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) (b) (4) 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/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

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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.
- (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.
- (b) (4)
- (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 (b) (4) 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 (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. (b) (4)

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.

(b) (4)

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.

[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 (b) (4) 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 (b) (4) sites that were requested for inspection were:

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

(b7)

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 (b) (4) General safety measurements (urinalysis, serum chemistry and complete blood count) were performed for the US sites at a (b) (4) and for the Netherlands study site at (b) (4), Switzerland.

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 (b) (4). General safety measurements (urinalysis, serum chemistry and complete blood count) were performed for the US sites at a (b) (4) and for the Netherlands study site at (b) (4). The Netherlands.

Site Monitoring. For Study **C-2000-042-01** (pg. 53.7/113-115), (b) (4) US sites (b) (4) 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.

For Study **C-2000-043-00** (pg. 53.14/159-160), (b) (4) 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. (b) (4) was responsible for initiating and monitoring sites.

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

- **(b) (4) is a well-known qualified clinical laboratory. (b) (4) are well known qualified Contract Research Organizations. Both are widely used by the pharmaceutical industry to conduct and/or monitor drug clinical trials.**
- **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 (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.

11.1.1 Sponsor Proposed Changes to CLINICAL PHARMACOLOGY Section

The sponsor proposes to delete the sentence:

> Pharmacokinetic information is not currently available.

And replace it with the following three sentences:

> Steady-state pharmacokinetics of oxybutynin chloride were studied in children ages 1-15 years. A trend toward lower oxybutynin clearance was noted in the pediatric populations as compared to adults. Oxybutynin was well tolerated in the pediatric populations studied.

Medical Officer's Comments

1) **It is the opinion of the reviewer that little information valuable to the practitioner is provided with the addition of these three sentences. The third sentence is promotional in nature and should definitely be deleted. The reviewer proposes to replace the deleted sentence with the following four sentences:**

   Oxybutynin chloride steady-state pharmacokinetics were studied in 36 children with detrusor hyperreflexia due to neurogenic conditions (e.g. spina bifida) aged 1-15 years. The children were on Ditropan syrup (n=25) with total daily dose ranging from 0.25 to 0.77 mg/kg or Ditropan tablets (n=11) with total daily dose ranging from 0.21 to 0.53 mg/kg. No clear relationship between the total daily dose administered (mg/kg) and the pharmacokinetic data was identified. No specific dosing regimen can be recommended based on this data.

11.1.2 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 administration have been safely demonstrated for pediatric patients 5 years of age and older (see DOSAGE AND ADMINISTRATION). However, as there is insufficient clinical data for pediatric populations under age 5, Ditropan is not recommended for this age group.

To:

> The safety and efficacy of DITROPAN® Tablets and Syrup have been safely demonstrated for pediatric patients 5 years of age and older (see DOSAGE AND ADMINISTRATION).
>
> The safety and pharmacodynamics of DITROPAN® Syrup were studied in children 1-5 years of age. As part of this 2-week open-label trial, 16 children were treated with DITROPAN® Syrup at doses of 3.6-9 mg per day. The patients treated had a diagnosis of detrusor hyperreflexia, used clean intermittent catheterization, and were current users of oxybutynin. Study results demonstrate that DITROPAN® Syrup was well tolerated. For patients less than 5 years of age or for any patient who has difficult swallowing, syrup is the recommended dosage form (see DOSAGE AND ADMINISTRATION).
>
> DITROPAN has not been studied in patients less than 1 year of age, and is therefore not recommended for this age group.

Medical Officer's Comments

1) **The reviewer proposes that no changes be made to the current Pediatric Use Subsection of the PRECAUTIONS Section since it continues to be true that "there is insufficient clinical data for pediatric populations under age 5" despite the completion of Study C-2000-043-00. It is the opinion of the reviewer that little information valuable to the practitioner is provided in the sponsor proposed changes. No information was provided regarding Study C-2000-042-01. No additional information was provided regarding pediatric use of Ditropan tablets. The only conclusion provided for Study C-2000-043-00**

(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:

> (b) (4) a 24-week open-label trial, (b) (4) used clean intermittent catheterization, and were current users of oxybutynin chloride. Study results demonstrated that (b) (4) 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**).

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 (b) (4) 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)

(b) (4)

(b) (4) **neurogenic conditions (e.g. spina bifida)** (b) (4) **used clean intermittent catheterization, and were current users of oxybutynin chloride** (b) (4)**. 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.

   (b) (4)

   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).

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

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

(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 only 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 (b) (4)

(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 (b) (6) and Surgery: release tethered cord (b) (6)	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 (b) (6) ventriculoperitoneal shunt revision (b) (6)	Not related

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.

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(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 (b) (4) 12 hours time points.

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)

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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.

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/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.