually all of these were for surgeries on the limbs, on the spinal cord, or on ventriculoperitoneal shunts. Only one "severe" adverse event was reported: worsening of baseline urinary leakage.

The most frequent "commonly-reported" adverse events regardless of causality were: urinary tract infection (57 patients, 49% of total group), headache (10 patients, 8.6%), surgical procedure (10 patients, 8.6%), constipation (9 patients, 7.8%), "pain" (8 patients, 6.9%), diarrhea (8 patients, 6.9%), otitis media (8 patients, 6.9%), pharyngitis (7 patients, 6.0%) and rhinitis (6 patients, 5.2%). There were no unexpected adverse events and no worrisome findings in terms of frequency or severity of adverse event reports.

In terms of the different formulations, the following clinically relevant adverse event frequencies are presented:

Headache: Ditropan XL – 4.9% (n=4), Ditropan Tablets – 14.3% (n=4), Ditropan Syrup – 10.0% (n= 3)

Constipation: Ditropan XL – 9.8% (n=6), Ditropan Tablets – 7.1% (n=2), Ditropan Syrup – 3.3% (n=1)

Diarrhea: Ditropan XL – 9.8% (n=6), Ditropan Tablets – 7.1% (n=2), Ditropan Syrup – 0% (n=0)

The most commonly reported adverse event judged to be treatment-related was constipation (6.9% of "all enrolled group" or 8 patients out of nine). While constipation and diarrhea were reported at an increased frequency in the Ditropan XL group, I believe these small numbers preclude definitive comparisons. All oxybutynin products are believed to induce some degree of constipation. Here, it is not clear to me that the XL product is either worse or better than the IR products. Further, I do not see a worrisome signal in terms of frequency of reports or severity of reports for constipation or for diarrhea in any of this data.

Other antichiolinergic adverse events reported in only one child each included: dry mouth, nervousness, insomnia, somnolence and asthenia. Dyspepsia was reported in two children.

To this reviewer, the lack of placebo group and fairly similar incidences does not allow for specific recommendations as to which drug has a better "safety profile". None of these profiles is concerning, especially in light of the background medical condition of these children and the clinical benefit noted. The labels already clearly delineate these adverse events in adults, including the potential for constipation and urinary retention with Ditropan products, especially in those with baseline intestinal or vesical atony or obstruction. This precaution is well known to the urologic community.

There were no clinically significant shifts in any laboratory parameter including chemistry and hematology. There were no significan changes in vital signs (heart rate or blood pressure). There were no specific changes in EKGs of note.

5. Data from Study 043

5.1. Demographics and Disposition in Study 043

A total of 16 patients were enrolled at 3 sites in the US and one site in the Netherlands. Ten of these children were enrolled at the Netherlands site. The median age was 3 years and range from 1 to 5 years. Five of the children were 2 years old. The majority of patients were male (69%) and Caucasian (75%). Median weight was 16 kg and ranged from 11 kg to 20 kg. Patients were all known to have detrusor hyperreflexia as a consequence of neurological conditions and were already on a stable dose of oxybutynin. Seventy percent reported a concurrent fecal impaction condition.

No patient withdrew prematurely from the two to four-week treatment period. There were numerous protocol deviations and violations mostly related to drug compliance. For example, some patients used more or less than the recommended dose of 3.6 mg/day to 9 mg/day, split into

2 to 4 daily doses. Some patients did not meet the entry criteria for detrusor hyperreflexia. Some missed urodynamic testing or pK blood draws.

4.2. Clinical Efficacy (Urodynamic) Results in Study 043
In Study 043, the efficacy was assessed by urodynamic studies at baseline and after at least two weeks on treatment. The urodynamic parameters of interest were maximal cystometric capacity, intravesical pressure, and presence of uninhibited contractions. The purpose of these measurements was to assess whether oxybutynin treatment improved capacity while lowering or maintaining intravesical pressure. All sixteen children had measurements of maximal capacity, while fifteen had the other measurements.

Maximal capacity increased from baseline by a mean of 71.5 mL with a range of improvement from 29 mL to 265 mL. On the other hand, mean detrusor pressure at maximal capacity increased slightly, as reflected by a mean increase of 0.6 cm H_20 (range from –21 cm H_20 to +50 cm H_20). There was a reduction in the percentage of patients demonstrating involuntary detrusor contractions (IDCs) of at least 15 cm H_20 from 11 of 16 patients (69%) to 2 of 16 patients (12.5%).

Thus, treatment of these children was associated with improvements in maximal vesical capacity and reduction in the percentage of patients demonstrating IDCs, but the most important factor, change-from-baseline in mean detrusor pressure, actually increased slightly. In fact, in some children, the detrusor pressures went up markedly (+50 cm H_20). In ten of the 16 children, detrusor pressures at baseline were fairly low (< 40 cm H_20).

In my opinion, until additional research supports clinical benefit of this mode of treatment or until a specific subgroup of children are defined in whom this treatment is effective without increasing bladder pressures (increasing capacity and decreasing or maintaining pressures), these results appear to preclude approval of the novel indication. This should not be construed by the reader to mean that this type of treatment may not one day be shown effective in at least some patients. In addition, this reviewer is aware of some supportive literature.

b(4)

4.4 Safety Results from Study –043
Sixteen patients took Ditropan Syrup for a range of 13 to 28 days. There were no deaths, no SAEs, and no premature discontinuations due to AEs. Thirteen of the 16 patients reported at least one "commonly-reported" AEs. Most AE terms were only listed for 1 patient each. The most frequently reported AE terms were urinary tract infection, constipation, diarrhea, vasodilation, otitis media, and ecchymoses. Treatment-related AEs were reported by only six patients and were all rated as mild – these included: constipation (2 events), diarrhea (1 event), abnormal stools (1 event), eructation (1 event), pruritis (1 event) and vasodilation (2 events). There were no clinically significant changes in heart rate. Routine laboratory values were without notable changes except for two instances of mildly elevated serum LDH

6. Reviewer's conclusion

It is my conclusion that the data generated from Study 042 demonstrates meaningful efficacy of Ditropan XL and the Ditropan IR formulations in children aged 6-15 with detrusor overactivity associated with a neurological condition (e.g. spina bifida). The treatment allows for increased bladder storage during the day and overnight, reduces wetting between catheterizations in children on CIC, reduces involuntary detrusor contractions, improves maximum vesical capacity, and reduces detrusor pressure at maximal capacity. The treatment appears safe. No expected safety concerns were noted. There is some degree of constipation associated with therapy. The pharmacokinetic information allows for an estimate of mean Cmax, AUC, Tmax and $T_{1/2}$. The pK data does not allow for a clear correlation between daily total dose (or body-weight adjusted daily dose) and serum concentrations, nor for a correlation between pK and pharmacodynamic efficacy criteria. Yet, we can still conclude that the range of doses used in the Study were safe and effective. [ ] b(4)

Therefore, I believe that a new indication has been supported for Ditropan XL label and additional clinical and clinical pharmacology information may be added to the Ditropan Tablets and Syrup label.

b(4)

APPEARS THIS WAY
ON ORIGINAL

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/s/

Mark S. Hirsch
4/10/03 11:28:16 AM
MEDICAL OFFICER
This is my April 10, 2003 memo.

Daniel A. Shames
4/10/03 05:29:52 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-577/S-032, S-033 &
18-211/S-014, S-016 &
20-897/S-009, S-010

STATISTICAL REVIEW(S)

Memorandum of Statistical Review

Date: June 11, 2002

Re: NDA 20-897 (SE8, serial 009, dated December 7, 2001)
Sponsor: ALZA Corporation
Product: Ditropan XL 5 mg, 10 mg, 15 mg
Indication: For the treatment of detrusor hyperreflexia due to neurogenic conditions in pediatric patients

This application was submitted by the sponsor as a response to a Written Request letter dated November 30, 2000 from the Division of Reproductive and Urological Drug Products to perform two pediatric studies with oxybutynin chloride and to prepare two critical analyses. Two studies were submitted, a pharmacokinetic-pharmacodynamic study and an efficacy study. This memo addresses the efficacy study.

A single, open-label, uncontrolled study (C-2000-042) with 116 enrolled pediatric patients (aged 4 to 16 years) was conducted to demonstrate efficacy and safety of the study drug over 24 weeks of daily dosing (10 mg/day or 15 mg/day) with either Ditropan tablets or Diptropan XL extended release tablets. The primary efficacy outcome was the change in urinary volume per cathertization from baseline to week 24.

The sponsor reports that 59 of the 116 patients (51%) had completed the study by November 7, 2001. This cut-off date was not prespecified in the protocol. In these 59 patients, the sponsor reports that an increase of 25.2 mL in the mean urine volume per cathertization was demonstrated from baseline to week 24.

From a statistical view, this study should be considered as observational only. No *a priori* criteria were established for efficacy, and the study results are descriptive only. No statistical review is necessary.

Sonia Castillo, Ph.D.
Mathematical Statistician
HFD-715

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/s/

Sonia Castillo
8/5/02 03:17:46 PM
BIOMETRICS

Mike Welch
8/8/02 02:00:10 PM
BIOMETRICS
Concur with reviewer's comments

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-577/S-032, S-033 &
18-211/S-014, S-016 &
20-897/S-009, S-010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20-897 S-009; *[also NDA 17-577 S033; NDA 18-211 S015]***	*Brand Name*	**DITROPAN XL**
OCPB Division (I, II, III)	**DPE II (HFD 870)**	*Generic Name*	**Oxybutynin chloride**
Medical Division	**DRUDP (HFD 580)**	*Drug Class*	**Urinary incontinence**
OCPB Reviewer	**Dhruba J. Chatterjee, Ph.D.**	*Indication(s)*	**Overactive bladder with urge incontinence, urgency & frequency**
OCPB Team Leader	**Ameeta Parekh, Ph.D.**	*Dosage Form*	**Extended release tablets**
Date of Submission	**12/7/2001**	*Dosing Regimen*	**Once daily**
Estimated Due Date of OCPB Review	**9/7/2002**	*Route of Administration*	**Oral**
PDUFA Due Date	**10/07/2002**	*Sponsor*	**Alza Corp.**
Division Due Date	**To be determined**	*Priority Classification*	**3S**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	**2**		
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
body wt.				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies	**2**			

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**X**	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above	**This is a supplement originally submitted as a study report in response to our Pediatric Study Written Request**	
Primary reviewer Signature and Date	**Dhruba J. Chatterjee, Ph.D.**	
Secondary reviewer Signature and Date	**Ameeta Parekh, Ph.D.**	

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

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/s/

Dhruba Chatterjee
2/6/02 01:55:33 PM
BIOPHARMACEUTICS
This pertains to 2 other NDAs as mentioned in the memo header.
Filable

Ameeta Parekh
2/8/02 12:29:58 PM
BIOPHARMACEUTICS
I concur

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Numbers	17-577, 18-211, 20-897 (Supplements)	*Brand Name*	DITROPAN IR, Syrup, & XL
OCPB Division (I, II, III)	DPE II (HFD 870)	*Generic Name*	Oxybutynin chloride
Medical Division	DRUDP (HFD 580)	*Drug Class*	Antimuscarinic
OCPB Reviewer	Dhruba J. Chatterjee, Ph.D.	*Indication(s)*	Urinary Incontinence
OCPB Team Leader	Ameeta Parekh, Ph.D.	*Dosage Form*	IR tabs, Syrup & XL tabs
OCPB Pharmacometrician	He Sun, Ph.D.	*Dosing Regimen*	BID, TID & QD
Date of Submission	10/17/2002	*Route of Administration*	Oral
Estimated Due Date of OCPB Review	3/30/2003	*Sponsor*	ALZA (J & J) Corp.
PDUFA Due Date	4/17/2003	*Priority Classification*	3S
Division Due Date	4/10/2003		

Clin. Pharm. and Biopharm. Information		Number of studies submitted	Number of studies reviewed	Critical Comments If any
	"X" if included at filing			
STUDY TYPE		6		
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X			
geriatrics:				
body wt.				
renal impairment:				
hepatic impairment:				
PD:				

Phase 2:				
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		***Comments***
	"X" if yes	
Application filable?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	**Is there enough PK and or PD information that may be included in the respective labels under pediatrics?**	
Other comments or information not included above	**This is a submission with study reports following PK/PD and efficacy/safety study in pediatric population.**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

OCPB Briefing held on 4/11/03, and attended by DJ Chatterjee, A. Parekh,

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

Clinical Pharmacology & Biopharmaceutics Review

NDA:	17-577, 18-211, 20-897
Product Trade Name:	DITROPAN Syrup, IR Tablet, XL Tablets
Active Ingredient/s:	Oxybutynin chloride
Indication:	Overactive bladder/urinary incontinence
Submission Dates:	10/17/2002 (pediatric supplemental NDA)
Sponsor:	ALZA Corporation (Johnson & Johnson)
Submission/Priority Type:	Supplement
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.
Pharmacometrics:	He Sun, Ph.D.

Overall Clinical Pharmacology and Biopharmaceutics Summary

? Following review of the three supplemental NDAs, the main outcome was incorporation of additional information into the DITROPAN (IR, Syrup and XL) labels following use in pediatric population.

? Based on non-parametric analysis of the pharmacokinetic data, pharmacokinetic profiles and parameters were obtained. Those plots and parameter tables are hereby included in the labels for DITROPAN IR tablets, Syrup and XL tablets (please see details under **Clinical Pharmacology**).

? Pharmacokinetic plots and parameter tables were finalized following detailed discussion with the sponsor via teleconference and continuous communication.

Background

Questions addressed in this section:

? What is urinary incontinence?
? What is the pharmacologic rationale for use of this drug?
? What is the regulatory history of this product?
? What are other available alternatives?
? What CPB studies have been submitted in support of this NDA?

Urinary incontinence, the involuntary loss of urine, is a clinical condition. Urinary incontinence affects all age groups and is particularly common in the elderly. Overactive bladder is one cause of urinary incontinence. Overactive bladder is a condition characterized by involuntary detrusor contractions during the bladder filling phase, which may be spontaneous or provoked, and which the patient cannot suppress. Overactive bladder causes troublesome symptoms, which result in a significant impairment of normal social functioning. These symptoms include frequency, nocturia, urgency, and urge incontinence. Uncontrolled bladder contractions give the feeling of urgency, and exaggerated sense of needing to urinate. In turn, urgency causes frequency and nocturia; voiding at abnormally reduced intervals. Urgency may lead to urge incontinence if the sphincter mechanism is unable to resist the uncontrolled bladder contraction. Patients may have any combination of these symptoms. Frequency may be a primary symptom of the underlying disease or may be secondarily self-induced to avoid incontinence. Frequency and urgency mean that patients must make frequent visits to the toilet, so that daily activities are conditioned by the need to be near a toilet. Sleeping patterns are disrupted when these symptoms occur at night.

Urinary incontinence is not solely due to overactive bladder. Stress urinary incontinence, particularly common in women, is a type of urinary incontinence in which the urethral closure mechanism is compromised and urine escapes when intra-abdominal pressure increases sufficiently. Leakage may also occur as a result of a combination of overactive bladder and the compromised urethral closure mechanism. Patients sometimes present with symptoms of both urge and stress incontinence, called mixed incontinence. Mixed incontinence is common in women, especially older women. Involuntary loss of urine associated with overdistension of the bladder is termed overflow incontinence. Overflow incontinence may be caused by an underactive or acontractile detrusor, or may be due to bladder outlet or urethral obstruction leading to overdistension and overflow. Urine loss may be caused by factors outside the lower urinary tract, such as, chronic impairment of physical or cognitive functioning, or both, a condition termed as functional incontinence. Urine loss may also occur without any warning or sensory awareness, such as, in paraplegics and in some patients without overt neurologic dysfunction.

Normal bladder contractions are mediated primarily through cholinergic muscarinic receptor stimulation. These receptors are believed to control normal bladder contractions, and possibly play a major role in overactive bladders. Hence, antimuscarinic drugs have

almost become a standard of therapy for overactive bladder. However, a most common side effect of these class of drugs is dry mouth (due to its effect on the salivary glands).

Several drug therapies including antimuscarinics, antispasmodics, tricyclic antidepressants and estrogen are available to treat the disease. Besides oxybutynin, tolterodine (another antimuscarinic) is available in the market as IR (DETROL) and extended release (DETROL LA) formulations.

Oxybutynin is a competitive muscarinic receptor antagonist. Oxybutynin has been available as IR tablets and syrup. More recently, an extended release formulation for oxybutynin (Ditropan XL) once-daily dosing was approved by the FDA in December, 1998. In the current application, the sponsor has presented clinical and clinical pharmacology related information following clinical studies in the pediatric population (1 – 15 year old). Based on this information, sponsor seeks pediatric dosing and PK information included in the labels for the IR tablets, syrup and XL formulations.

Clinical Pharmacology Studies

There were two clinical and clinical pharmacology studies undertaken by the sponsor for safety, efficacy, pharmacokinetics and pharmacodynamic assessment of Ditropan immediate release (IR) tablets, syrup and extended release (XL) formulation in the age appropriate pediatric population.

Design of the Two Clinical Studies

Study C-2000-042-01. This was a multicenter, 24-week treatment duration, open label, multiple-dose level, dose-response and safety study of oxybutynin (administered either as Ditropan XL, Ditropan tablets, or Ditropan syrup) in 116 pediatric subjects diagnosed with detrusor hyperreflexia due to neurogenic conditions and aged 6 to 15 years. The dose-effect (urodynamic) and concentration-effect (urodynamic) of oxybutynin chloride were evaluated. A PK study was conducted in a sub section of 42 patients at steady state: 12 on Ditropan syrup, 11 on Ditropan tablets, and 19 on Ditropan XL (QD, BID or BID).

Study C-2000-043-00. This was multicenter, open label, repeated dose, multiple-dose level, minimum 2-week treatment duration, pharmacokinetic (PK) and pharmacodynamic (PD [urodynamic]) study of Ditropan syrup in 16 pediatric patients diagnosed with detrusor hyperreflexia due to neurogenic conditions and aged one to five years. The steady state PK profiles and the dose-effect (urodynamic) and concentration-effect (urodynamic) of Ditropan syrup were evaluated.

[Please refer to Medical Officer's Review for details of the study designs, and table below]

Table 1 Tabular Listing of Submitted Clinical Investigations

Study No. Study Title	Study Design Status	No. Sites/Country	No. Patients/Sex Age Range Race	No. Patients Treatment Dose/Route/Regimen
C-2000-042-01 A Phase 3, multicenter, open-label, 24-week treatment duration, open label, multiple-dose level, dose response, safety study of oxybutynin chloride (administered either as Ditropan XL, Ditropan tablets, or Ditropan syrup) pediatric subjects aged 6 to 15 years and diagnosed with detrusor hyperreflexia due to neurogenic conditions.	Multicenter Open-label Uncontrolled Ongoing- data through November 9, 2001 was submitted as an interim report	24 sites/USA (100 of all enrolled patients and 56 of the Initial Cohort patients) and Netherlands (6 of all enrolled patients and 4 of the Initial Cohort patients)	116 pediatric patients (55 male and 61 female) with 60 in the Initial Cohort (29 male and 31 female) Range: 4 - 16 yr <6 yr=5 6-10 yr=67 11-15 yr=43 >15 yr=1 PK substudy was conducted in 42 pediatric patients 74 Caucasian 17 African American 23 Hispanic 1 Asian 1 Other	116 pediatric patients on a total daily dose of 10 or 15 mg oxybutynin chloride (administered either as Ditropan XL, Ditropan tablets, or Ditropan syrup). In the Initial Cohort of 60 patients, 17 were exposed to Ditropan syrup, 13 to Ditropan tablets and 31 to Ditropan XL. (Note: one patient switched formulation after enrollment from Ditropan syrup to Ditropan XL and was exposed to more than one formulation) PK substudy was conducted in 42 patients: 12 on Ditropan syrup, 11 on Ditropan tablets, and 19 on Ditropan XL
C-2000-043-00 A multicenter, open-label, repeated dose, multiple-dose level, minimum 2-week treatment duration, pharmacokinetic and pharmacodynamic study of Ditropan syrup in patients aged one to five years and diagnosed with detrusor hyperreflexia due to neurogenic conditions	Multicenter Open-label Uncontrolled Completed	4 sites/USA (6 patients) and Netherlands (10 patients)	16 pediatric patients (11 male and 5 female) Range: 1-5 yr. (1yr.=1; 2yr.=5; 3 yr.=4; 4yr.=4; 5yr.=2) 12 Caucasian 1 African American 3 Hispanic 0 Asian	16 patients on Ditropan syrup with their total daily dose ranging from 3.6 to 9 mg/day. Their total daily dose was split into two, three or four doses per day. 1 patient was on 3.6 mg/day split into 3 doses 1 patient was on 4 mg/day split into 2 doses 1 patient was on 4.5 mg/day split into 3 doses 1 patient was on 5 mg/day split into two doses 1 patient was on 5 mg/day split into four doses 1 patient was on 5.1 mg/day split into 3 doses 5 patients were on 6 mg/day split into 3 doses 3 patients were on 7.5 mg/day split into 3 doses 2 patients were on 9 mg/day split into 3 doses

Source: Modified from December 2001 submission, pg 53.2/8, 53. 2/78, 53.2/81, 53.2/130, 53.13/1, 53.13/246, and 53.14/325-326

PK Assessment Methods and Results

Following administration of all the three dosage forms and determination of serum levels of the parent drug and metabolite, comprehensible PK parameter tables and PK profiles were constructed. For the purposes of simplicity and practicability, mean profiles were determined. This was done by averaging out sampling time points and plotting the dose normalized (to 5 mg BID or TID) concentration levels of each patient against those time points. For Ditropan IR tablets and syrup, the steady state AUC and C_{max} were determined from pooled data and reported in the parameter table. Following such analysis, the plots and parameter tables generated were included in the respective product labels.

Additionally, parametric analysis was also performed with the aid of Non-Linear Mixed Effect Modeling (NONMEM) using the average PK information as the base model.

Assuming constant values for volume of distribution and clearance, rate of absorption was parameterized for each formulation. Post-hoc simulation for individual subjects led to individual PK parameters. Mean of those PK parameters were determined, which very closely matched parameters obtained following non-parametric determination (results of the NONMEM analysis is not included in this review). Please see Attachment 1.

For the sake of simplicity in comprehension, the average PK profiles and parameters (non-parametric) are presented in the proposed product label, as follows:

[Note: The following plots and tables were finalized following detailed discussion with the sponsor via teleconference and continuous communication.]

DITROPAN IR Tablets and Syrup:

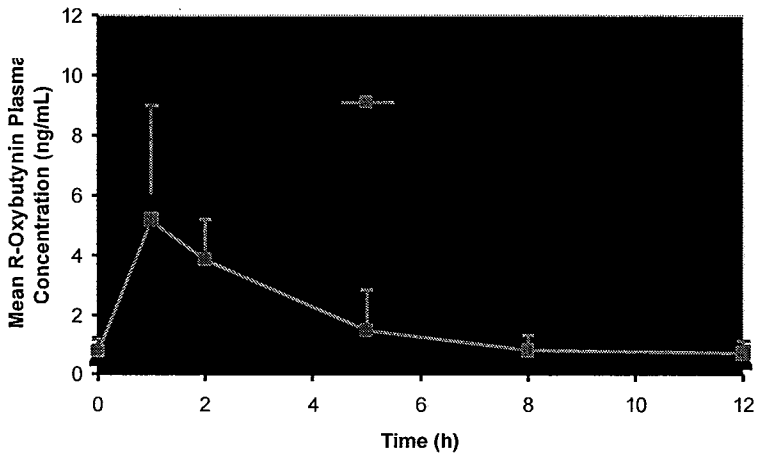


Figure 1. *Mean steady-state (?SD) R-oxybutynin plasma concentrations following administration of total daily Ditropan dose of 5 mg to 30 mg (0.21 mg/kg to 0.77 mg/kg) in children 5-15 years of age – Plot represents all available data normalized to the equivalent of Ditropan 5 mg BID or TID at steady state*

Table 2a

Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 7.5 mg to 15 mg Total Daily Dose of Ditropan Tablets (N=11)

All Available Data Normalized to An Equivalent of Ditropan Tablets 5 mg BID or TID at Steady State

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}*(ng/mL)	6.1± 3.2	10.1 ± 7.5	55.4 ± 17.9	28.2 ± 10.0
T_{max} (hr)	1.0	1.0	2.0	2.0
AUC** (ng.hr/mL)	19.8 ± 7.4	28.4 ± 12.7	238.8 ± 77.6	119.5 ± 50.7

*Reflects C_{max} for pooled data

**$AUC_{0\text{-end of dosing interval}}$

Table 2b

Mean ± SD R- and S-oxybutynin and R- and S-desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 5 mg to 22.5 mg Total Daily Dose of Ditropan Syrup (N=12)

All Available Data Normalized to An Equivalent of Ditropan Syrup 5 mg BID or TID at Steady State

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}^{*} (ng/mL)	5.7 ± 6.2	7.3 ± 7.3	54.2 ± 34.0	27.8 ± 20.7
T_{max} (hr)	1.0	1.0	1.0	1.0
AUC^{**} (ng.hr/mL)	16.3 ± 17.1	20.2 ± 20.8	209.1 ± 174.2	99.1 ± 87.5

*Reflects C_{max} for pooled data

**$AUC_{0\text{-end of dosing interval}}$

DITROPAN XL Tablets:

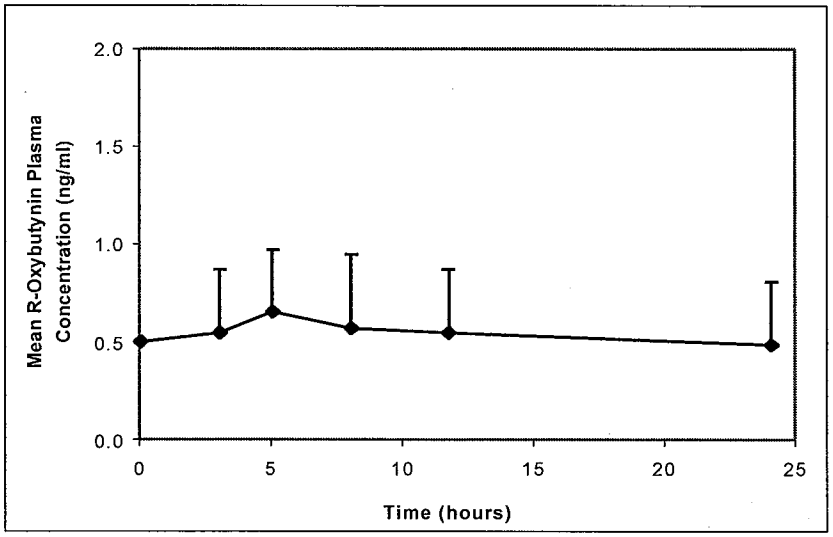


Figure 2. *Mean steady state (±SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg Ditropan XL once daily in children aged 5-15. - Plot represents all available data normalized to an equivalent of Ditropan XL 5 mg once daily*

Table 3

Mean R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5 to 20mg Ditropan XL Once Daily (N=19): All Available Data Normalized To An Equivalent of Ditropan XL 5 mg Once Daily

	Mean ± SD		Mean ± SD
	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng.hr/mL)
R-Oxybutynin	0.7 ± 0.4	5.0	12.8 ± 7.0
S-Oxybutynin	1.2 ± 0.8	5.0	23.7 ± 14.4
R- Desethyloxybutynin	6.8 ± 3.5	5.0	125.1 ± 66.7
S- Desethyloxybutynin	3.8 ± 2.2	5.0	73.6 ± 47.7

Reviewer's Comments:

? Note that the T_{max} values above are obtained from the mean PK profiles presented in the plots above.
? The above PK information is inserted into the product label for the first time for DITROPAN (IR tablets, Syrup and XL). Inclusion of this information may be useful for a physician while prescribing this product in the pediatric population.

Analytical Methodology

The sponsor used a sensitive and rapid stereoselective LC/MS/MS assay method to determine the serum concentrations of R and S oxybutynin and R and S desethyloxybutynin (primary active metabolite).

The method showed good sensitivity, linearity and specificity. Recovery vales for the molecules of interest were generally above 80%. All inter-day and intra-day accuracy and precision C.V. values were generally < 5% (all < 10%). Higher deviation values were observed at the lower limits of quantification (as expected).

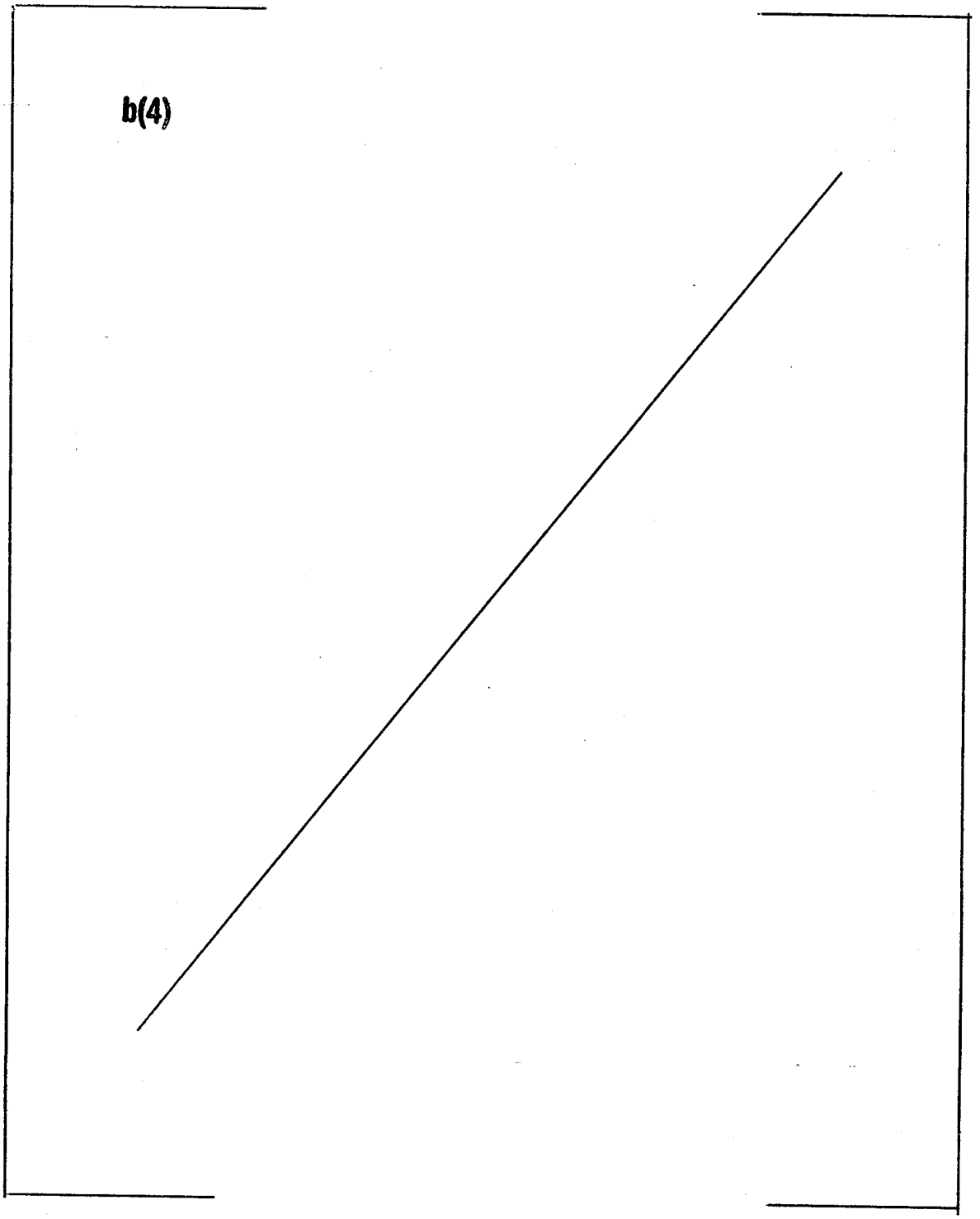
Overall, the analytical methodology and results were acceptable for CPB purposes.

Labeling

Following review of this application, a significant body of CPB information was obtained in pediatric patients (for this first time with this product) and hence, including that in the

product label was one of the primary objective of a review of this NDA Supplement. The following are excerpts of DITROPAN IR tablet, syrup and XL labels that is ***only relevant*** to OCPB (with proposed changes on the final version):

b(4)



7 Page(s) Withheld

Clinical Pharmacology / Biopharmaceutics Review
(4/14/03)

_____ Trade Secret / Confidential (b4)

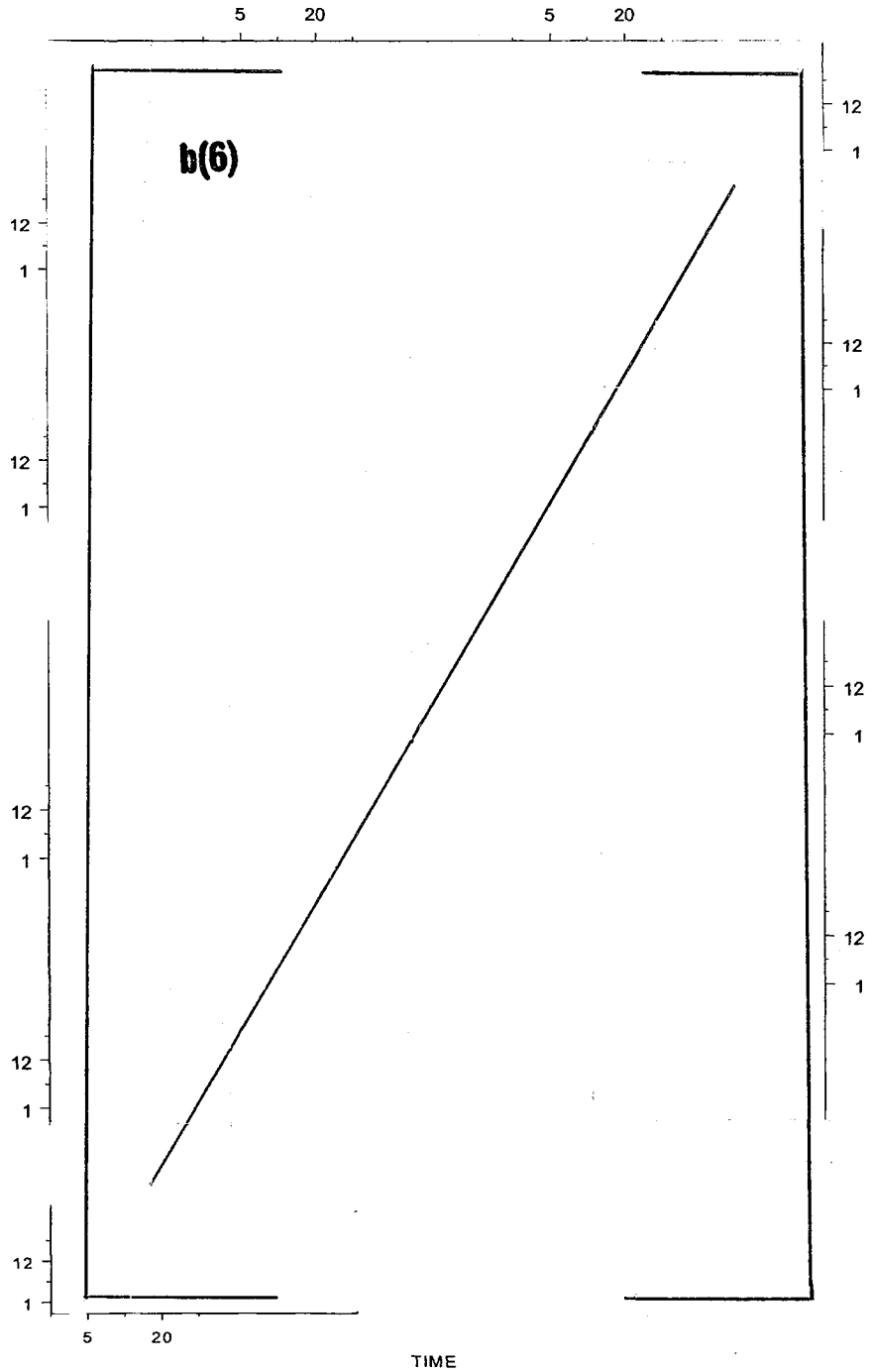
X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Attachment 1

The following are individual observed and fitted plasma concentration vs. time profiles for pediatric subjects administered with IR tablets, syrup and XL tablets (using parametric method using NONMEM; N = 42).



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/s/

Dhruba Chatterjee
4/11/03 05:00:26 PM
BIOPHARMACEUTICS
DFS Worked!
Final Review

Ameeta Parekh
4/14/03 12:29:18 PM
BIOPHARMACEUTICS
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-577/S-032, S-033 &
18-211/S-014, S-016 &
20-897/S-009, S-010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 17-577/S-033
NDA 18-211/S-016
NDA 20-897/S-009
Ditropan Tablets, Syrup, and XL

EXCLUSIVITY SUMMARY for NDA # NDA 17-577, NDA 18-211, NDA 20897
SUPPL #033, 016, 009 respectively
Trade Name DitropanTablets, Ditropan Syrup,and Ditropan XL, respectively
Generic Name oxybutynin chloride
Applicant Name Johnson & Johnson for Alza HFD- 580
Approval Date April 17, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /__ X _/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE-8 (NDA 17-577 and 18-211), SE-5 (NDA 20897)

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe

the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X__/ NO /___/

Peditaric exclusitivy was granted on 2/8/02 for oxybutynin chloride,Ditropan XL, NDA 20897 (see enclosed copy).

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /__X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-897 Ditropan XL

NDA # 18-211 Ditropan Syrup

NDA # 17-511 Ditropan Tablets

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an

application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A / __X__ YES /___/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /_X__/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available

data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # C-2000-043-00

Investigation #2, Study # C-2000-042-01

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an

already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /__X_/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # C-2000-042-01

Investigation #2, Study # C-2000-043-00

Investigation #_3_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [redacted] YES /_X_/ NO /___/ Explain: b(4)

Investigation #2

IND # [redacted] YES /_X__/ NO /___/ Explain: b(4)

Investigation #3

IND # [redacted] YES /_X__/ NO /___/ Explain: b(4)

Investigation #4

IND # 48,930 YES /_X__/ NO /___/ Explain:

Investigation #5

IND # [redacted] YES /_ X_/ NO /__X_/ Explain: b(4)

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

NDA 17-577/S-033
NDA 18-211/S-016
NDA 20-897/S-009
Ditropan Tablets, Syrup, and XL

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Jean R. King
4/15/03 11:11:27 AM
CSO

Daniel A. Shames
4/15/03 11:23:13 AM
MEDICAL OFFICER

NDA 17-577/S-033
NDA 18-211/S-016
Ditropan Tablets and Syrup

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 17-577 and 18-211 **Supplement Type (e.g. SE5):** SE-8
Supplement Number: 033 and 016 respectively

Stamp Date: December 7, 2001; October 17, 2002 **Action Date:** April 17, 2003

HFD 580

Trade and generic names/dosage form: DITROPAN® Tablet contains 5 mg of oxybutynin chloride. Each 5 mL of DITROPAN® Syrup contains 5 mg of oxybutynin chloride.

Applicant: Johnson & Johnson Pharmaceutical Research & Development on behalf of ALZA Corporation

Therapeutic Class: 1S and 3S respectively

Indication(s) previously approved: NDA 17-577 and NDA 18-211: "Ditropan is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria)."

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of overactive bladder

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **X No: Please check all that apply: X Partial Waiver __ Deferred X Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min 0	**kg**	**mo.**	**yr.** birth	**Tanner Stage**	
Max <5	**kg**	**mo.**	**yr.** X	**Tanner Stage**	

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- X **Other: Use of Ditropan Tablets and Syrup in children less than five years of age is rare.**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min __5__ kg_____ mo._____ yr.__x__ Tanner Stage_____
Max__15__ kg_____ mo._____ yr.__x__ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Jean R. King
4/15/03 12:17:36 PM
CSO

pediatric page for nda 18211 and 17577

Daniel A. Shames
4/15/03 01:20:34 PM
MEDICAL OFFICER

NDA 20-897/S-009
Ditropan XL

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 20-897 **Supplement Type (e.g. SE5): SE-5**
Supplement Number: 009

Stamp Date: December 7, 2001; October 16, 2002 **Action Date: April 17, 2003**

HFD 580

Trade and generic names/dosage form: DITROPAN XL® (oxybutynin chloride. Each DITROPAN XL® Extended Release Tablet contains 5 mg, 10 mg or 15 mg of oxybutynin chloride USP).

Applicant: Johnson & Johnson Pharmaceutical Research & Development on behalf of ALZA Corporation

Therapeutic Class: 3S

Indication(s) previously approved: NDA 20-897: "Ditropan XL is a once daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency."

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of overactive bladder

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: X Partial Waiver __ Deferred X Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min 0	**kg**	**mo.**	**yr. birth**	**Tanner Stage**	
Max < 5	**kg**	**mo.**	**yr. X**	**Tanner Stage**	

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☒ **Other: Current formalution of Ditropan XL can not be appropriately administered orally as single dose tablet to children under 6 years old.**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min __5__ kg_____ mo._____ yr.__X__ Tanner Stage_____
Max__15_ kg_____ mo._____ yr.__X__ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Jean R. King
4/15/03 11:20:31 AM
CSO

Daniel A. Shames
4/15/03 11:26:28 AM
MEDICAL OFFICER

NDA 20-897 **SE8**-009
NDA 17-577 **SE8**-033
NDA 18-211 **SE8**-016

BPCA Clinical Summary Review

Drugs: Ditropan XL extended release tablets (oxybutynin chloride)
Ditropan Tablets (oxybutynin chloride)
Ditropan Syrup (oxybutynin chloride)

On the basis of the clinical and clinical pharmacology reviews, these three pediatric efficacy supplements may be **approved**. The sponsor has provided substantial new clinical efficacy and safety information to support a new pediatric indication for Ditropan XL. Additional clinical and clinical pharmacology information in children has been submitted to support new labeling in the corresponding sections of the Ditropan Tablets and Syrup label, two products already approved for use in children.

Two studies were conducted. The first (**C-2000-042-01**) was a large efficacy, safety and pharmacokinetic evaluation in approximately 116 children with detrusor overactivity related to neurogenic conditions (e.g. spina bifida). This was 24 weeks in duration, included all three Ditropan formulations and assessed efficacy using both clinical parameters (via voiding diary and catheterization schedules) and urodynamic parameters (maximum bladder capacity, detrusor pressures at maximum capacity, and volume at first involuntary detrusor contraction). In addition, sparse sampling for serum oxybuynin chloride concentrations was used to derive pharmacokinetic parameters for each formulation. Finally, safety was assessed by clinical adverse events, serum laboratories and EKGs. The second study (**C-2000-043-01**) was a smaller pilot (or exploratory) study of Ditropan Syrup in children less than aged six with known myelomeningocele. The rationale in this case was that "prophylactic" anticholinergic treatment might improve long-term bladder function in these children. This type of treatment had been reported in the clinical literature and was being used by some practicing pediatric urologists. Therefore, the study was a short (13 to 28 days) and small study (n=16). The efficacy parameters were from urodynamic studies (especially focusing on bladder pressures).

For **Study 042**, the mean duration of exposure to oxybutynin was 24.3 weeks (range 6 to 31 weeks). Sixty-one patients received Ditropan XL, 30 received Ditropan Syrup and 28 received Ditropan Tablets. (These numbers tally >116 because 3 patients switched formulation during the trial.) The doses taken during the trial for Ditropan XL were either 10 or 15 mg once daily. The total daily doses taken for Syrup were 5mg to 30mg, and for Tablets 5mg to 15mg, both in BID, TID or QID divided doses. The total daily oxybutynin dose on a mg/kg basis was either 0.20-<40 mg/kg (46%), or 0.40-<0.60mg/kg (34%) in the majority of patients. Clinical efficacy results demonstrated the benefit of oxybutynin on urine storage. Improvements were noted in the "all enrolled" group (N=116) in terms of increasing average urine volume per catheterization, increasing urine volume after morning awakening, and increasing percentage of catheterizations without a leaking accident. The exact figures for these endpoints may be found in Dr. Gierhart's March 21, 2003 review in Tables #2, #3 and #4. A summary of this data was translated to the appropriate product labels as follows:

At total daily doses ranging from 5 mg to 15 mg, treatment with **Ditropan Tablets** was associated with an increase from baseline in mean urine volume per catheterization from 122 mL to 145 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 168 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 43% to 61%.

At total daily doses ranging from 5 mg to 30 mg, treatment with **Ditropan Syrup** was associated with an increase from baseline in mean urine volume per catheterization from 113 mL to 133 mL, an increase from baseline in mean urine volume after morning awakening from 143 mL to 165 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 63%.

Administration of **DITROPAN XL** 5 to 20 mg/day was associated with an increase from baseline in mean urine volume per catheterization from 108 mL to 136 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 189 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 51%.

Urodynamic results measured over time were consistent with these clinical results. These included: increases in maximum cystometric bladder capacity, decreases in detrusor pressure at maximal bladder capacity (a particularly welcome finding), and an increases in the percentage of patients with no inhibited detrusor contractions. These results were translated to the labels as follows:

Treatment with **Ditropan Tablets** was associated with an increase from baseline in maximum cystometric capacity from 230 mL to 279 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 36 cm H_20 to 33 cm H_20, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_20) from 39% to 20%.

Treatment with **Ditropan Syrup** was associated with an increase from baseline in maximum cystometric capacity from 192 mL to 294 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 46 cm H_20 to 37 cm H_20, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_20) from 67% to 28%.

Administration of **DITROPAN XL** resulted in an increase from baseline in mean maximum cystometric capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 cm H_2O to 33 cm H_2O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_2O) from 60% to 28%.

Forty-two (42) patients out of the total 116 "all enrolled group" underwent sparse sampling for oxybutynin chloride serum concentrations. In this group, 19 were taking Ditropan XL, 11 were taking Ditropan Tablets, and 12 were taking Ditropan Syrup. The total daily dose was 10mg in 43% of these patients and 15mg in 41%. The total daily dose on a mg/kg basis was 0.20-<0.40 mg/kg in 50% and 0.40-<60mg/kg in 31% of these patients. Twenty-five children in the pK subgroup were <=10 years of age and 17 were older than 10 years. The medical officer was unable to determine any relationship between total daily dose or total daily dose in mg/kg and pharmacokinetic parameters. However, our clinical pharmacology were successful in using all the available data to derive some pK conclusions. Specifically, for Ditropan Tablets and Syrup,

when all available data were normalized to a total dose of 5 mg BID or TID, the pK parameters at steady state were translated to the label as Tables #1 and #2 and Figure #1 that follow:

Table 1. Mean (± SD) R- and S-oxybutynin and R- and S-desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 7.5 mg to 15 mg Total Daily Dose of Ditropan Tablets. All Available Data Normalized to An Equivalent of 5 mg BID or TID at Steady State (N=11).

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}*(ng/mL)	6.1± 3.2	10.1 ± 7.5	55.4 ± 17.9	28.2 ± 10.0
T_{max} (hr)	1.0	1.0	2.0	2.0
AUC** (ng.hr/mL)	19.8 ± 7.4	28.4 ± 12.7	238.8 ± 77.6	119.5 ± 50.7

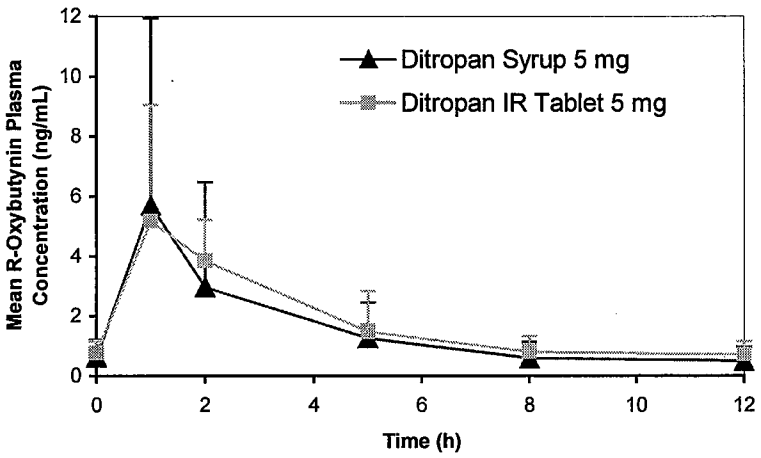
*Reflects C_{max} for pooled data **$AUC_{0\text{-end of dosing interval}}$

Table 2. Mean (± SD) R- and S-oxybutynin and R- and S-desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5-15 Following Administration of 5 mg to 22.5 mg Total Daily Dose of Ditropan Syrup. All Available Data Normalized to An Equivalent of 5 mg BID or TID at Steady State (N=12).

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C_{max}* (ng/mL)	5.7 ± 6.2	7.3 ± 7.3	54.2 ± 34.0	27.8 ± 20.7
T_{max} (hr)	1.0	1.0	1.0	1.0
AUC** (ng.hr/mL)	16.3 ± 17.1	20.2 ± 20.8	209.1 ± 174.2	99.1 ± 87.5

*Reflects C_{max} for pooled data **$AUC_{0\text{-end of dosing interval}}$

Figure 1. *Mean steady-state (±SD) R-oxybutynin plasma concentrations following administration of total daily Ditropan dose of 5 mg to 30 mg (0.21 mg/kg to 0.77 mg/kg) in children 5-15 years of age. – Plot represents all available data normalized to the equivalent of Ditropan 5 mg BID or TID at steady state*

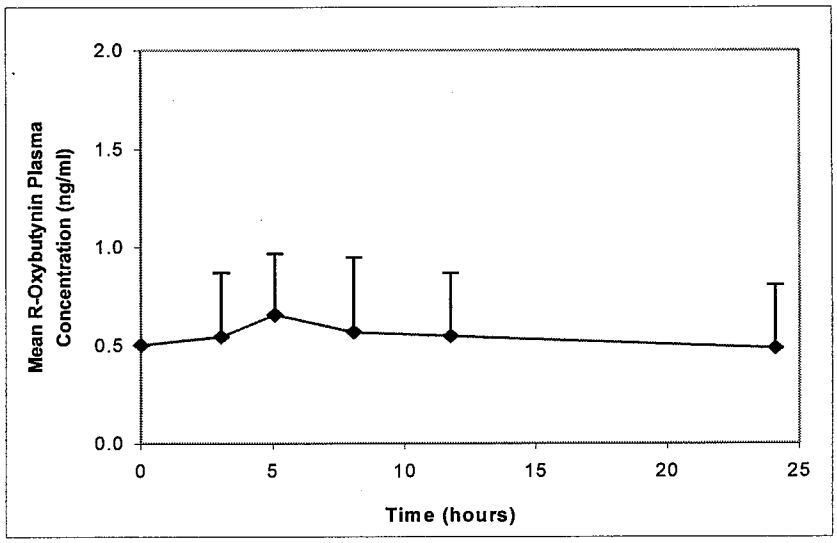


For Ditropan XL, the label reflects the following derived pharmacokinetic parameters in children:

Table 3. Mean R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5 to 20mg Ditropan XL Once Daily. All Available Data Normalized To An Equivalent of Ditropan XL 5 mg Once Daily. (N=19)

	R-Oxybutynin	S-Oxybutynin	R-Desethyloxybutynin	S-Desethyloxybutynin
C_{max} (ng/mL)	0.7 ± 0.4	1.2 ± 0.8	6.8 ± 3.5	3.8 ± 2.2
T_{max} (hr)	5.0	5.0	5.0	5.0
AUC (ng.hr/mL)	12.8 ± 7.0	23.7 ± 14.4	125.1 ± 66.7	73.6 ± 47.7

Figure 2. *Mean steady state (±SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg Ditropan XL once daily in children aged 5-15. - Plot represents all available data normalized to an equivalent of Ditropan XL 5 mg once daily*



For additional information relevant to this pharmacokinetic information, the reader is referred to Dr. Chatterjee's detailed review of these supplements.

In terms of safety, there were no unexpected adverse events and no worrisome findings in terms of frequency or severity of adverse event reports.

For **Study 043**, a total of 16 patients were enrolled at 3 sites in the US and one site in the Netherlands. Ten of these children were enrolled at the Netherlands site. The median age was 3 years and range from 1 to 5 years. Five of the children were 2 years old. The majority of patients were male (69%) and Caucasian (75%). Median weight was 16 kg and ranged from 11 kg to 20 kg. Patients were all known to have detrusor hyperreflexia as a consequence of neurological conditions and were already on a stable dose of oxybutynin. Seventy percent reported a concurrent fecal impaction condition. Efficacy was assessed by urodynamic studies at baseline and after at least two weeks on treatment. The urodynamic parameters of interest were maximal cystometric capacity, intravesical pressure, and presence of uninhibited contractions. The purpose of these measurements was to assess whether oxybutynin treatment improved capacity while lowering or maintaining intravesical pressure.

Maximal capacity increased from baseline by a mean of 71.5 mL with a range of improvement from 29 mL to 265 mL. On the other hand, mean detrusor pressure at maximal capacity increased slightly, as reflected by a mean increase of 0.6 cm H_20 (range from –21 cm H_20 to +50 cm H_20). There was a reduction in the percentage of patients demonstrating involuntary detrusor contractions (IDCs) of at least 15 cm H_20 from 11 of 16 patients (69%) to 2 of 16 patients (12.5%). Thus, treatment of these children was associated with improvements in maximal vesical capacity and reduction in the percentage of patients demonstrating IDCs, but the most important factor, change-from-baseline in mean detrusor pressure, actually increased slightly. In fact, in some children, the detrusor pressures went up markedly (+50 cm H_20). In ten of the 16 children, detrusor pressures at baseline were fairly low (< 40 cm H_20).

Until additional research supports clinical benefit of this mode of treatment or until a specific subgroup of children are defined in whom this treatment is effective without increasing bladder pressures (increasing capacity and decreasing or maintaining pressures), these results appear to preclude approval of this novel indication. This should not be construed by the reader to mean that this type of treatment may not one day be shown effective in at least some patients.

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/s/

Daniel A. Shames
4/10/03 05:33:51 PM

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 11/3/00 Application Written Request was made to: NDA/IND# {NDA 17-577, NDA 18-211, NDA 20-897, IND 48,930}
Timeframe Noted in Written Request for Submission of Studies 12/15/02
NDA# 20-897 Supplement # 009 Choose one: (SE1) SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
Sponsor ALZA Corporation
Generic Name oxybutynin chloride Trade Name Ditropan XL®
Strength 5mg, 10mg, 15mg Dosage Form/Route oral extended release tablets
Date of Submission of Reports of Studies 12/7/01
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies)

Was a formal Written Request made for the pediatric studies submitted?	Y ✓	N
Were the studies submitted after the Written Request?	Y ✓	N
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y ✓	N
Was the timeframe noted in the Written Request for submission of studies met?	Y ✓	N
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y	N ✓ *
Did the studies fairly respond to the Written Request?	Y	N ✓ *

SIGNED Brenda S. Grehart MD DATE: 12/21/01
(Reviewing Medical Officer)
* Agree w/ Dr. Hirsh's memo - [redacted] 1/23/02
Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity ✓ **Granted** ___ **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
20897	NP	16-DEC-2001
20-897	[redacted], 5082668	16-SEP-2003
	461/2003	
20-897	5674895, 5840754	22-MAY-2015

b(4)

SIGNED [redacted] DATE 2/8/02

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/s/

Terrie Crescenzi
2/11/02 09:09:27 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: January 3, 2002

From: Jeanine Best, M.S.N., R.N.
Senior Regulatory Associate
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 20-897/S-009
NDA 17-577/S-033
NDA 18-211/S-016

I have reviewed the financial disclosure information submitted by ALZA Corporation in support of their SNDAs, 20-897/S-009 for Ditropan XL® (oxybutynin chloride) Extended Release Tablets, 17-577/S-033 for Ditropan® Tablets (oxybutynin chloride), and 18-211/S-016 for Ditropan® Syrup (oxybutynin chloride).

Two pediatric studies (as specified by the Written Request) were conducted to request pediatric exclusivity for oxybutynin chloride. The study numbers and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	**Study Status**	**Financial Disclosure Review**
Study C-2000-042 / "The Safety and Tolerability of Oxybutynin Chloride 9Ditropan XL®, Ditropan® Syrup or Ditropan® Tablets) in the treatment of Detruser Hyperreflexia Due to Neurogenic Conditions in Children Aged 6 to 15 Years"	Study Start: February 16, 2001 Study Complete: November 7, 2001	Complete, appropriate documentation received, no disclosable information reported
Study C-2000-043/ "The Pharmacokinetics and Pharmacodynamic Effects of Oxybutynin Chloride (Ditropan® Syrup) in the Treatment of Detruser Hyperreflexia Due to Neurogenic Conditions in Children Aged 1 to 5 Years"	Study Start: April 20, 2001 Study Complete: October 15, 2001	Complete, appropriate documentation received, no disclosable information reported

Documents Reviewed:

- FDA Form 3454, Certification: Financial Interests and Arrangements of Clinical Investigators
- Clinical Study Reports

Conclusion:
Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of the trials.

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/s/

Jeanine Best
1/3/02 01:00:46 PM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 17-577 NDA 18-211 NDA 20-897 Ditropan Tablets, Syrup, and XL	Efficacy Supplement Type: SE-8 SE-8 SE-5	Supplement Number: NDA 17-577/ S 033 NDA 18-211/ S 016 NDA 20-897/ S 009
Drug: Ditropan Tablets, Ditrpan Syrup, and Ditropan XL (oxybutinin chloride), respectively		Applicant: Johnson & Johnson for ALZA Corporation
RPM: Jean King, M.S., R.D.	HFD-580	Phone # 301-827-4620
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	1S (Ditropan Tablets), 3S (Ditropan Syrup and Ditropan XL)
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	April 17, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1)

	( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X
General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE for S-009; S 016, and S-033 (10/07/02)
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None ( ) Press Release () Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X (DDMAC, 4/3/2003)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X [copy of Oxytrol transdermal system included]
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X

❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	45-day Filing Meeting (2/4/02)
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X (Team Leader, 4/10/03)
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X (3/21/03; 2/5/02)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	X
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X (4/14/03)
❖ Statistical review(s) *(indicate date for each review)*	X (6/11/02)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X (4/14/03)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X (2/12/02; 6/11/02)
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	N/A
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) N/A ( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A

❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

Jean R. King
4/14/03 01:56:15 PM
CSO

Jean R. King
4/14/03 01:58:46 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-577/S-033 and S-032
NDA 18-211/S-016 and S-014

Liliana Arbelaez
Associate Director, Regulatory Affairs
Global Marketed Products
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Ms. Arbelaez:

We acknowledge receipt of your March 12, 2004 submission containing final printed labeling in response to our April 15, 2003 letter approving your supplemental new drug applications for the use of DITROPAN® (oxybutynin chloride) Tablets and DITROPAN® (oxybutynin chloride) Syrup for the treatment of overactive bladder in children aged six years of age and older.

We have reviewed the labeling that you submitted in accordance with our April 15, 2003 letter, and we find it acceptable.

If you have any questions, call Jean Makie, Sr. Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
2/23/05 10:57:17 AM
Chief, Project Management Staff

Division of Reproductive and Urologic Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number:	**NDA 17-577\SLR 032 and 033: FA** **NDA 18211\SLR 014 and 016: FA** DITROPAN® (oxybutynin chloride) Tablets, DITROPAN® (oxybutynin chloride) Syrup
Sponsor:	ALZA Corporation.
Material Reviewed:	**NDA 17-577\SLR 032 and 033: FA** **NDA 18211\SLR 014 and 016: FA** **Submission Date:** March 12, 2004 **Receipt Date:** March 15, 2004

Background and Summary:

These supplemental new drug applications provide for the use of DITROPAN® (oxybutynin chloride) Tablets and DITROPAN® (oxybutynin chloride) Syrup for the treatment of overactive bladder in children aged six years of age and older.

The sponsor has submitted their final printed label (FPL) for package insert (PI) in response to the Division's Approval Letter dated April 15, 2003.

Review:

Labeling submitted in NDA 17-577\SLR 032 and 033: FA and NDA 18211\SLR 014 and 016: FA were identical. The PI was compared to the final draft labeling enclosed in the Division's Approval letter dated April 15, 2003. The FPL was found to be identical to the final draft labeling.

Conclusions:

An Acknowledge and retain letter should be issued for the NDA 17-577\SLR 032 and 033: FA and NDA 18211\SLR 014 and 016: FA.

Jean Makie, M.S., R.D.
PM, HFD-580

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/s/

Jean Makie
2/22/05 02:17:51 PM
CSO

Margaret Kober
2/23/05 10:53:26 AM
CSO
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-897/S-009 and 010

Liliana Arbelaez
Associate Director, Regulatory Affairs
Global Marketed Products
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560

Dear Ms. Arbelaez:

We acknowledge receipt of your July 16, 2003 submission containing final printed labeling in response to our April 15, 2003 letter approving your supplemental new drug applications (S 009 and S 010) for Ditropan XL (oxybutynin chloride) 5, 10, and 15 mg extended release tablets.

We have reviewed the labeling that you submitted in accordance with our April 15, 2003 letter and we find it acceptable. However, during our review, we identified a typographical error in Figure 2, entitled "Mean R-Oxybutynin Plasma Concentration." On the Y-axis of this figure, plasma concentration is labeled as "ngml". To correctly reference plasma concentration levels, and to remain consistent throughout your labeling, we request that "ngml" be changed to "ng/ml". This change should be reflected in your annual report submission.

If you have any questions, call Jean King, Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
9/30/03 06:21:51 PM

Division of Reproductive and Urologic Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number:	**NDA 20-897/FA Ditropan XL** (oxybutynin chloride) Extended Release tablets
Sponsor:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Material Reviewed:	NDA 20-897/FA: final printed labeling
	Submission Date: April 16, 2003
	Receipt Date: April 17, 2003

Background and Summary:

This product was approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

The sponsor has submitted their final printed label (FPL) for package insert (PI), patient package insert (PPI), and carton/container labels in response to the Approval Letter dated April 15, 2003.

Review:

The labeling submitted in NDA 20-897/FA, was compared to the final draft labeling enclosed in the Division's Approval letter dated April 15, 2003. Other than the following minor changes to the PI, it was found to be identical:

- During the April 2003 label negotiations with the Division, J&J was provided with the FDA guidance for Industry and the Ocsalate-labeling Enforcement Policy, May 2003. J&J is in compliance with the May 2003 policy and has therefore revised the FPL to the established name, hypromellose, and removed the listed name hydropryl methylcellulose.

- During the review it was noted that the graph with table 2, "Mean R-Oxybutynin Plasma Concentration", J&J refers to concentration as, ngml. To properly indicate concentration, and to be consistent, the Agency suggests that ngml, be changed to ng/ml. This change should be reflected in the annual report.

- Minor editorial changes were also made to 1). Parenthetically add reference to the generic name (oxybutynin chloride) after the trade name Ditropan XL. 2). Delete parenthetical reference of generic name (oxybutynin chloride) when it appears redundant.

Conclusions:

An acknowledge and retain letter should be issued for the NDA 20-897/FA.

Albert Perrine, RN, BSN
PM, HFD-580

Drafted: AP 08/08/03
Revised: AP/08/22/03

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/s/

Albert Perrine
8/22/03 02:34:56 PM
CSO

Margaret Kober
8/25/03 09:28:15 AM
CSO
Chief, Project Management Staff

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

Applicant: NDA 17-577/S-033 Ditropan Tablets
NDA 18-211/S-016 Ditropan Syrup
NDA 20-897/S-009 Ditropan XL

Date of Application:	December 7, 2001
Date of Receipt:	December 7, 2001
Date of Approvable Letter:	October 7, 2002
Complete Response Resubmitted:	October 16, 2002
Date of Complete Response Filing Meeting:	February 4, 2002
Filing Date:	February 5, 2002
PDUFA Date:	April 17, 2003

Indication(s) requested: Currently, NDA 20-897 is approved as: "Ditropan XL is a once daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency." Currently, NDA 17-577 and NDA 18-211 are approved as: "Ditropan is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria)."

NDA 17-577/S-033, NDA 18-211/S-016 Ditropan Syrup, and NDA 20-897/S-009 provide for use of Ditropan Tablets, Ditropan Syrup, and Ditropan XL Extended Release Tablets for pediatric claims for the treatment of overactive bladder.

Type of Application: Full NDA _____ Supplement _____X_____
(b)(1) _____X____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S___X___ P_____
Resubmission after a withdrawal or refuse to file ___N/A____
Chemical Classification: (1,2,3 etc.)_1S_(NDA 17-577), 3S (NDA 18-211 and NDA 20897)____
Other (orphan, OTC, etc.)___N/A_____

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid N/A Waived (e.g., small business, public health) N/A
Exempt (orphan, government) Pediatric supplement exempted
Form 3397 (User Fee Cover Sheet) submitted: YES X NO
User Fee ID# N/A
Clinical data? YES X NO Referenced to NDA# 17-577, 18-211, and 20-897
Date clock started after UN N/A

User Fee Goal date: April 17, 2003

Action Goal Date (optional) April 17, 2003

- Does the submission contain an accurate comprehensive index? YES NO

- Form 356h included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES NO N/A
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? YES NO N/A

- Patent information included with authorized signature? YES NO

- Exclusivity requested? YES; If yes, ___ NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, …."

- Financial Disclosure included with authorized signature? YES NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
  If no, for what ages and/or indications was a waiver and/or deferral requested:

Partial waiver for children from birth to age 5 was granted because the current formulation of Ditropan XL can not be appropriately administered orally as single dose tablet to children under 6 years old and use of Ditropan Tablets and Syrup in children less than five years of age is rare.

- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A (this is a pediatric labeling supplement) YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: [ ] 48,930 [ ] b(4)

End-of-Phase 2 Meeting? N/A (this is a pediatric labeling supplement) Date_____ NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? N/A (this is a pediatric labeling supplement) Date_____ NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?

N/A (this is a pediatric labeling supplement) YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
N/A (this is a pediatric labeling supplement; no PPI was submitted) YES NO

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO N/A

Advisory Committee Meeting needed? YES, date if known _____ NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES NO N/A
  If no, did sponsor submit a complete environmental assessment? YES NO N/A

If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO N/A

- Establishment Evaluation Request (EER) package submitted? YES NO N/A
- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO N/A

If 505(b)(2), complete the following: N/A

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)

YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

****MEMO OF FILING MEETING (DATED 2/4/02) is attached as hard copy only to this administrative review. Electronic signed copy of filing meeting minutes is available as separate document in DFS.**

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/s/

Jean R. King
4/14/03 12:46:10 PM
CSO

Jean R. King
4/14/03 12:48:45 PM
CSO

Teleconference Meeting Minutes

Date: Oct. 3, 2002 **Time**: 1:00 –1:30 PM **Location**: PKLN; 17B43

NDA 17-577/S033 **Drug:** Ditropan
18-211/S016
20-897/S009

Indication: Overactive Bladder

Sponsor: Johnson & Johnson

Type of Meeting: Guidance

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Jennifer Mercier - Project Manager, DRUDP (HFD-580)

FDA Attendees:
Mark Hirsch, MD – Medical Team Leader, DRUDP (HFD-580)
Jennifer Mercier – Project Manager, DRUDP (HFD-580)
Karen Anderson – Project Manager, DRUDP (HFD-580)

External Attendees:
Michael Bailey, Director, Regulatory Affairs
Elizabeth M. Turek, Therapeutic Area Leader, Regulatory Affairs
Liliana Arbelaez, Manager, Regulatory Affairs

Meeting Objective: [redacted] b(4)

Discussion/Decisions Made:

1. [redacted] b(4)

2. Concern about the use of the term "Overactive Bladder" in describing a pediatric condition.
   - The Division and sponsor will need to reconsider the exact indication in pediatric patients focusing on the specific inclusion criteria.

Action Items:
- Fax the meeting minutes to the sponsor within 30 days.
- The sponsor could request a meeting with the Division to discuss the 2 concerns.
- The sponsor should include any available updated information in their resubmission to the applications.

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/s/

Karen Anderson
10/22/02 02:14:32 PM
CSO

Mark S. Hirsch
10/24/02 09:03:30 AM
MEDICAL OFFICER

Meeting Minutes

Date: August 5, 2002 **Time**: 11:00-12:00 PM, EST **Location**: PKLN; 17B43

NDA 20-897 S-009 **Drug:** Ditropan XL® tablet
Indication: overactive bladder

NDA 18-211 S-016 **Drug:** Ditropan® syrup
Indication: relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder

NDA 17-577 S-033 **Drug:** Ditropan® tablet
Indication: relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder

Sponsor: Alza Corporation

Type of Meeting: 8 Month Status Meeting

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Jennifer Mercier, Project Manager, DRUDP (HFD-580)

FDA Attendees:
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Sonia Castillo, Ph.D. – Statistician, Division of Biometrics II (HFD-715)
Dhruba Chatterjee, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
He Sun, Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
David Lin, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
Jennifer Mercier – Project Manager, DRUDP (HFD-580)

Meeting Objective: To establish the review status of this NDA.

Background: Alza corporation submitted a pediatric supplement on December 7, 2001, under three oxybutynin chloride NDAs (20-897 for Ditropan XL, 18-211 for Ditropan Syrup, and 17-577 for Ditropan Tablets) in response to a Written Request issued by the Agency on November 20, 2000. The sponsor submitted two reports: a final study report, C-2000-043-00 (a pharmacokinetic and pharmacodynamic study in 15 patients), and an interim study report, C-2000-42-01 (a safety and dose-response study currently ongoing in 116 patients), as well as two critical analyses.

Discussion/Decisions Made:
Clinical comments:

- First draft of review completed and given to medical Team Leader already.
- The medical officer noted the following review issues:
  - In study 042 there were many protocol violations and many issues related to non-compliance.
  - Study 042 was reviewed in its interim format. A very large submission (the complete report) is reported to have been submitted on July 29, 2002. The MO has not yet received it. She will not have sufficient time to review this important new information prior to the PDUFA date.
  - The MO did her own analysis of the PK and found no correlation between actual dose given and PK (for any formulation).
  - Study 043 was a very small trial in children 1-5 years old. It also had many protocol deviations. [ ] b(4)
  - Any new labeling for Ditropan XL must not imply that this drug is intended to treat children with "overactive bladder". Labeling must describe the condition as "detrusor[ ] b(4) [ ]conditions".
  - Currently, the MO concludes that only the most minimal labeling could be supported from the data submitted and already reviewed.

Clinical Pharmacology and Biopharmaceutics comments:

- No review has been accomplished yet.
- Dr. He Sun has been recruited to do this review. He received the NDA one business day prior to this status meeting.
- Dr. He Sun would clearly prefer to review the final study report of 042 and not the interim report.
- Dr. he Sun will be seeking evidence of a concentration response (or AE) relationship.
- Dr. He Sun will address whether missing data or invalid data precludes labeling the findings of their trials.

Statistical comments:

- No formal statistical review has been done; the study was observational; memo to the file reflecting no need for a formal review, has been written already (draft)

Action Items:

- The Division will not have sufficient time to review the information in the July 29, 2002 amendment prior to the 10-month goal date. The information is important to the review. Therefore, the Division will take an approvable action on this application and will review the July 29, 2002 submission in the next review cycle. The sponsor will be informed of this decision (done: 8-12-02).

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/s/

Mark S. Hirsch
9/26/02 05:36:48 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-897

PRIOR APPROVAL SUPPLEMENT

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Agent for: ALZA Corporation
Attention: Liliana Arbelaez
Manager, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Ms. Arbelaez:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	DITROPAN XL® (oxybutynin chloride)
NDA Number:	20-897
Supplement number:	S-010
Date of supplement:	July 2, 2002
Date of receipt:	July 3, 2002

This supplement provides for revised draft labeling as requested in our letter dated May 8, 2001.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 3, 2002, in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplement should be addressed as follows:

U.S.Postal/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Kassandra Sherrod, Regulatory Project Manager, at (301) 827-4260.

Sincerely yours,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
7/17/02 12:46:32 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 11, 2002

TO: Jennifer Mercier, Regulatory Project Manager, HFD-580
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: Khin Maung U, M.D.
Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

FROM: Roy Blay, Ph.D.,
Director Regulatory Review Officer
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDAs: 17-577/S-033, 18-211/S-016,and 20-897/S-009

APPLICANT: Alza Corporation

DRUG: Ditropan® (oxybutynin chloride)

THERAPEUTIC CLASSIFICATION: 3(S)

INDICATION: Treatment of [ ] b(4)

REVIEW DIVISION GOAL DATE: August 31, 2002
ACTION GOAL DATE (PDUFA Date): October 7, 2002

I. BACKGROUND:

The goals of inspection included validation of submitted data and compliance of study activities with Federal regulations and good clinical practices. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events.

II. RESULTS (by site):

NAME	CITY, COUNTRY	ASSIGNED DATE	INSPECTION DATES	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
Richard W. Grady, M.D.	Seattle, WA	11 Mar 02	April 15-19, 2002	02 May 02	NAI/010611
Israel Franco, M.D.	Hawthorne, NY	11 Mar 02	April 9-11, 2002	16 May 02	NAI/010628

Site #1
Richard W. Grady, M.D.
4800 Sand Point Way, N.E.
P.O. Box 5371
98105-0371
See **Assessment and Recommendations**, below

a. 10 subjects were screened for the study with one screen failure. Nine subjects completed the study. All nine study files were reviewed and compared with source data.

b. There were no limitations on the inspection.

c. A Form 483 was not issued.

Site #2
Israel Franco, M.D.
Pediatric Urology Associates
19 Bradhurst Avenue, Suite 2575
Hawthorne, New York 10532
See **Assessment and Recommendations**, below

a. The site enrolled 30 subjects. The records of six subjects were reviewed and no discrepancies were noted between the data listings provided by the sponsor and source documents.

b. There were no limitations on the inspection.

c. A Form 483 was not issued.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of these NDA supplements by Drs. Grady and Franco appear acceptable.

Roy Blay, Ph.D.,
Clinical Reviewer/ DSI/GCPBI

CONCURRENCE:

Khin Maung U, M.D.
Acting Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

DISTRIBUTION:

NDAs 17-577, 18-211, and 20-897
HFD-45/Division File
HFD-46/Program Management Staff (electronic copy)
HFD-580/Project Manager/Farinas
HFD-46/Clinical Reviewer/Blay
HFD-46/CIB/GCP File #s 010611 and 010628
HFD-46/Reading File

O:/blay/ditropansummary.doc

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/s/

Sherry George
7/15/02 04:24:13 PM
TECHNICAL
Original was signed by Drs. Blay and U on 7/12/02

Filing Meeting Minutes

Date: February 4, 2002 **Time**: 10:30-11:30 AM, EST **Location**: PKLN; 17B43

NDA 20-897 S-009 **Drug:** Ditropan XL® tablet
Indication: overactive bladder

NDA 18-211 S-016 **Drug:** Ditropan® syrup
Indication: relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder

NDA 17-577 S-033 **Drug:** Ditropan® tablet
Indication: relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder

Sponsor: Alza Corporation

Type of Meeting: Filing

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:
Shelley Slaughter, M.D. – Acting Deputy Director, DRUDP (HFD-580)
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Ashok Batra, M.D. – Medical Officer, DRUDP (HFD-580)
Sonia Castillo, Ph.D. – Statistician, Division of Biometrics II (HFD-715)
Dhruba Chatterjee, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, OCPB @ DRUDP (HFD-580)
Diane V. Moore– Project Manger, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To establish if the submissions are fileable.

Background: Alza corporation submitted a pediatric supplement on December 7, 2001, under three oxybutynin chloride NDAs (20-897 for Ditropan XL, 18-211 for Ditropan Syrup, and 17-577 for Ditropan Tablets) in response to a Written Request issued by the Agency on November 20, 2000. The sponsor submitted two reports: a final study report, C-2000-043-00 (a pharmacokinetic and pharmacodynamic study in 15 patients), and an interim study report, C-2000-42-01 (a safety and dose-response study currently ongoing in 116 patients), as well as two critical analyses. The 60-day filing date is February 5, 2002, and the 10-month goal date is October 7, 2002.

Discussion:
Regulatory comments:

- it was clarified that the designation of "efficacy supplement" is made by the Chief of the Project Management staff
- to qualify as an efficacy supplement for an existing NDA, the submission must include clinical data in support of an additional indication, a new dose, or a new patient population
- a labeling supplement may also contain safety data which would require clinical review, but it will not lead to major changes as indicated in the previous comment
- if this submission is deemed not fileable, then the Pediatric Exclusivity Board will not make a determination on granting pediatric exclusivity; it was noted that the Division was not informed that fileability was a precondition to granting pediatric exclusivity
- it was confirmed that the review of the Financial Disclosure documents indicated that there was no disclosure of financial interests that could bias the outcome of the trials

Clinical comments:

- of concern is that the sponsor submitted an interim report for study C-2000-042-01 (Study #2), and has not stated whether additional data will be submitted as a final report; it was confirmed with sponsor that Study #2 is ongoing
- it was verified that the submission contains clinical data in Study #2, which is sufficient to allow an assessment of safety and efficacy [ ] however, Study #2 includes complete data in only 60 patients who completed the 24-week trial; it is not clear if the sponsor will submit a final study report, including information from all the 116 patients enrolled in the trial; Study #2 also includes some urodynamic data and some additional diary data from the "all enrolled" population b(4)
- study C-200-043-00 (Study #1) provides pharmacodynamic and pharmacokinetic information in 15 patients for two weeks; of concern is that this study contains data in only a very small number of patients, and for a short duration; however, it was noted that Study #1 met the requirements stated in the Written Request
- published literature and critical analyses in children and adults, with emphasis on the safety profile of oxybutynin in children, was also submitted in support of this application
- the medical reviewer believes that the [ ] some relevant information for labeling may be derived b(4)
- filing of this submission is recommended

Clinical Pharmacology and Biopharmaceutics comments:

- Study # 1 and Study #2 contain sufficient data to allow for review as a Written Request response
- of concern is whether the sponsor may not have submitted sufficient information to allow for review of an efficacy supplement
- filing of this submission is recommended

Statistical comments:

- it was stated that the submission does not appear to require statistical analysis of the data; the Medical Team Leader indicated that additional statistical analysis may be required during the review process
- of concern is that an interim report, only containing partial data, was submitted

- it was noted that Study # 2 is an observational study; the reviewer will write a memo concerning study #2
- filing of this submission is recommended

Toxicology comments:

- Dr. Jordan conveyed through the Project Manager that there were no preclinical or toxicology issues
- filing of this submission is recommended

Chemistry:

- subsequent to the filing meeting, the Chemistry reviewer stated that there were no CMC issues with this submission
- filing of this submission is recommended

Decisions made:

- DRUDP will file this submission pending concurrence from the Acting Division Director (*Dr. Shames supported the decision to file this submission, 2.4.02)*

Action Items:

- Project Manager to contact the Chemistry reviewers and ask for their recommendations (*Dr. Salemme and Dr. Lin indicated that there were no issues with this submission, and that it should be filed, 2.4.02*)
- Project Manager to provide a list of investigators to DSI for inspections as soon as possible

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/s/

Mark S. Hirsch
5/28/02 01:07:20 PM
I concur.

Filing Meeting Minutes

Date: February 4, 2002 **Time**: 10:30-11:30 AM, EST **Location**: PKLN; 17B43

NDA 20-897 S-009 **Drug:** Ditropan XL® tablet
Indication: overactive bladder

NDA 18-211 S-016 **Drug:** Ditropan® syrup
Indication: relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder

NDA 17-577 S-033 **Drug:** Ditropan® tablet
Indication: relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder

Sponsor: Alza Corporation

Type of Meeting: Filing

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:
Shelley Slaughter, M.D. – Acting Deputy Director, DRUDP (HFD-580)
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Ashok Batra, M.D. – Medical Officer, DRUDP (HFD-580)
Sonia Castillo, Ph.D. – Statistician, Division of Biometrics II (HFD-715)
Dhruba Chatterjee, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, OCPB @ DRUDP (HFD-580)
Diane V. Moore– Project Manger, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To establish if the submissions are fileable.

Background: Alza corporation submitted a pediatric supplement on December 7, 2001, under three oxybutynin chloride NDAs (20-897 for Ditropan XL, 18-211 for Ditropan Syrup, and 17-577 for Ditropan Tablets) in response to a Written Request issued by the Agency on November 20, 2000. The sponsor submitted two reports: a final study report, C-2000-043-00 (a pharmacokinetic and pharmacodynamic study in 15 patients), and an interim study report, C-2000-42-01 (a safety and dose-response study currently ongoing in 116 patients), as well as two critical analyses. The 60-day filing date is February 5, 2002, and the 10-month goal date is October 7, 2002.

Discussion:
Regulatory comments:

- it was clarified that the designation of "efficacy supplement" is made by the Chief of the Project Management staff
- to qualify as an efficacy supplement for an existing NDA, the submission must include clinical data in support of an additional indication, a new dose, or a new patient population
- a labeling supplement may also contain safety data which would require clinical review, but it will not lead to major changes as indicated in the previous comment
- if this submission is deemed not fileable, then the Pediatric Exclusivity Board will not make a determination on granting pediatric exclusivity; it was noted that the Division was not informed that fileability was a precondition to granting pediatric exclusivity
- it was confirmed that the review of the Financial Disclosure documents indicated that there was no disclosure of financial interests that could bias the outcome of the trials

Clinical comments:

- of concern is that the sponsor submitted an interim report for study C-2000-042-01 (Study #2), and has not stated whether additional data will be submitted as a final report; it was confirmed with sponsor that Study #2 is ongoing
- it was verified that the submission contains clinical data in Study #2, which is sufficient to allow an assessment of safety and efficacy [ ] b(4) [ ] however, Study #2 includes complete data in only 60 patients who completed the 24-week trial; it is not clear if the sponsor will submit a final study report, including information from all the 116 patients enrolled in the trial; Study #2 also includes some urodynamic data and some additional diary data from the "all enrolled" population
- study C-200-043-00 (Study #1) provides pharmacodynamic and pharmacokinetic information in 15 patients for two weeks; of concern is that this study contains data in only a very small number of patients, and for a short duration; however, it was noted that Study #1 met the requirements stated in the Written Request
- published literature and critical analyses in children and adults, with emphasis on the safety profile of oxybutynin in children, was also submitted in support of this application
- the medical reviewer believes that the [ ] b(4) [ ] some relevant information for labeling may be derived
- filing of this submission is recommended

Clinical Pharmacology and Biopharmaceutics comments:

- Study # 1 and Study #2 contain sufficient data to allow for review as a Written Request response
- of concern is whether the sponsor may not have submitted sufficient information to allow for review of an efficacy supplement
- filing of this submission is recommended

Statistical comments:

- it was stated that the submission does not appear to require statistical analysis of the data; the Medical Team Leader indicated that additional statistical analysis may be required during the review process
- of concern is that an interim report, only containing partial data, was submitted

- it was noted that Study # 2 is an observational study; the reviewer will write a memo concerning study #2
- filing of this submission is recommended

Toxicology comments:

- Dr. Jordan conveyed through the Project Manager that there were no preclinical or toxicology issues
- filing of this submission is recommended

Chemistry:

- subsequent to the filing meeting, the Chemistry reviewer stated that there were no CMC issues with this submission
- filing of this submission is recommended

Decisions made:

- DRUDP will file this submission pending concurrence from the Acting Division Director (*Dr. Shames supported the decision to file this submission, 2.4.02)*

Action Items:

- Project Manager to contact the Chemistry reviewers and ask for their recommendations (*Dr. Salemme and Dr. Lin indicated that there were no issues with this submission, and that it should be filed, 2.4.02*)
- Project Manager to provide a list of investigators to DSI for inspections as soon as possible

Drafted: Farinas/2.5.02
Concurrence: Slaughter 4.25.02/Hirsch 2.14.02/Gierhart 2.5.02/Batra 4.25.02/Parekh 4.25.02/Chatterjee 2.5.02/Castillo 2.6.02/Best 2.7.02
Finalized: Farinas/4.26.02

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/s/

Mark S. Hirsch
4/26/02 02:36:57 PM
I concur.

Teleconference Minutes

Date: March 5, 2002 **Time:** 11:00-11:15 AM, EST **Location:** PKLN; 17B45

NDA 20-897 S-009 **Drug:** Ditropan XL® tablet
Indication: overactive bladder

NDA 18-211 S-016 **Drug:** Ditropan® syrup
Indication: relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder

NDA 17-577 S-033 **Drug:** Ditropan® tablet
Indication: relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder

Sponsor: Alza Corporation

Type of Meeting: Clarification

Meeting Chair: Margaret Kober, R.Ph., Acting Chief, Project Management Staff, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Azim Shazamani, Associate Director, Regulatory Affairs

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Margaret Kober, R.Ph., Acting Chief, Project Management Staff, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Azim Shazamani, Associate Director, Regulatory Affairs

Meeting Objective: To answer the sponsor's question regarding final report submission.

Background: Alza corporation submitted a pediatric supplement on December 7, 2001, under three oxybutynin chloride NDAs (20-897 for Ditropan XL®, 18-211 for Ditropan® Syrup, and 17-577 for Ditropan® Tablets) and one IND (48,930), in response to a Written Request issued by the Agency on November 20, 2000. Subsequently, in a letter dated February 11, 2002, DRUDP requested that the sponsor clarify whether the study report for Protocol C-2000-042-01 was an interim report, and if so, provide an estimated date of completion and plans for submission of any additional data. In a February 25, 2002, facsimile, the sponsor requested feedback from the DRUDP regarding the acceptability of August 1, 2002, as the date of submission for a final report for Study C-2000-042 to IND 48,930.

Discussion:

- DRUDP reiterated that the final report should be submitted to the three NDAs, as well as to the IND
- DRUDP indicated that the logistics of the review would be decided after the submission is received, whenever that may be; DRUDP indicated that agreements can't be reached prior to review of the data and recommended that the sponsor submit the report as early as possible
- the sponsor reiterated that it is their belief that the data should not be submitted in a piecemeal fashion; the sponsor also restated that because the last patient will finish the study in April, 2002, it does not seem possible at this time to submit a final study report prior to August 1st, 2002

Decisions made:

- DRUDP's recommendations and feedback will be considered by the sponsor

Action Items:

- the sponsor will provide responses to DRUDP's letter of February 11, 2002, in the near future
- minutes from this teleconference will be provided to the sponsor in 30 days

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Drafted: Farinas/March 7, 2002
Concurrence: Kober 3.26.02
Finalized: Farinas 3.26.02

MEETING MINUTES

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/s/

Evelyn Farinas
3/26/02 05:48:40 PM
CSO

Margaret Kober
3/27/02 02:25:29 PM
UNKNOWN

M E M O R A N D U M

DEPARTMENT OF HEALTH AND
HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: February 12, 2002

To: Roy Blay, Ph.D., Department of Scientific Investigations (DSI) HFD-46

From: Brenda Gierhart, MD, Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580
Evelyn R. Farinas, R.Ph., MGA, Regulatory Project Manager, DRUDP; HFD-580

Subject: Request for Clinical Inspections for:
NDA 20-897 SE1-009
Ditropan XL® (oxybutynin chloride)

NDA 18-211 SE1-016
Ditropan® Syrup (oxybutynin chloride)

NDA 17-577 SE1-033
Ditropan® Tablet (oxybutynin chloride)

ALZA Corporation
Correspondence Date: December 7, 2001
Date Received: December 7, 2001

In support of the above mentioned NDA Supplements for Ditropan (oxybutynin), the sponsor (Alza Corporation) has submitted the results of the following pivotal protocols identified below:

Pivotal Protocol #/ Investigator's Name/Address/Randomized subjects

Trial C-2000-042 Israel Franco, M.D. — 30 randomized subjects
19 Broadhurst Avenue, Suite 2575
Hawthorne, NY 10532
914 493 8628

Richard Grady, MD — 10 randomized subjects
Children's Hospital & Regional Medical Center
4800 Sand Point Way NE
PO Box 5371
Seattle, WA 98105
205-526-0551 (Pediatric Urology Clinic 206-526-2509 is where he sees patients)

We have identified the above protocols/sites for inspection. (This supplemental NDA provides a response to a Written Request to obtain pediatric exclusivity [ ] b(4)

We request that the inspections be performed and the Inspection Summary Results be provided by August 31, 2002. We intend to make a regulatory decision on this application by October 7, 2002.

Should you require any additional information please contact Evelyn R. Farinas, at 301-827-4245.

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/s/

Evelyn Farinas
2/12/02 08:54:49 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-897\S-009
NDA 18-211\S-016
NDA 17-577\S-033

INFORMATION REQUEST LETTER

Alza Corporation
Attention: Steve Ketchum, Ph.D.
Senior Director, Regulatory Affairs
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Dear Dr. Ketchum:

Please refer to your December 7, 2001, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ditropan XL® (oxybutynin chloride) Tablet, Ditropan® (oxybutynin chloride) Syrup and Ditropan® (oxybutynin chloride) Tablet.

We are reviewing the clinical section of your submission and have the following comment and information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please clarify if the study report for C-2000-042-01 is an interim study report.

2. If the study report for C-2000-042-01 is an interim study report, provide the projected completion date for the study, and your plans for any additional submissions of data, either in interim or final report format.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jeanine Best
2/11/02 10:44:40 AM
Signing for Terri Rumble

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-211

PRIOR APPROVAL SUPPLEMENT

Alza Corporation
Attention: Janne Wissel
Senior Vice President, Operations
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210

Dear Ms. Wissel:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Ditropan XL®
NDA Number:	18-211
Supplement number:	S-016
Date of supplement:	December 07, 2001
Date of receipt:	December 07, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 5, 2002, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 17B 20
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 17B 20
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260

Sincerely,

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Terri F. Rumble
12/20/01 01:04:22 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-897

PRIOR APPROVAL SUPPLEMENT

Alza Corporation
Attention: Janne Wissel
Senior Vice President, Operation
1900 Charlestown Road
P.O. Box 7210
Mountain View, CA 94039-7210

Dear Ms. Wissel:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Ditropan XL®
NDA Number:	20-897
Supplement number:	S-009
Date of supplement:	December 7, 2001
Date of receipt:	December 7, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 5, 2002 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 17B20
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call Evelyn R. Farinas, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Terri F. Rumble
12/10/01 05:15:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-577

PRIOR APPROVAL SUPPLEMENT

Alza Corporation
Attention: Janne Wissel
Senior Vice President, Operation
1900 Charlestown Road
P.O. Box 7210
Mountain View, CA 94039-7210

Dear Ms. Wissel:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Ditropan®
NDA Number:	17-577
Supplement number:	S-033
Date of supplement:	December 7, 2001
Date of receipt:	December 7, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 5, 2002 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 17B20
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call Evelyn R. Farinas, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Terri F. Rumble
12/10/01 05:18:41 PM

Division of Reproductive and Urologic Drug Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: **NDA 17-577 S-032**

Name of Drug: Ditropan (oxybutynin chloride) Tablets

Sponsor: Alza Corporation

Material Reviewed: Proposed label changes to the approved labeling

Submission Date: September 10, 1999

Receipt Date: September 13, 1999

Background and Summary Description:
Alza Corporation submitted revised draft labeling to the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **OVERDOSAGE** sections of the approved draft labeling. These revisions are based upon the following: a) language in the approved product labeling for Ditropan XL (oxybutynin chloride) Extended Release Tablets; b) two literature reports to support the revised language concerning metabolism and potential drug-drug interactions; and c) a recommendation from Alza Medical and Safety Services to include adverse events reported for the immediate-release formulation of oxybutynin chloride used in the clinical trials for the Ditropan XL. Approval dates for the current labels for Ditropan (oxybutynin chloride) Tablets and Ditropan XL are March 19, 1991 and June 22, 1999 respectively.

Review:
Proposed changes are compared to the existing Ditropan labeling for each of the sections mentioned in the preceding paragraph. For each section, the proposed wording is listed first and it is highlighted. The approved labeling is included in the following paragraph.

CONTRAINDICATIONS

DITROPAN® (oxybutynin chloride) is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.
DITROPAN® is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product. b(4)

Ditropan (oxybutynin Chloride) is contraindicated in patients with untreated angle-closure glaucoma and in patients with untreated narrow anterior chamber angles since anticholinergic drugs may aggravate these conditions.
It is also contraindicated in partial or complete obstruction of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, megacolon, toxic megacolon complicating ulcerative colitis, severe colitis and myasthenia gravis. It is contraindicated in patients with obstructive uropathy and in patients with unstable cardiovascular status in acute hemorrhage.
Ditropan is contraindicated in patients who have demonstrated hypersensitivity to the product.

Sponsor's comments: These revisions are generally based upon the language of the approved labeling for Ditropan XL Extended Release Tablets. Some elements of the approved label have been modified and

relocated to the **PRECAUTIONS** section, under the *Urinary Retention* and *Gastrointestinal Disorders* subsections

RPM's comment: The proposed language deletes or moves to another section many of the contraindications stated in the approved label (i.e. partial or complete obstruction of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, megacolon, etc.). The modified language in the **PRECAUTIONS** section, which is the section where the modified contraindications will reside, is not as emphatic; it changes contraindications to a recommendation of administration with caution.

Medical Officer's comments, CONTRAINDICATIONS section: Recommends accepting the sponsor's proposed changes to the **CONTRAINDICATIONS** section, with the exception to the misspelling of the word retention in the first sentence of the section submitted in "Section 2: Strikeout/Underlined."

WARNINGS

Deleted

DITROPAN (oxybutynin Chloride), when administered in the presence of high environmental temperature, can cause heat prostration (fever and heat stroke due to decreased sweating.
Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with DITROPAN would be inappropriate and possibly harmful.
DITROPAN may produce drowsiness or blurred vision. The patient should be cautioned regarding activities requiring mental alertness such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug. Alcohol or other sedative drugs may enhance the drowsiness cause by DITROPAN.

Sponsor's comments: The **WARNINGS** section has been deleted and modified or moved when no specific evidence in the primary literature was found identifying such effects as known hazards in conjunction with the use of oxybutynin. Such theoretical hazards have been moved to the **PRECAUTIONS** section, under subsections *Information for Patients* and *Gastrointestinal Disorders*.

RPM's comments: Removal of the **WARNINGS** section lessens the concerns noted and described in the approved labeling.

Medical Officer's comments: Recommends deleting the **WARNINGS** section as proposed by the sponsor.

PRECAUTIONS

General
DITROPAN® should be used with caution / patients with hepatic or renal impairment. b(4)

Urinary Retention:
DITROPAN® should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (See CONTRAINDICATIONS).

Gastrointestinal Disorders:

DITROPAN® should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see CONTRAINDICATIONS).

DITROPAN®, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, intestinal atony [redacted] b(4)

DITROPAN® should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

Information for Patients

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Drug Interactions

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents that produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

[redacted] b(4)

Mean oxybutynin plasma concentrations were approximately 3-4 fold higher when DITROPAN® was administered with ketoconazole, a potent CYP3A4 enzyme inhibitor.

Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (eg, itraconazole and miconazole) or macrolide antibiotics (eg, erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (ie, C_{max} and AUC). The clinical relevance of such potential interactions is not known. *

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum human exposure, based on surface area.

Pregnancy: **

Nursing Mothers: **

Pediatric Use: **

* Biopharmaceutics Team Leader recommends adding the following sentence at this point: "Caution should be used when such drugs are coadministered."

** Proposed change is the underlining of the subheadings, and conversion from all capitals to only first letter capitalized; text in each subsection did not change.

DITROPAN (oxybutynin chloride) should be used with caution in the elderly and in all patients with autonomic neuropathy, hepatic or renal disease. DITROPAN may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, and prostatic hypertrophy. Administration of DITROPAN (oxybutynin chloride) to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at dosages up to approximately 400 times the recommended human dosage showed no evidence of carcinogenicity

Pregnancy: *
Nursing Mothers: *
Pediatric Use: *

* Subheading not underlined in the approved immediate-release labeling

Sponsor's comments: The proposed language for the subsections *General, Urinary Retention, Gastrointestinal Disorders* and *Information for Patients* is based on the Ditropan XL approved product labeling. The proposed language for the *Drug Interactions* subsection is based on editorial modification of the Ditropan XL approved labeling, a literature article (Yaich, M et al., The Metabolism of Oxybutynin is Dependent on CYP3A4 and Not on CYP2D6, Therapie [1995]) and a report provided by the sponsor (Sathyan G. and S. Gupta, Effect of ketoconazole on the pharmacokinetics of oxybutynin: Comparison between Ditropan XL and immediate release formulation, ALZA Corporation [1999]).

RPM's comments: The proposed labeling introduces minor changes, such as the additional underlining of several subsection headings (ex. Pregnancy, Nursing Mothers, etc.). It also introduces two new subsections, *Information for Patients* and *Drug Interactions*. Under the subsection *Gastrointestinal Disorders* of the proposed **PRECAUTIONS** section, the sponsor is adding two cautionary statements not previously included in the approved label. These are: a) use with caution on patients who have gastroesophageal reflux, and b) use with caution in patients who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis. Many of the **WARNING** statements were modified and moved to the Information for Patients subsection, minimizing the safety message of the approved labeling. The Biopharmaceutics Team Leader recommends adding a cautionary statement (see * above) to the Drug Interactions subsection.

Medical Officer's comments, **General** subsection: Recommends accepting the proposed changes to the General subsection of the **PRECAUTIONS** section regarding patients with hepatic or renal impairment, Urinary Retention, Gastrointestinal disorders, and Information for Patients, except for the following:

- Delete the proposed underlining of the subsection title General. None of the subsection titles in the **PRECAUTIONS** section should be underlined.
- In the proposed General subsection of the **PRECAUTIONS** section, add a new sentence:
  Ditropan ® may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension [ ] prostatic hypertrophy. b(4)
- In the proposed Gastrointestinal disorders subsection of the **PRECAUTIONS** section, add a new second sentence:
  Administration of Ditropan® to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

Medical Officer's comments, **Drug Interactions** subsection: Recommends accepting all five sentences proposed in the Drug Interactions subsection addition to the **PRECAUTIONS** section, and the addition of a sixth sentence, so that the Drugs Interactions subsection reads as follows:

> The concomitant use of oxybutynin with other anticholinergic drugs or with other agents that produce dry mouth, constipation, somnolence (drowsiness), and /or other anticholinergic-like effects may increase the frequency of and/or severity of such effects.
> Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

Mean oxybutynin chloride plasma concentrations were approximately 3-4 fold higher when DITROPAN was administered with ketoconazole, a potent CYP3A4 inhibitor.
Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (eg, itraconazole and miconazole) or macrolide antibiotics (eg, erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (ie, C_{max} and AUC). The clinical relevance of such potential interactions is not known.
Caution should be used when such drugs are co-administered.

The Medical Officer also recommends the Ditropan® XL Drug Interactions subsection of the **PRECAUTIONS** section replace the current third and fourth sentences with the proposed third, fourth, fifth and sixth sentences.

Medical Officer's comments, **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection: Recommends accepting the proposed changed to the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection of the **PRECAUTIONS** section. Recommends that none of the subsection titles in the **PRECAUTIONS** section should be underlined.

ADVERSE REACTIONS

Dermatologic: Dry skin, rash.
Gastrointestinal/Genitourinary: [ ], constipation, [ ], decreased gastrointestinal motility, dry mouth, [ ] nausea, urinary hesitance and retention. b(4)
Nervous System: Asthenia, dizziness, drowsiness, hallucinations, [ ] insomnia, restlessness.
Ophthalmic: [ ] cycloplegia, dry eyes, mydriasis.
Other: Impotence, [ ] suppression of lactation.

Dermatologic: Decreased sweating, rash.
Gastrointestinal/Genitourinary: Constipation, decreased gastrointestinal motility, dry mouth, nausea, urinary hesitance and retention.
Nervous System: Asthenia, dizziness, drowsiness, hallucinations, insomnia, restlessness.
Ophthalmic: amblyopia, cycloplegia, decreased lacrimation, mydriasis.
Other: Impotence, suppression of lactation.

Sponsor's comments: Revisions are based on the adverse events reported for the immediate-release formulation of oxybutynin chloride used in the clinical trials for Ditropan XL.

RPM's comments: While sponsor's modifications resulted in the inclusion of additional adverse events, it also deleted three previously included adverse events (i.e., decreased sweating, amblyopia, and decreased lacrimation).

Medical Officer's comments: Recommends rejecting the proposed changes to the **ADVERSE REACTIONS** section. The **ADVERSE REACTIONS** section for this label should follow the formatting of the Ditropan XL label **ADVERSE REACTIONS** section. Recommends changing the **ADVERSE REACTIONS** section to:

ADVERSE REACTIONS:
The safety and efficacy of Ditropan® (oxybutynin chloride) was evaluated in a total of 199 patients in three clinical trials with Ditropan® XL (Table 1). These participants were treated with 5-20 mg/day for up to 6 weeks. [ ] b(4)

Table 1
Incidence (%) of Adverse Events Reported by ≥5% of Patients Using Ditropan® (5-20 mg/day) b(4)

Body System	Adverse Event	Ditropan® (5-20 mg/day) (n=199)
General	Abdominal pain	6.5%
	Headache	6.0%
Digestive	Dry mouth	71.4%
	Constipation	12.6%
	Nausea	10.1%
	Dyspepsia	7.0%
	Diarrhea	5.0%
Nervous	Dizziness	15.6%
	Somnolence	12.6%
Special senses	Blurred vision	[ ]%
	[ ]	[ ]%
Urogenital	Urination impaired	10.6%
	Post void residual increase	5.0%
	Urinary tract infection	5.0%

b(4)

The most common adverse events reported by patients receiving 5-20 mg/day Ditropan® were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

In addition, the following adverse events were reported by 2 to <5% of patients using Ditropan® (5-20 mg/day) in [ ] studies. *General*: asthenia, dry nasal and sinus mucous membranes; *Cardiovascular*: palpitation; *Metabolic and Nutritional System*: peripheral edema; *Nervous System*: insomnia, nervousness, confusion; *Skin*: dry skin; *Special Senses*: dry eyes, taste perversion. b(4)

Other adverse events [ ]: tachycardia, hallucinations, cyclopegia, mydriasis, impotence, suppression of lactation, vasodilatation, rash, decreased gastrointestinal motility, flatulence[ ] decreased sweating. b(4)

OVERDOSAGE

Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.
Overdosage with oxybutynin [ ] been associated with anticholinergic effects including [ ] excitation, [ ] fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention.
[ ] of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13-year-old boy who experienced memory loss, and a 34-year-old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment. b(4)

The symptoms of overdosage with DITROPAN (oxybutynin chloride) may be any of those seen with other anticholinergic agents. Symptoms may include signs of central nervous system excitation (e.g., restlessness, tremor, irritability, convulsions, delirium, hallucinations), flushing, fever, nausea, vomiting, tachycardia, hypotension or hypertension, respiratory failure, paralysis and coma.

In the event of an overdose or exaggerated response, treatment should be symptomatic and supportive. Maintain respiration and induce emesis or perform gastric lavage (emesis is contraindicated in precomatose, convulsive, or psychotic state). Activated charcoal may be administered as well as a cathartic. Physostigmine may be considered to reverse symptoms of anticholinergic intoxication. Hyperpyrexia may be treated symptomatically with ice bags or other cold applications and alcohol sponges.

Sponsor's comments: Revisions are based on the adverse events reported for the immediate-release formulation of oxybutynin chloride used in the clinical trials for Ditropan XL.

RPM's comments: The proposed language adds two case reports of overdosage and three additional symptoms (i.e., dehydration, cardiac arrhythmias and urinary retention).
But the proposed labeling deletes the following two items which are included in the approved immediate-release labeling:
a) several symptoms associated with overdose (i.e., restlessness, tremor, irritability, convulsions, delirium, hallucinations, [ ] hypotension, hypertension, respiratory failure, paralysis and coma), and b(4)
b) the detailed therapy recommendations for overdose (" Maintain respiration and induce emesis or perform gastric lavage (emesis is contraindicated in precomatose, convulsive, or psychotic state). Activated charcoal may be administered as well as a cathartic. Physostigmine may be considered to reverse symptoms of anticholinergic intoxication. Hyperpyrexia may be treated symptomatically with ice bags or other cold applications and alcohol sponges.").

The deletion of these two items eliminates important information for recognition and treatment of an overdose situation.

Medical Officers comments: Recommends accepting the proposed changes to the **OVERDOSAGE** section except for the following:
In the proposed third sentence of the **OVERDOSAGE** section after the phrase "[ ]excitation" add: b(4)
(e.g., restlessness, tremor, irritability, convulsions, delirium, hallucinations)
In the proposed **OVERDOSAGE** section, add a new fourth sentence:
Other symptoms may include hypotension or hypertension, respiratory failure, paralysis and coma.
Begin a new paragraph with the proposed third sentence in the **OVERDOSAGE** section.

Conclusion:

Clinical and Biopharmaceutics recommendations should be conveyed to the sponsor in an Approvable letter.

Evelyn R. Farinas, R.Ph., M.G.A.
Regulatory Project Manager

Concurrence: Rumble 3.12.01, Gierhart 3.15.01, Hirsch 3.15.01, Parekh 3.15.01, Shames 3.15.01, Allen 3.30.01
Final: Farinas 4.4.01

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Evelyn Farinas
4/4/01 09:25:08 AM
CSO

Terri F. Rumble
4/12/01 04:33:44 PM
CSO
I concur.

Brenda Gierhart
4/12/01 04:43:01 PM
MEDICAL OFFICER

Mark S. Hirsch
4/13/01 11:52:02 AM
MEDICAL OFFICER

Ameeta Parekh
4/13/01 04:01:16 PM
BIOPHARMACEUTICS
I concur. I have added DJ's name to the CC list.

Daniel A. Shames
4/18/01 03:23:29 PM
MEDICAL OFFICER

Susan Allen
4/18/01 04:07:41 PM
MEDICAL OFFICER