CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20-897

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-897

Trade Name: DITROPAN XL 5 mg and 10 mg Tablets

Generic Name:(oxybutinin chloride)

Sponsor: Alza Corporation

Approval Date: December 16, 1998

Indication: Provides for the use of Ditropan XL (oxybutinin chloride) for the treatment of overactive bladder with symptoms of urge urinary incontience, urgency, and frequency.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-897

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-897

DEC 16 1998

Alza Corporation
Attention: Steve Ketchum, Ph.D.
Director, Regulatory Affairs
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Dear Dr. Ketchum:

Please refer to your new drug application (NDA) dated December 17, 1997, received December 19, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ditropan® XL (oxybutinin chloride) 5 mg and 10 mg tablets.

We acknowledge receipt of your submissions dated April 30, June 30, July 30, August 6, September 15 and 30, October 27, 28 and 30, November 16 and 20, and December 4, 7, 11, 15 and 16, 1998.

This new drug application provides for the use of Ditropan XL (oxybutinin chloride) for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

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

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

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-897." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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

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

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

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

If you have any questions, contact Randy Olmstead, Project Manager, at (301) 827-4260.

Sincerely,

/S/

Lisa D. Rarick, M.D.
Director, Division of Reproductive and
Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-897

MEDICAL REVIEW(S)

Medical Officer Review

NDA 20-897
NDA Submitted: 12/17/97
NDA Received: 12/19/97
MOR Completed: 11/25/98
Revisions Completed: 12/14/98

DEC 14 1998

Sponsor: Alza Corporation
Drug: **Generic: Oxybutynin** Chloride
Tradename: Ditropan XL
Chemical: Benzeneacetic acid, a-cyclohexyl-a-hydroxyl-,4-(diethyamino)-butynyl esther hydrochloride
Route: Oral
Dosage Form: Oral Osmotic Tablet
Strength: 5 and 10 mg
Proposed Indication: The treatments of urge urinary incontinence, urgency and frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia.
Related References: IND Alza Corporation
NDA 17-577 (Ditropan® -oxybutynin), Hoescht Marion Roussel
Note: NDA was transferred to Alza in Jan. 1998.

Table of Contents

1.0 Resume

Efficacy: The sponsor submitted three controlled trials in support of the efficacy of Ditropan XL for the treatment of overactive bladder:

1. **C-95-031**, a double-blind, placebo and active-controlled (IR oxybutynin), forced dose-escalation trial involving 82 women.

2. **C-95-049-05**, a double-blind, active-controlled (IR oxybutynin), dose-titration study involving 105 men and women with overactive bladder.

3. **C-97-020-03**, a double-blind, active–controlled (IR oxybutynin) trial, dose-titration trial involving 226 men and women.

It is important to note, that in all three of these trials, the patient populations were "enriched" because many of the patients were individuals known to be responsive to anticholinergic medications. Two of the studies (C-95-049-05, C-97-020-03), utilized a "Therapeutic Responder Trial" as an enrollment criteria. In this segment of the trials, patients were eliminated who did not "respond " to oxybutynin. For example, in trial C-97-020-03, of the 180 patients that were "screened" in the Therapeutic Responder Trial, 62 were "failures" and 118 proceeded to randomization. The reviewer believes that this form of enrichment does not invalidate the comparative efficacy results demonstrated in these trials. However, the absolute and relative changes in urinary incontinence episodes, continence rates and many other parameters reported in these trials may not reflect values observed in the "unenriched" incontinence population visiting a physician's office.

In all three studies, the primary efficacy parameter was the mean number of weekly episodes of urge urinary incontinence. In trial C-95-031, the sponsor demonstrated that Ditropan XL was statistically better than placebo in reducing the mean number of weekly urge incontinence episodes from baseline to the end of the study. In trial C-95-049-05, the efficacy of Ditropan XL and IR oxybutynin tended toward but did not meet the statistical criteria for equivalence. However, they were not statistically equivalent. In trial C-97-020-03, Ditropan XL and IR oxybutynin were statistically equivalent. **The evidence presented in the submission support the hypothesis that Ditropan XL, administered once daily, is efficacious for the treatment of overactive bladder.**

Safety and Dry Mouth Issues: This safety review was based on the updated Integrated Summary of Safety submitted to the Agency August 6, 1998 as well as the clinical data in the December 17, 1997 New Drug Application submission. Eight studies were conducted in a total of 670 patients and 151 healthy subjects. Some of these patients were enrolled in more than one trial. For example, approximately 20% of the patients in trial C-97-020 had been enrolled in previous trials. Study C-95-031 had a forced dose escalation design to 15mg/day. Studies C-95-049 and C-97-020 incorporated individual dose adjustment designs, reflecting current clinical practice, escalating dosage to a maximum of 30mg/day. Study C-96-070, an uncontrolled, open-label trial encompassed 256 patients

treated with Ditropan XL for up to 23 weeks. Efficacy and tolerability were adjusted to a maximum dose of 30mg/day. Four clinical pharmacology studies in 151 healthy subjects treated for 1-4 days were also evaluated.

No deaths and 2 serious adverse events occurred in the controlled studies, both in patients treated with immediate release oxybutynin. One patient suffered a fall and subdural hematoma. The other was diagnosed with a small bowel obstruction 6 days after starting medication. It resolved with nonoperative management. . There were 18 patients in the uncontrolled study with serious adverse events. The one death in the uncontrolled Ditropan XL study involved a woman with a history of cardiac disease who developed a myocardial infarction, thought by the investigator to be unrelated to the study medication. Two events, both related to gastroesophageal reflux, were considered by the investigator to be possibly related to the study drug. One patient experienced serious exacerbation of known gastroesophageal reflux. The other patient, a 73 year old women with diverticulitis and osteoporosis, developed epigastric pain, nausea, and vomiting, ultimately diagnosed as gastritis, gastroesophageal reflux, and gastric dysmotility. It is unclear whether alendronate sodium may have also contributed to the symptoms. The remaining 15 serious adverse events were classified by the investigator as unrelated to study drug. All original case report forms were examined by this reviewer who concurs that aside from the two patients who experienced gastroesophageal reflux, the serious adverse events were not plausibly related to the use of Ditropan XL.

Adverse events culminating in discontinuation of study medication occurred in similar percentages of Ditropan XL and immediate release oxybutynin treated patients (6.2% vs 7%). Dry mouth (1.1%), nausea (1.8%) dyspepsia (0.9%), and somnolence (0.9%) accounted for the majority of Ditropan XL dropouts.

In the controlled studies, 79.8% of patients taking Ditropan XL experienced at least one adverse event vs 86.3% in the uncontrolled study. Reviewing all studies, at least one anticholinergic adverse event was reported by 68.9% of patients taking Ditropan XL. Dry mouth (59%), constipation (12.6%), somnolence (11.5%), nausea (8.4%), blurred vision (7.3%), dyspepsia (6.4%), asthenia (6.4%), and dizziness (5.9%) predominated. At titration levels of 5-30mg/day, impaired urination occurred in 4.4% of patients, insomnia in 4.6%, and confusion in 2.4%. Studies in which dosing tried to balance tolerability with efficacy, (C-95-049 and C-97-020), resulted in dry mouth in 51.8% of Ditropan XL patients. This was classified as moderate or severe in 19.5% of patients. Similar percentages (58.6% and 23%) were identified in the uncontrolled study of similar design. Overall, moderate or severe anticholinergic events were reported in 31.5% of patients taking Ditropan XL.

The reviewer concludes that there are no major safety concerns with Ditropan XL.

Immediate release oxybutynin chloride has been widely used for over 20 years, and the safety profile is well established. Ditropan XL employs a capsule design shown to be safe and reliable when used to deliver a variety of other pharmaceutical agents. An

osmotically active bilayer core surrounded by a semipermeable membrane perforated by laser-drilled holes releases suspended drug at a controlled rate.. The data submitted by the sponsor does not reveal any additional safety concerns over and above those well known and reported with immediate release oxybutynin chloride. A review of blood chemistries, hematology data, and electrocardiogram data shows no significant changes in these parameters that would constitute a safety concern.

The sponsor attempts to prove with data from the three controlled trials that Ditropan XL has increased tolerability in terms of **dry mouth** compared to IR oxybutynin at equally efficacious doses. However, data from the controlled trials does not demonstrate that there is either a statistical or clinically meaningful difference in incidence of dry mouth between Ditropan XL and IR oxybutynin. In addition, there are significant design flaws within the trials that inhibit the ability of the trial to accurately reflect the differential incidence of dry mouth.

The "maintenance period" for a trial that accurately assesses the incidence of dry mouth should be longer than the average of one week in the controlled trials submitted in this NDA. A period of 6-12 weeks would be more appropriate. Oxybutynin is a chronically administered drug and thus a longer "maintenance period" would more appropriately reflect clinical practice allowing for more accurate assessment of withdrawals and "quality of life" issues. In addition, anticholinergic adverse events are known to lessen in severity or even disappear in some patients over time[6]. Because of a possible change over time in anticholinergic events, it would be optimal to measure dry mouth and the end of an appropriately long (6-12 week) "maintenance period".

A visual analogue scale would be a more accurate method to measure a subjective end point such as dry mouth rather than the more vague and ill-defined approaches used in the submitted trials. In addition, the sponsor should propose and support the difference in dry mouth that would be clinically meaningful. The clinically meaningful difference for this type of endpoint should be determined in a trial separate from the efficacy trial.

The reviewer concludes that Ditropan XL is safe and effective for treatment of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence. Increased tolerability for Ditropan XL compared to immediate release oxybutynin with respect to dry mouth, however was not demonstrated.

2.0 Background

2.1 Regulatory History: The immediate release form of oxybutynin (Ditropan® was approved (NDA 17-577) in 1976. This NDA was transferred from Hoescht Marion Roussel to Alza in Jan. 1998. Alza submitted an IND for Ditropan XL on Oct. 2,1995. During a face-to-face meeting on 1/27/97 and two teleconferences on 2/28/97 and 7/8/97 major clinical and statistical issues regarding the proposed trials were addressed. On

[6] Douglas WW: Histamine and 5-hydroxytryptamine and their antagonists. In: Goodman and Gillman's The Pharmacologic Basis of Therapeutics. 7th edition. New York: Macmillan Publishing Company; 1985. P.621.

12/17/97 Alza submitted an NDA for Ditropan XL. On 4/30/98, Alza submitted a 4-month safety update to the NDA. On 8/6/98 Alza submitted a final study report for C-97-020 which was intended to support a claim of superiority of Ditropan XL over IR oxybutynin regarding tolerance. The sponsor also provided a safety update in this submission.

Clinical Background and Scientific Rationale:

Urinary incontinence is defined by the International Continence Society as "the involuntary loss of urine that represents a hygienic or social problem to the individual." In addition to the large numbers of patients with incontinence there are equally large numbers who experience an abnormal pattern of urination - urgency, frequency, and nocturia - that interferes with daily activities. Both of these populations are increasing as society ages. Survey data reports that the prevalence of incontinence for adult women under age 65 ranges from 2% to 46%, with 10% to 20% the most common estimate. For the elderly, the estimates for community dwelling groups is 30 to 40 % for women and 15% for men.[1]

The social costs of this disabling condition are great. Many incontinent patients will "suffer silently" without reporting their problems to a health care provider. They will often limit or eliminate work, recreation, and travel activities to avoid incontinence or fear of leakage. Urinary incontinence also has significant social and economic implications for family members, caregivers, and society. The economic costs for the estimated 4.6 million incontinent individuals in the United States was about [based on 1994 dollars], with about one third of that amount directed to the care of an estimated 800,000 nursing home residents. Hu reported that 5% of community dwellers and 2% of nursing home residents received appropriate medical evaluation and treatment for their incontinence.[2]

The Agency for Health Care Policy and Research [AHCPR] has published[3] evidence-based guidelines for evaluation and treatment of urinary incontinence. Of the several categories of incontinence described, the most common is urge incontinence. Urge incontinence is the involuntary loss of urine associated with a strong desire to void. Overactivity of the motor or sensory nerves or decreased inhibition from spinal or brain control centers causes early or false signals of fullness. These signals may trigger a premature and unwanted detrusor contraction. The Urodynamic Society has published recommended terminology for this condition. *Detrusor overactivity* is the preferred term when the etiology of the involuntary contraction is unclear, *Detrusor hyperreflexia*, when there is a neurologic etiology and *Detrusor instability* when a non-neurological cause is present.

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[1] Burgio KL, Matthews KA, Engel BT. Prevalence, incidence and correlates of urinary incontinence in healthy, middle-aged women. J Urol 1991; 146:1255-9.

[2] Hu T. Impact of urinary incontinence on health-care cost. J Am Geriatr Soc 1990:38:292-5.

[3] U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, Rockville, MD, Publication No. 96-0682, March 1996.

Urinary control problems are often caused by multiple interacting factors. Some of these factors are anatomic, physiologic, and pathologic changes in the urinary tract; others are non-genitourinary. Systemic diseases such as diabetes mellitus and congestive heart failure can have secondary effects on bladder control.[4]

Initial evaluation for urge incontinence should include a complete history and physical exam to identify any systemic or social factors that are readily reversible [e.g. constipation, immobility, adverse effects of other medications]. Once all reversible factors are addressed, use of pharmaceuticals to treat unwanted bladder overactivity is the primary therapy. Pharmaceutical interventions are aimed at increasing bladder storage capacity. Normal bladder storage allows accommodation of volumes of urine in the range of 150 to 400 ml. at low intravesical pressure. A bladder outlet that is closed at rest and with filling along with the absence of involuntary bladder contractions are also necessary for normal storage.

The ability of the urinary bladder to store urine comfortably for reasonable lengths of time and then empty completely requires complex coordination through neural pathways. Control centers in the cerebral cortex, brain stem, and sacral spinal cord provides positive feedback to the bladder. Early signals of fullness with bladder filling are normally suppressed. The urge and need to empty can then be delayed until socially appropriate.

The parasympathetic nerves are the primary control pathways between cortex, brain stem, spinal cord, and bladder detrusor. Parasympathetic nerve signals are mediated by the chemical, acetylcholine. Transmitters other than acetylcholine have been suspected, since many animal studies show that a nerve-mediated bladder contraction cannot be completely blocked with atropine. To control urinary incontinence, drugs have been identified that diminish the effects of acetylcholine release at the neuroeffector junction.

Muscarinic receptors on the detrusor muscle cells are the targets for acetylcholine released from cholinergic neurons. The anti-cholinergic effects useful in treatment of urinary bladder symptomatology occur primarily due to the effects of drugs on these muscarinic receptors. The mass release of acetylcholine results in the uniform contraction of the detrusor, and, when coordinated with bladder outlet relaxation, the emptying of the bladder.

Antagonists act at the muscarinic receptor to prevent the effects of acetylcholine by blocking its binding to these receptors at neuroeffector site on bladder smooth muscle. All known drugs that act to block the effects of acetylcholine on the bladder are non-selective competitive antagonists. There are five muscarinic subtype receptors, with variable distribution in different end organs. The bladder receptors are mainly of the M2 and M3 types. This information may allow for future development of drugs with selective action on the bladder.

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[4] Ouslander J, Bruskewitz R. Disorders of micturition in the aging patient. Adv Int Med 1989; 34:165-90.

Parasympathetic muscarinic neuroeffector junctions are present in many organs besides the bladder, but different sites are variably sensitive to muscarinic receptor antagonists. With even small doses of antagonist, the salivary gland stimulation is diminished and production of saliva is decreased with resultant dry mouth. At these same doses, bronchial secretions and sweat are diminished. With larger doses, the pupil dilates and anticholinergic effects on the heart may produce an increased rate. Only with relatively high doses are the bladder receptors blocked, producing a decrease in bladder tone and diminished frequency and urgency with suppression of uninhibited contractions.

This hierarchy of organ sensitivities has made it difficult to develop a drug that is clinically useful in treatment of bladder symptoms without producing adverse effects in patients. These adverse effects may not be serious but are sufficiently bothersome to patients to significantly decrease compliance.

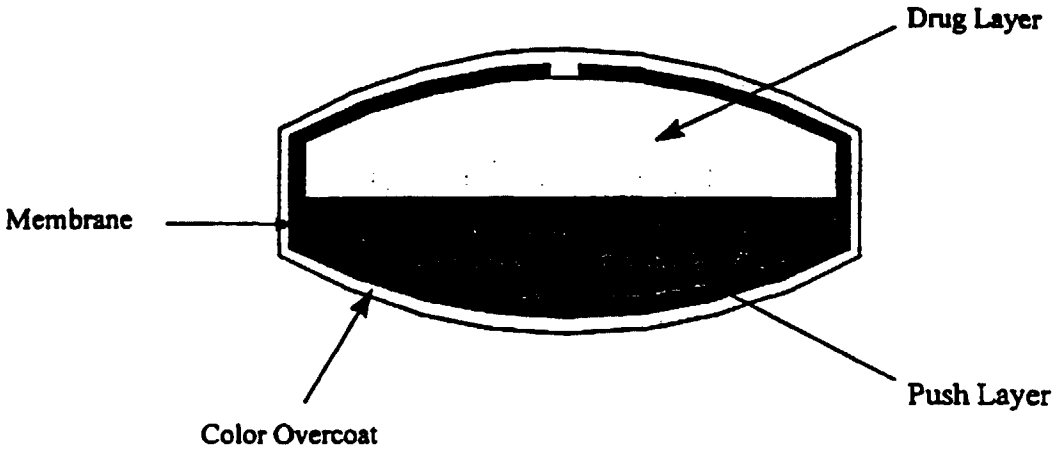
Physiology and Metabolism

Oxybutynin is an anticholinergic-antispasmodic, a tertiary amine ester, that inhibits the muscarinic action of acetylcholine on smooth muscle and exerts direct antispasmodic effect on smooth muscle. Some studies also suggest direct local anesthetic properties. Ditropan exhibits only one fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. In humans, the anticholinergic action of the drug is thought to be the primary mechanism by which oxybutynin effects urinary incontinence. In studies of patients with involuntary bladder contractions, cystometrogram studies show that oxybutynin increases bladder capacity, diminishes the frequency of uninhibited contractions of the detrusor and delays the initial desire to void.

Oxybutynin is currently available as in immediate release [IR] formulation [Ditropan]. Ditropan XL is an extended release form of Ditropan and is the subject of this review. The extended release form has been developed as a once a day oral dosage. The drug product uses a proprietary controlled-release delivery capsule that has previously been used in several products marketed in the United States since 1983 [Glucatrol XL, Procardia XL]. The OROS [oxybutynin chloride] system is composed of a semipermeable membrane enclosing a bilayer core [see following diagram]. One layer contains the oxybutynin chloride and excipients. The other layer contains osmotic agents and excipients. In the aqueous environment of the gastro-intestinal tract, water is drawn through the membrane at a controlled rate. The properties of the membrane and the osmolality of the core substances determine the rate. The expansion of the osmotic agents against the drug compartment causes the oxybutynin in suspension to exit the capsule at a controlled rate through an orifice that is laser-drilled in the membrane. The delivery capsule will not dissolve and is excreted intact per rectum (see Figure 1).

Figure 1
Diagram of Controlled Release Delivery Capsule

OROS® (oxybutynin chloride)



Oros is a previous name for Ditropan XL

Pharmacokinetics-

The absolute bioavailability of oxybutynin was not determined for this NDA; however, Douchamps *et al.*, 1988, report an absolute bioavailability of about 6%. The bioavailability of oxybutynin and desethyloxybutynin following Ditropan XL administration relative to those following immediate release Ditropan were evaluated in Studies C-94-010 and C-96-074. The results are listed in Table 1.

Table 1. Steady state pharmacokinetic parameters and relative bioavailability of oxybutynin and desethyloxybutynin following administration of Ditropan XL (3 x 5 mg) and immediate release (IR) Ditropan (5 mg TID).

Parameter	IR oxybutynin	Ditropan XL
Oxybutynin		
C_{max} (ng/mL)	12.4 (4.1)	6.7 (2.1)
C_{min} (ng/mL)	1.4 (1.2)	2.8 (1.6)
AUC_{0-24} (ng.hr/mL)	80.6 (42.5)	109 (42.5)
$T_{1/2}$ (hr)	9.0 (2.4)	13.8 (2.9)
Relative Bioavailability (%)	Reference	153 (67.1)
Desethyloxybutynin		
C_{max} (ng/mL)	44.7 (20.3)	22.5 (13.6)
C_{min} (ng/mL)	5.8 (6.5)	7.1 (6.0)
AUC_{0-24} (ng.hr/mL)	483 (281)	304 (145)
$T_{1/2}$ (hr)	4.0 (1.4)	8.3 (2.5)
Relative Bioavailability (%)	Reference	69 (22.8)

Dose Selection – The range of therapeutic doses for IR oxybutynin is generally between 5 and 20 mg daily, administered in a dose of 5 mg every six to eight hours. The initial dose selected for Ditropan XL, 5 mg, was based on the lowest recommended dose reported in the literature for the immediate release formulation. At steady state, given the same daily dose of Ditropan XL and IR oxybutynin, the plasma concentrations of the Ditropan XL were approximately one half the peak C_{max} concentrations found with the TID dosing of IR Ditropan and higher than its trough concentrations [C_{min}]. Because of the stable plasma concentrations over the daily dosing interval for Ditropan XL, the drug was evaluated to an upper limit of 30 mg in a dose titration study. At this dose, the peak

plasma concentration of oxybutynin would be in approximately the same as a 5 mg TID or QID dose of IR oxybutynin.

Metabolism – Ditropan XL is rapidly metabolized to a racemic mixture of desethyloxybutynin, an active metabolite. This metabolite has pharmacological activity similar to that of oxybutynin in in-vitro studies. The OROS system releases drug continuously over twenty-four hours. Because the delivery capsule reaches the colon from four to six hours after ingestion, a major portion of the drug dose is released in the colon. In contrast, the IR form of oxybutynin is released in the stomach and small intestine. Studies show that the enzymes that metabolize this drug are more concentrated in the small bowel than in the colon.[5] This may be the reason that oxybutynin's bioavailability is greater with Ditropan XL (153%) compared to IR oxybutynin while the bioavailability of desethyloxybutynin is lower (69%) with Ditropan XL compared to IR oxybutynin. CYP3A4 enzymes primarily metabolize the drug. Concomitant use of drugs that induce or inhibit this enzyme system may effect the pharmacokinetics of oxybutynin.

Reviewer's comment: Because of differences in pharmacokinetics, metabolism and bioavailability, dose by dose comparisons between IR oxybutynin and Ditropan XL are not appropriate.

No significant differences in pharmacokinetics of Ditropan XL were noted for race and gender in studies in normal healthy volunteers. The sponsor believes that there was no significant difference in plasma concentrations of the enantiomers of oxybutynin following Ditropan XL administration between those <65 years of age and those 65 and older. The pharmacokinetics of Ditropan XL was not studied in children under age 18 or in special populations with hepatic or renal impairment.

2.3 International Marketing Experience: Ditropan XL has never been subject to any foreign regulatory authority marketing authorization application. The US application is the first marketing authorization application for this product.

3.0 Summary of NDA Clinical Section: The clinical section of this NDA initially contained two "controlled" studies in support of the application along with four clinical pharmacology studies and an open label "safety" study. During the review another controlled study was submitted for evaluation.

3.1 Summary of Controlled Trials of Ditropan XL - "Core Studies"

Clinical Trial C-95-031

This was a multicenter (9, US), randomized, double-blind, double-dummy, fixed dose-escalation, controlled trial with five treatment arms comparing immediate release (IR) oxybutynin (n=32), Ditropan XL (n=34), experimental therapy (n=35) with oral (n=16) and experimental therapy placebos (n=17). In the oral treatment groups 82 women enrolled at the nine sites. The first patient was recruited on December 2, 1995 and the

[5] Caldwell J Marsh MV. Metabolism of drugs by the gastrointestinal tract. In George CF, Shands DG, eds., Clinical Pharmacology and Therapeutics 1: Presystemic Drug Elimination. London: Butterworth Scientific, 1982, pp. 29-42.

last patient completed the study on December 2, 1996. The sponsor's stated objective of this study was to compare the efficacy of Ditropan XL with placebo in middle-aged and elderly women with urge incontinence and to comparatively evaluate the adverse event profiles of Ditropan XL, IR oxybutynin and oral placebo. Therefore, the review will focus on these three oral treatment arms. Female patients over 40 years of age with urge urinary incontinence (U-UI), at screening were enrolled in the study. Urge urinary incontinence was defined as having a urinary frequency of at least 10 voids per day and at least 10 (but less than 60) U-UI episodes per week. In addition, a cystometrogram (CMG) must have demonstrated a detrusor contraction and/or a severe (score =2) urge to void at filling volume of less than or equal to 400 ml. Patients with mixed urinary incontinence were included provided that the symptoms or signs of stress incontinence were not predominant. Patients were eligible if they were in good health, had a creatinine clearance of greater than 50 ml/minute, were normotensive (could be on anti-hypertensives) and on an appropriate form of birth control if premenopausal. Patients must have successfully completed the screening diary for seven days and otherwise follow the study schedule. The primary efficacy variable was the change in the mean number of U-UI episodes per week from baseline to the end of the study as recorded in PUD.

This was a randomized, multicenter (13 US), double-blind, double-dummy, parallel-group, dose-titration study comparing the efficacy and safety of Ditropan XL with immediate release (IR) oxybutynin (Ditropan®) in male and female patients with urge and mixed urinary incontinence. One hundred and five patients ages 40 to 75 years of age were enrolled in the study (97 female, 8 male). The first patient was enrolled in the study on July 30, 1996 and the last patient completed the study on February 26,1997. The primary objective of the study was to compare the efficacy of Ditropan XL and IR oxybutynin at the final dose level.

Three categories of patients were included in this trial:

- Patients who had been taking and tolerating IR oxybutynin, hyoscyamine sulfate, or propantheline for the treatment of urge incontinence at the dose prescribed by their physicians.

- Patients who had previously been on IR oxybutynin and discontinued because of anticholinergic adverse events, but not because of lack of efficacy.

- Patients who had never taken the above drugs for urge incontinence but who demonstrated to be responsiveness to oxybutynin in a Therapeutic Responder Screening Trial (described on page 15)

Patients who had at least 6 urge UI urinary incontinence episode per week as recorded in the PUD during the baseline week were randomized equally at each study site into one of two arms (Ditropan XL and IR oxybutynin) and then entered into the Dose-Titration Period. A blocking procedure was employed at each center. The duration of this period

varied depending on the individual needs of the patients. The study had three dose-titration endpoints. They were defined as follows:

- MED (minimum effective dose); this was the dose at which the patient had no episodes of urge urinary incontinence during the final 2 days of the 4-7 day dosing interval.

- MTD (maximum tolerated dose); this dose was 5 mg lower than the dose at which the patient reported intolerable anticholinergic effects.

- MAD (maximum allowable dose); this was either 20 mg/day of IR oxybutynin or 30 mg /day of Ditropan XL.

During the Dose-Titration Period, each patient was started at a dose of 5 mg of oxybutynin (IR or XL). The doses were increased in increments of 5 mg at intervals of 5 to 7 days. The dose increases were discontinued when either MED, MTD or MAD was reached. Once the endpoint was reached, the patient received an additional week of therapy at the defined dose level (Dose-Confirmation Period- one-week). After this, the patient entered a one week Maintenance Period in which the patient received study drug at the established MED, MTD or MAD for one week, (see Figure 2).
The primary efficacy variable was the change in the mean number of U-UI episodes per week from baseline (Off-medication Run-in period just prior to randomization) to the end of the study as recorded in the Patient Urinary Diary (PUD).

Clinical Trial C-97-020-03
This was a randomized, multicenter (20 US), double-dummy, double-blind, parallel-group, dose-titration trial designed to compare the difference in dry mouth in patients with urge urinary incontinence treated with Ditropan XL and IR oxybutynin. In addition, the study compared the efficacy, quality of life, patient satisfaction and safety of the two comparators. Two hundred and twenty-six male and female patients ages 40-75 years were enrolled in the study. The first patient was enrolled in the study on December 3, 1997 the last patient completed the study on May 18, 1998.

Three categories of patients were included in this trial:

- Patients who had been taking IR oxybutynin, Levsin®, or Pro-Banthine® or any other anticholinergic medications for the treatment of urge incontinence.

- Patients who had previously been on anti-cholinergic medications and discontinued because of reasons other than lack of efficacy.

- Patients who had never taken the above drugs for urge incontinence but who were demonstrated to be responsive to oxybutynin in a Therapeutic Responder Screening Trial (described on page 28)

The study was divided into three periods: Run-in, Dose-titration and Maintenance (see Figure 4). During the Run-in Period (2 weeks), the patients received no medication for urge incontinence. During week 1 of this period, all the medications for incontinence were discontinued. During the second week, a placebo (single-blind) was administered and baseline assessments were obtained. The baseline assessments included recording data in a Patient Urinary Diary (PUD), filling out a study medication card, and completing the Urge-Incontinence Impact Questionnaire (U-IIQ) during the clinic visit at the end of the week.

The Dose-Titration Period lasted up to four weeks. Patients made one to four clinic visits at intervals of approximately 7 days for dose titration after randomization. At the first visit during this period, the patients were randomized to the Ditropan XL or the IR oxybutynin arm. Patients began at the 5-mg/day dose in both arms. During the subsequent visits patient doses were escalated up to 20 mg/day using the following criteria:

- The patient achieved a target efficacy endpoint of no urge urinary incontinence episodes for the last three days of the period.

- The patient received the maximum allowable dose (20 mg/day).

- The patient reported a tolerable anticholinergic effect but believed that the symptom would be intolerable if the medication were increased. In this case, the patient entered the Maintenance Period at the present dose.

- The patient experienced an intolerable anticholinergic effect. In this case, the dose was decreased to the next lower dose or the patient was discontinued from the study at the discretion of the study physician.

Patients who achieved any of the above conditions entered into the Maintenance Period for one week. During this period, the patients completed a Patient Urinary Diary (PUD), filled out the medication card, and responded to the patient satisfaction questionnaire and U-IIQ during the clinic visit at the end of the week. The two co-primary endpoints were measurement of dry mouth at the end of the trail and mean change in incontinence episodes per week form baseline to end of study.

3.2 Summary of Other Clinical Trials of Ditropan

C-96-070- This was an open-label safety study which involved about 250 patients for at least 3 months.

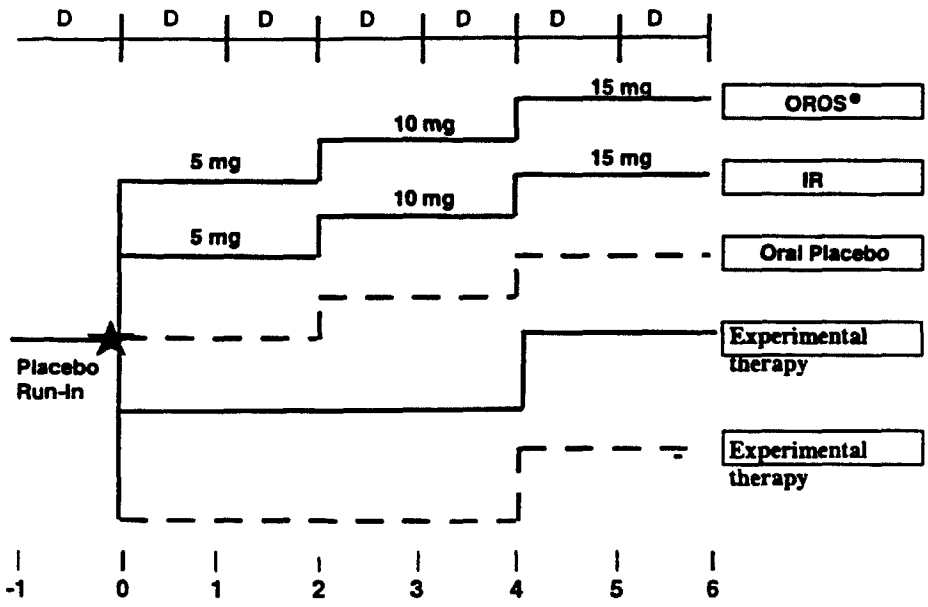
4.0 Clinical Trial C-95-031

4.1 Design and Conduct of the Trial:

This was a multicenter (9, US), randomized, double-blind, double-dummy, fixed dose-escalation, controlled trial with five treatment arms comparing immediate release (IR) oxybutynin (n=32), Ditropan XL (n=34), experimental therapy (n=35) with oral (n=16) and experimental therapy placebos (n=17). Patients were enrolled and randomized with dose escalation as described in Figure 2.

Figure 2*

Study Flow Schema



D = Patient Urinary Diary
OROS = OROS® (oxybutynin chloride)
IR = IR oxybutynin
* Sponsor figure V1.46/38
(OROS® is a previous name for Ditropan XL)

The sponsor is seeking approval for Ditropan XL with this NDA. In the oral treatment groups 82 women enrolled at the nine sites. The first patient was recruited on December 2, 1995 and the last patient completed the study on December 2, 1996. The sponsor's stated objective of this study was to compare the efficacy of Ditropan XL with placebo in middle-aged and elderly women with urge incontinence and to comparatively evaluate the adverse event profiles of Ditropan XL, IR oxybutynin and oral placebo. Therefore, the review will focus on these three oral treatment arms. Female patients over 40 years of age with urge urinary incontinence (U-UI), at screening were enrolled in the study. Urge urinary incontinence was defined as having a urinary frequency of at least 10 voids per day and at least 10 (but less than 60) U-UI episodes per week. In addition, a cystometrogram (CMG) must have demonstrated a detrusor contraction and/or a severe (score =2) urge to void at filling volume of less than or equal to 400 ml. Patients with mixed urinary incontinence were included provided that the symptoms or signs of stress incontinence were not predominant. Patients were eligible if they were in good health, had a creatinine clearance of greater than 50 ml/minute, were normotensive (could be on

anti-hypertensives) and on an appropriate form of birth control if premenopausal. Patients must have successfully completed the screening diary for seven days and otherwise follow the study schedule.

Patients were excluded from the trial if they took drugs other than oxybutynin, hyoscyamine or propantheline that were considered to be effective in the treatment of urge incontinence within 1 month of the start the study or the equivalent of five half-lives. Patients who were previously treated with anti-cholinergic medications for U-UI and found to be refractory were excluded. Patients with glaucoma, obstructive disease of the gastrointestinal or urinary tract, or myasthenia gravis were excluded form the trial.

Reviewer's comment: Excluding patients who were previously found to be refractory to anticholinergics enriched the patient population for this trial. Thus, the response to active treatment noted in these patients will not be reflective of what one would expect in a more generalized population.

Patients were selected to participate in the trial from a population of women 40 years of age and older with urge urinary incontinence. The patient characteristics most important to be a candidate for this study were incontinence resulting primarily from presumed detrusor contraction (urge incontinence) or severe urge to void. Subjects who demonstrated responsiveness to anticholinergic medications were encouraged to participate although this was not a requirement. After a wash-out/screening period of at least up to one month which included filling out a patient urinary diary (PUD) for one week, the patients began a placebo run-period of one week which included filling out a complete patient urinary diary (PUD). After review of the PUD, patients were randomized to one of five treatment groups (figure 2). However only three of the arms (A, B, C, Table 2) will be considered in this review since the remaining arms involved the experimental therapy..

TABLE 2*

Treatment Schedule

(OROS® is a previous name for Ditropan XL)

Treatment	Week 1	2-3	4-5	6-7
Placebo Run-in OROS® placebo & IR placebo capsule & experimental placebo	1 OROS® placebo 1 IR placebo capsule q8h 1 experimental placebo q3.5 days	N/A	N/A	N/A
A OROS® (oxybutynin chloride) & IR placebo	N/A	1 (5 mg) OROS® (oxybutynin chloride) qAM 1 IR placebo q8h	2 (5 mg) OROS® (oxybutynin chloride) qAM 2 IR placebos q8h	3 (5 mg) OROS® (oxybutynin chloride) qAM 2 IR placebos q8h
B IR oxybutynin & OROS® placebo	N/A	1 (1.7 mg) IR oxybutynin q8h 1 OROS® placebo qAM	2 (1.7 mg) IR oxybutynin q8h 2 OROS® (placebos) qAM	2 (2.5 mg) IR oxybutynin q8h 3 OROS® (placebos) qAM
C OROS® placebo & IR placebo	N/A	1 OROS® placebo qAM 1 IR placebo q8h	2 OROS® (placebos) qAM 2 IR placebos q8h	3 OROS® (placebos) qAM 2 IR placebos q8h

N/A = Not applicable

*Vol 1.46/40

During the placebo run-in period, patients had one Ditropan XL placebo in the AM, one IR placebo q 8 hours and one skin patch placebo every 3.5 days. Following the placebo run-in, the patients in the oral portion of the study were randomized to one of the following three treatment groups: A) Ditropan XL plus IR placebo, B) IR oxybutynin plus Ditropan XL placebo, and C) Ditropan XL placebo plus IR placebo.

Ditropan XL placebos were identical to Ditropan XL except that the placebo contained no drug. To allow for tid dosing of 5, 10 or 15 mg of IR oxybutynin, a granulated form of oxybutynin was manufactured into a capsule. The capsules contained mg of drug. Immediate release placebo capsules were identical in appearance to the active IR capsule but contained no drug.

Patients were randomized evenly to Ditropan XL, IR oxybutynin, or placebo at each site after completion of the one-week placebo run-in. To ensure balance within the treatment arms a blocking procedure was used at each site. The study was double-blinded using a

double-dummy technique. Dose escalation occurred routinely at weeks 2 and 4 of the study in each treatment arm as depicted in Figure 1. All medications were taken on an empty stomach.

Medication compliance was monitored by counting unused drug, having the patients record time and date of medication administration in daily diaries, and having clinic staff call the patients to check on medication schedule.. In addition, blood and urine samples were collected periodically for levels of oxybutynin and desethyloxybutynin.

The primary efficacy variable was the change in the mean number of U-UI episodes per week from baseline to the end of the study as recorded in PUD. Clinical staff monitored the patients compliance with completing the PUD by periodic telephone calls. Patients recorded events in their PUD at the time of each incontinence episode (they were instructed to differentiate between stress and urge), each voluntary void and the number of incontinence pads used per day. Other variables that were analyzed from the PUD were: The diurnal and nocturnal micturitions per week, the number of incontinence pads changed for wetness per day and change in weight of the incontinence pads.

Reviewer's comment: Incontinent pad use may vary among ambulatory versus nonambulatory patients although randomization should correct for this. Compliance regarding accurately returning pads could also be a problem.

Urodynamic measurements included post-void residual determined by bladder ultrasound within 15 minutes of voiding or catheterization within 30 minutes of voiding. During the periodic cystometrograms (CMG), urge to void score (0-2), bladder pressure and detrusor contractions were measured at every 100 ml of bladder filling volume.

Two tools were used to assess the patients' subjective assessment of treatment. They were the Subjective Assessment of Urinary Symptom Severity (SAUSS) and the Patient Satisfaction and Overall Rating (PSOR). The SUASS used a 5-point scale (0-4) for the patients to assess the severity of various symptoms. The PSOR asked the global question; "Are you satisfied with the treatment?" and further asked the patients to rate the positive or negative effect of their treatment on a 5 point scale where 1 was "very negative" and 5 was "very positive".

At each weekly clinic visit, as part of the safety assessment, patients took the Subjective Assessment of Anticholinergic Effects (SAAE) questionnaire. The questionnaire was administered just prior to dosing and one-hour post dosing. The SAAE asked the patients to score the degree to which various anticholinergic effects (dry mouth, blurred vision, nausea, drowsiness and constipation) bothered them on a 4-point scale. In terms of "bothersomeness", the scale was defined as follows: 0 = not at all, 1 = mild ("a little bit"), 2= moderate ("more then a little") and 3=severe ("a great deal"). An anticholinergic event with a score of 2 or more was recorded as an adverse event on the CRF. --

During the weekly clinic visit, patients were encouraged to discuss adverse events not mentioned on the SAAE. In addition, phone calls were made between clinic visits to inquire about adverse events or unusual symptoms. Adverse event severity and relationship to study medication were recorded in a routine fashion.

Pre and one-hour post-dose vital signs were obtained with the patient sitting as well as orthostatic measurements at the beginning and end of the study. EKG, routine blood work, urinalysis and urine for drug screen were obtained at screening and at the end of the study. Blood and urine collections were obtained at various times during the study to assess plasma concentration of R and S oxybutynin and desethyloxybutynin as well as urine concentration of oxybutynin and desethyloxybutynin.

4.2 Study Population: Among the oral treatment groups, there were 82 randomized patients enrolled in 9 study sites and all had evaluable baseline data. There were 34 in the Ditropan XL group, 32 in the IR oxybutynin group and 16 in the oral placebo group.

Baseline Demographics were similar between the three groups. All of the patients in the three groups were female. The mean age was 59.6 years in the Ditropan XL group, 56.0 years in the IR oxybutynin group and 56.8 years in the oral placebo group. Approximately 90 % of each group was Caucasian, 5% Black with a few percent Hispanic and other. Mean weight was about 78 kg with a mean height of 163 cm.

More than 50% of patients in all groups had incontinence for more than 5 years. Use of tissues or pads in the undergarments was the primary method of incontinence management. This method was utilized by over 80% of the patients in all groups.

4.3 Withdrawals and Compliance: Two of 34 patients (5.9%) in the Ditropan XL group withdrew before the end of the study because they left town. Two of 32 (6.3%) patients in the IR oxybutynin group withdrew because of adverse events (patient esophagitis, patient chills, dizziness, dry mouth). One out of 16 (6.3%) patients in the placebo group discontinued because of an adverse event (sinus infection).

Reviewer's comment: Ditropan XL did not appear worse than IR oxybutynin or placebo regarding study withdrawals.

Medication compliance was assessed from data in the diaries and medication counts during clinic visits. Median compliance rate was 99% for all treatment groups. Median compliance rates were 100% for the 5/day and 10 mg /day doses for all treatment groups and 97% for the 15-mg/day dose for all treatment groups.

4.4 Protocol Violations and Deviations: There were two major types of protocol violations:

1. Randomization of patients with fewer than seven urge urinary incontinence episodes per week. Three of 82 patients (4%) were randomized to oral treatments despite the fact that they had less than 7 urge urinary incontinence episodes for the placebo run-in week. These three patients included two patients (6%) in the Ditropan XL group -2 episodes, -0 episodes) and one patient (6%) in the placebo group (0 episodes).

2. Randomization of patients with fewer than 10 voids per day. Ten patients entered the treatment period with fewer than a mean of 10 voids per day (a range of 6 to 9 voids/24 hours): nine of these were randomized to the Ditropan XL group (26%) and one to the IR oxybutynin (3%).

Reviewer's comment: The imbalance regarding many patients with fewer voids than 10 per 24 hours at baseline being randomized to the Ditropan XL group could affect efficacy outcome. The patients in the Ditropan XL group may have had less severe symptoms.

4.5 Efficacy Analysis

4.51 Statistical Methods: For analyses of the primary and all secondary parameters, the intent-to-treat (ITT) population was used. The ITT population included all randomized patients. If a patient terminated treatment before the final, the last observation carried forward method was used to provide data for the endpoint.

A two-way ANOVA model or a two-way ANCOVA model was originally proposed for the analysis of the primary and secondary endpoints. This had included the skin patch placebo as part of the placebo analysis. During a teleconference on July, 8 1997, the Division agreed to include only oral placebo in analysis used for the purposes of this NDA. The model selected depended on whether baseline values affected treatment outcome. The least squares estimate of the mean between two treatments and its 95% confidence intervals was used in the analysis.

The primary hypothesis tested in this study was the mean change in the number of urge urinary incontinence episodes per week from baseline to the end of the study between Ditropan XL and oral placebo was equal to zero (null hypothesis).

Reviewer's comment: The sponsor states in V. 1.46/100 that "The study was not designed to demonstrate equivalence between Ditropan XL and the active control IR oxybutynin." Therefore, superiority regarding adverse events cannot be claimed.

Secondary parameters analyzed included other variables derived from data in the Patient Urinary Diary such s urinary frequency, and incontinence pad use. Urodynamic data such as post-void residual, volume voided and cystometrogram data were also analyzed as well as well as data from several quality of life instruments.

4.52 Efficacy Results: The unadjusted mean number of urge urinary incontinence episodes decreased significantly from baseline in all arms of the study, including placebo (see Table 3).

Table 3
Mean Number of Urge Urinary Incontinence Episodes per week (unadjusted)
Study C-95-031-08

	Ditropan XL (n=34)	IR Oxybutynin (N=32)	Oral Placebo (N=16)
Baseline	15.9	25.3	20.9
Endpoint (week 6)	1.5	5.1	10.3

Reviewer's comment: The IR oxybutynin group had patients with the most severe baseline symptoms, followed by placebo and Ditropan XL. This baseline imbalance probably reflects the small sample size of the study, and makes efficacy determination difficult.

Because there was a significant difference (p= 0.071 between the number of urge urinary incontinence episodes at baseline between the three groups, the least-square mean(LS mean)was estimated from the ANOVA model for the analysis of baseline measurements. An ANCOVA model with baseline value as a covariant was used for the analysis of change from baseline to endpoints. Table 4 illustrates the information derived from these analyses.

Table 4
Mean Number of Urge Urinary Incontinence Episodes per week
(adjusted with ANCOVA/ANOVA models)
Study C-95-031-08

	Ditropan XL (n=34)	IR Oxybutynin (n=32)	Oral Placebo
Baseline (adjusted)	20.7	20.7	20.7
Endpoint (adjusted)	2.1	5.2	10.6
Change from Baseline	-18.6	-15.6	-10.2
Active Drugs vs. Placebo (95% C.I.)	-8.4 (-13.4, -3.5)	-5.4 (-10.6, -0.2)	
p value	.001	.041	
Ditropan XL vs. IR Oxybutynin (95% C.I.)	-3.0 (-7.5, 1.4)		
P value	0.181		

Both Ditropan XL and IR oxybutynin were significantly better than placebo in reducing the episodes of urge incontinence from baseline to week six. There were no significant differences between the effects of Ditropan XL and IR Oxybutynin on improvement of incontinence.

Reviewer's comment: Although the study did not demonstrate a difference between Ditropan XL and IR Oxybutynin, one cannot conclude the drugs studied are equivalent. The only efficacy conclusion that can be derived from this data is that Ditropan XL is more efficacious than placebo in improving urge urinary incontinence. This supports the approval of Ditropan XL for the indication of overactive bladder.

An analysis of weekly incontinence pad use revealed that the reduction in the use of pads was higher in the active drug arms compared to placebo (–12.4 for Ditropan XL, -10.3 for IR oxybutynin, and –4.8 for placebo). The estimated overall baseline mean was 14.7.

Reviewer's comment: There was a clinically significant reduction in the use of incontinence pads for the active drug arms. There was no statistically or clinically significant difference, however Ditropan XL and IR oxybutynin. It is unclear as to whether incontinence pad use is an accurate indicator of the degree of urge urinary incontinence.

In addition, a dropout-adjusted analysis was performed in which the change in weekly urge incontinence episodes from baseline to endpoint was set at zero for those patients who discontinued study medication early. In this analysis Ditropan XL still proved to be significantly more effective than placebo (p=0.002) in reducing urge urinary incontinence episodes.

Total voids per week (accidental plus normal voids) was analyzed. Because of variation in baseline means an adjusted analysis was carried out. The mean number of total voids at baseline was adjusted to 90 for all three groups. By the end of the study, all the patients in all three groups had significantly fewer voids per week (-20.5 for Ditropan XL, -17.5 for IR oxybutynin and –11.2 for placebo). The reduction in voids per week was greater for the active drug groups compared to placebo but did not reach statistical significance.

Reviewer's comment: The tendency for Ditropan XL vs. placebo to reduce mean total voids per week may have reached statistical significance if more patients were enrolled and this would have supported efficacy.

The mean baseline voided volume was approximately 160 cc for the three groups. The voided volumes increased in all three groups (38 for Ditropan XL, 52 for IR oxybutynin, and 110 for placebo). None of these changes were statistically significant.

Reviewer's comment: Anticholinergic medication should increase the volume voided as it relaxes the bladder detrusor muscle. It is somewhat surprising that the patients in the active drug arms of this study tended to do worse on this endpoint.

4.6 Safety Analysis

Deaths: There were no deaths reported in this study.

Serious Adverse Events: There were no serious adverse events reported in this study.

All Adverse Events: The large majority of adverse events reported in this trial were consistent with anticholinergic effects. Ninety-two percent of the patients in the Ditropan XL group, 100% of the patients in the IR oxybutynin group and 69% of the patients in the placebo group reported at least one event that was consistent with an anticholinergic effect. The most common anticholinergic effect reported was dry mouth (85% of the Ditropan XL patients, 100% of the IR oxybutynin patients and 50% of the placebo patients). Moderate or severe dry was reported by 18/34 (52.9 %) of the Ditropan XL patients, 17/32 (53.1%) of the IR oxybutynin patients and 3/16 (18%) of the placebo patients. The differences between the active arms and placebo were statistically significant for all dry mouth episodes (p=.002) as well as moderate to severe dry mouth (p=.002)

Reviewer's comment: In this study, the proportion of patients that reported moderate or severe dry mouth was the same between Ditropan XL and IR oxybutynin.

Somnolence (38.2%, 18.8%, 12.5%), constipation (29.4%, 31.3%, 12.5%), blurred vision (23.5%, 25.1%, 18.8%) and nausea (20.6%, 25.0%, and 12.5%) were the next most frequently reported adverse events in the Ditropan XL, IR oxybutynin and placebo arms respectively. The frequencies of these events reported by patients in the two active arms were generally similar and tended to be higher than that reported by patients in the placebo arm. These differences, however, did not achieve statistical significance.

Laboratory and Clinical Safety Parameters: There were no clinically significant overall trends in mean laboratory parameters for any of the three treatment groups (CBC, electrolytes, liver function tests, creatinine clearance, and urinalysis). There were several clinically significant individual changes in laboratory values from baseline to endpoint. Theses included microhematuria (2), signs of UTI (2), increased glucose (1), decreased hgb.(1) and increased LFT's (1). After review of the patient synopses, the reviewer does not believe there was a consistent pattern. Relationship to study drug is unknown.

Blood pressure and heart rate were measured at baseline, endpoint and all clinic visits. There were no clinically significant changes in mean heart rate or blood pressure within or between treatment groups.

Electrocardiograms (ECG's) were obtained at baseline and endpoint. No statistically significant differences were observed within or between treatment groups for PR, QRS, or QT intervals from baseline to the end of the study.

Nine of 34 (26.5%) patients treated with Ditropan XL, 6/31(19.4%) patients treated with IR oxybutynin and 2/15 (13.3%) treated with placebo had ECG changes at the end of the study. The most frequent finding was sinus bradycardia which occurred in 18% of the Ditropan XL group, 10% of the IR oxybutynin group and 13% of the placebo group. Patients in the active treatment group also developed such abnormalities such as premature atrial contractions, first-degree heart block, premature ventricular contractions and others.

Reviewer's comment: There does not appear to be a clinically consistent pattern that would suggest a study drug related cause of the ECG changes. Again, small sample size limits the conclusions one can make about this endpoint.

4.7 Reviewer's Assessment of Safety and Efficacy: The sponsor's major conclusions from this study were as follows:

1. Ditropan XL was significantly more effective than placebo and comparable to IR oxybutynin in reducing mean number of urge urinary incontinence episodes from baseline to the end of the study.

2. Ditropan XL was well tolerated and safe with a lower incidence of dry mouth and other anticholinergic adverse events compared to IR oxybutynin.

While this study is of very short duration and relatively small, the reviewer believes that the sponsor has provided adequate evidence that Ditropan XL is more effective than placebo in reducing mean number of urge incontinence episodes during the study. Because the study was not designed to demonstrate equivalence, and there was significant baseline variation in the primary variable between the two active drugs, no definitive statements can be made regarding "comparability" between Ditropan XL and IR oxybutynin.

Any statements regarding the superiority of Ditropan XL with respect to anticholinergic effects and more specifically dry mouth are not supported by this trial. There are several reasons for this:

1. The trial was not designed to demonstrate equivalence of efficacy between Ditropan XL and IR oxybutynin; therefore, comparative statements regarding adverse events cannot be fairly made.

2. The study was not long enough.

3. The sponsor measured dry mouth throughout the study rather than at the end; tolerance to dry mouth may occur over time, and therefore an evaluation of dry mouth at week 12 or longer is recommended.

4. The measurement of dry mouth was not well defined (see Reviewer's Overall Assessment of Safety and Efficacy)

5. Even with these design flaws, the results regarding dry mouth were not compelling. The sponsor states (V.1.46/115) that " Fewer patients reported dry mouth with Ditropan XL than with IR oxybutynin (85.3% vs. 100%, p=0.054)." A 15% overall difference in dry mouth is not remarkable.

6. The proportion of patients that reported moderate or severe dry mouth was essentially the same (52.9% vs. 53.1%) between the Ditropan XL and IR oxybutynin groups.

Reviewer's comment: The sponsor has not demonstrated superior tolerability of Ditropan XL compared to IR oxybutynin. However, the sponsor has provided evidence that Ditropan XL is safe for its intended use.

5.0 Clinical Trial C-95-049-05

5.1 Design and Conduct of the Trial: This was a randomized, multicenter (13 US), double-blind, double-dummy, parallel-group, dose-titration study comparing the efficacy and safety of Ditropan XL with immediate release (IR) oxybutynin (Ditropan®) in male and female patients with urge and mixed urinary incontinence. One hundred and five patients ages 40 to 75 years of age were enrolled in the study (97 female, 8 male). The first patient was enrolled in the study on July 30, 1996 and the last patient completed the study on February 26,1997. The primary objective of the study was to compare the efficacy of Ditropan XL and IR oxybutynin at the final dose level.

Three categories of patients were included in this trial:

- Patients who had been taking and tolerating IR oxybutynin, hyoscyamine sulfate, or propantheline for the treatment of urge incontinence at the dose prescribed by their physicians.

- Patients who had previously been on IR oxybutynin and discontinued because of anticholinergic adverse events, but not because of lack of efficacy.

- Patients who had never taken the above drugs for urge incontinence but who demonstrated to be responsiveness to oxybutynin in a Therapeutic Responder Screening Trial (described on page 15)

The original protocol of this study defined three study periods. They were Run-in, Treatment and Maintenance. However, the final study report redefines these periods for clarification (Table 5). Only those patients who were already taking IR oxybutynin were

entered into a 1-week IR Oxybutynin Run-in Period. During this period a Patient Urinary Diary (PUD) was completed.

TABLE 5*

Periods of the Study as Defined In this Report and in the Protocol

Name of Study Period Used in this Report	Name of Study Period Used in the Protocol
IR Oxybutynin Run-in	Run-in
Washout	Run-in
Off-medication Run-in (baseline)	Run-in
Dose Titration	Treatment
Dose Confirmation	Treatment
Maintenance	Maintenance

*Sponsor's Table-V.1.58/42

After the IR oxybutynin Run-in period, all patients who had previously taken IR oxybutynin and patients in all other categories were entered into a 1-week Washout period. At the beginning of this period, all anticholinergic medications were discontinued. All patients then entered a 1-week Off-medication Run-in Period (baseline).

Patients who had at least 6 urge UI urinary incontinence episode per week as recorded in the PUD during the baseline week were randomized equally at each study site into one of two arms (Ditropan XL and IR oxybutynin) and then entered into the Dose-Titration Period. A blocking procedure was employed at each center. The duration of this period varied depending on the individual needs of the patients. The study had three dose-titration endpoints. They were defined as follows:

- MED (minimum effective dose); this was the dose at which the patient had no episodes of urge urinary incontinence during the final 2 days of the 4-7 day dosing interval.

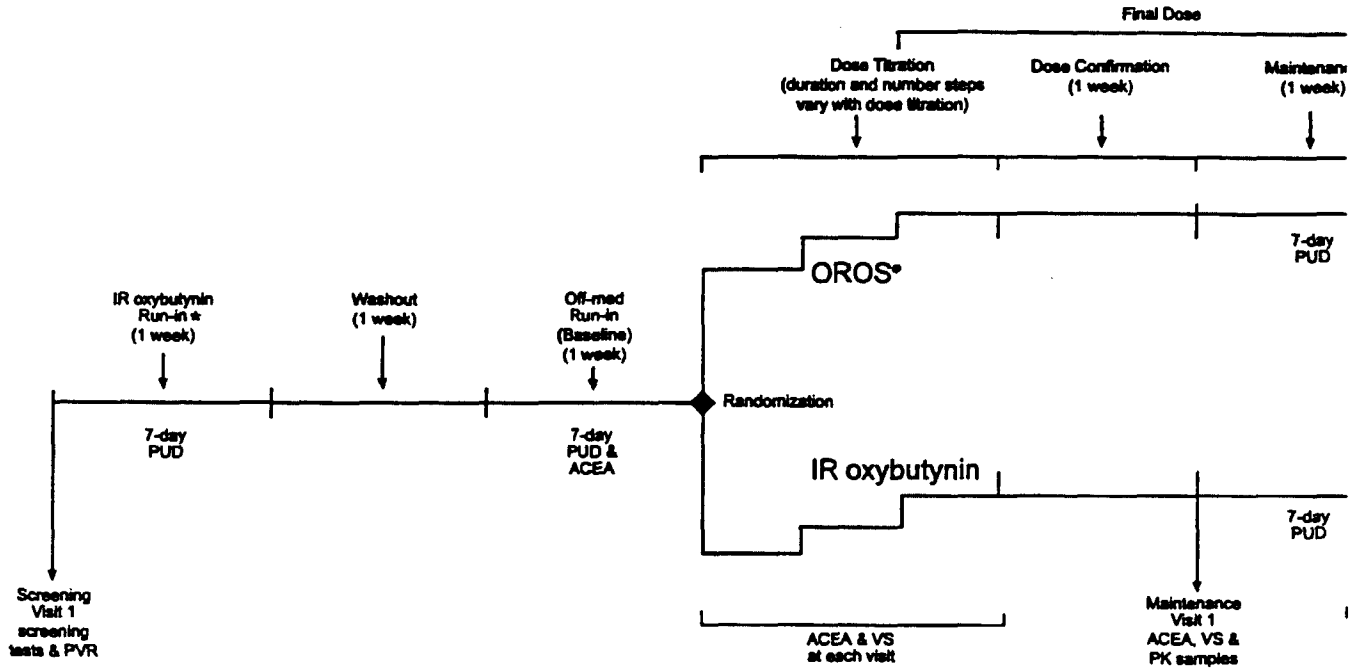
- MTD (maximum tolerated dose); this dose was 5 mg lower than the dose at which the patient reported intolerable anticholinergic effects.

- MAD (maximum allowable dose); this was either 20 mg/day of IR oxybutynin or 30 mg /day of Ditropan XL.

During the Dose-Titration Period, each patient was started at a dose of 5 mg of oxybutynin (IR or XL). The doses were increased in increments of 5 mg at intervals of 5

to 7 days. The dose increases were discontinued when either MED,MTD or MAD was reached. Once the endpoint was reached, the patient received an additional week of therapy at the defined dose level (Dose-Confirmation Period- one-week). After this, the patient entered a one week Maintenance Period in which the patient received study drug at the established MED, MTD or MAD for one week, (see Figure 3).

FIGURE 3* (OROS® is a previous name for Ditropan XL)



* Only patients taking Ditropan® before study enrollment entered this IR Oxybutynin Run-in Period (and completed a Patient Urinary Diary during this period). All other patients started the study in the Washout Period.

Abbreviations: ACEA=Anticholinergic Effects Assessment questionnaire; ECG=electrocardiogram; MAD=maximum allowable dose; MED=minimum effective dose; MTD=maximum tolerated dose; PK=pharmacokinetic; PSOR=Patient Satisfaction and Overall Rating questionnaire; PUD=Patient Urinary Diary; PVR=post-void residual; SAUSS=Subjective Assessment of Urinary Symptom Severity questionnaire; VS=orthostatic vital signs

***Sponsor's Figure-V.1.58/43**

Patients for this study were selected from the practices of the investigators and through advertising. Patients who would have otherwise qualified for the study but had not been previously treated with anticholinergic medication were allowed to enter a Therapeutic Responder Trial. During this period, the patients took 5 mg bid or tid of IR oxybutynin, if the investigator believed the patient was responsive to the treatment, the patient was

entered into the Washout Period and was involved in the study in the same manner as all other patients.

Patients were included in the study if they were male or female, 40 to 75 years of age with clinically defined urge or mixed incontinence in which stress incontinence was not the predominant factor. They were to have at least 6 episodes of urge incontinence during the Run-in period as recorded in the PUD. Patients were to be in good general health and females of childbearing potential agreed to use a medically acceptable form of birth control.

Patients were excluded from the study if they had a known treatable genitourinary condition that caused incontinence, had PSA more than 10 ng/ml or had a post-void residual more than 100 ml. Patients with a creatinine clearance of less than 50 ml/min., evidence of urinary tract infection, or a history of drug or alcohol abuse were excluded from the study. Patients who had been enrolled in study C-95-031-08 could be enrolled in this study.

Both Ditropan XL and IR oxybutynin were over-encapsulated with opaque, self-locking, gelatin capsules that were identical to one another and to the placebo capsules. The IR oxybutynin used in this study was Ditropan®. The patients took study medication (active and /or placebo) during four dosing periods (7-8 AM, 12-1 PM, 5-6 PM, and 10-11 PM). The recommended adult dose of Ditropan® is 5 mg two to four times per day. The maximum dose of Ditropan® administered in this study was 5 mg four times per day. The Ditropan XL preparation used in this study contained 5 mg of oxybutynin and was designed to deliver this amount over 24 hours. The maximum dose of Ditropan XL administered in this study was 6 capsules (30 mg) once in the AM.

Patients were given one or two blister packs containing active and placebo capsule with instructions about when to take the medication (See Figure4).

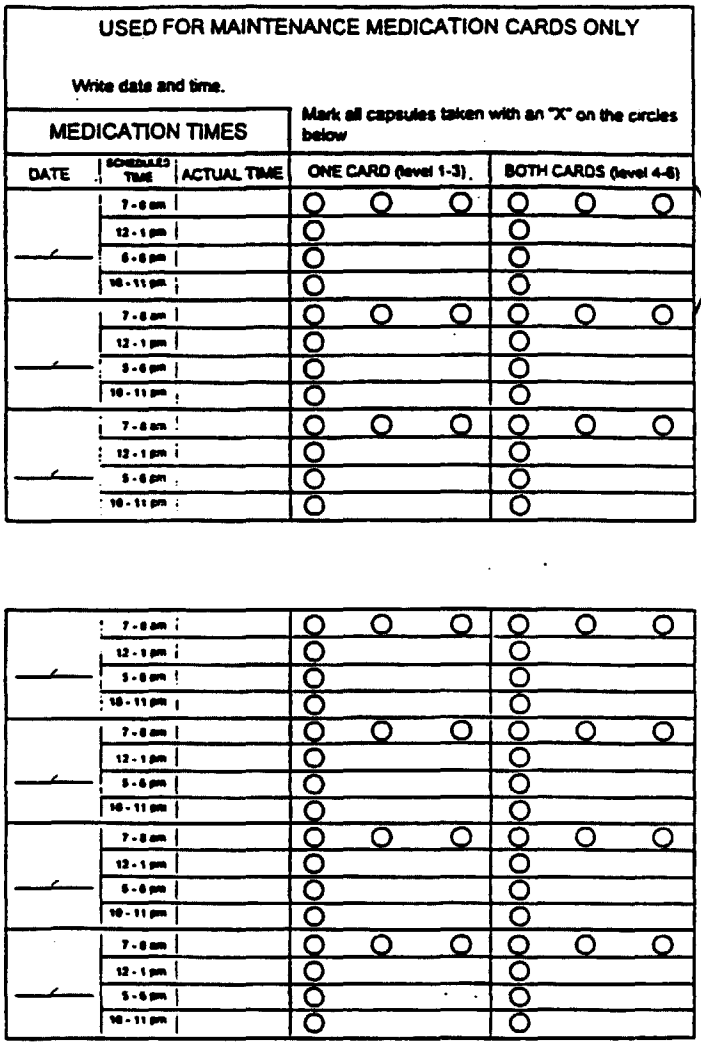


Figure 4*
Medication Cards and Dosing Schedule

*Sponsor's Figure-V.1.60/102

The amount of active and placebo medication administered depended on the dose level (See Table 6.)

TABLE 6*

OROS® (oxybutynin chloride) and IR Oxybutynin (Ditropan®) Dose Levels

Treatment Group	Dose Level	Total Oxybutynin Dose	No. Capsules/Day	
			Active Drug (5 mg/capsule)	Placebo
OROS®	1	5 mg	1	5
	2	10 mg	2	4
	3	15 mg	3	3
	4	20 mg	4	8
	5	25 mg	5	7
	6	30 mg (MAD)	6	6
IR oxybutynin	1	5 mg	1	5
	2	10 mg	2	4
	3	15 mg	3	3
	4	20 mg (MAD)	4	8
	5	20 mg (MAD)	4	8
	6	20 mg (MAD)	4	8

Abbreviation: MAD=maximum allowable dose

*Sponsor's Table-V.1.58/59 (OROS is the previous name of Ditropan XL)

Returned dose cards and the daily dosing record in the case report were assessed to determine patient compliance. If patients missed more than 2 doses during a period, they repeated the period at the same dose level. In addition, plasma concentrations of oxybutynin and desethyloxybutynin were measured at the beginning and end of the Maintenance Period.

The primary efficacy variable was the change in the mean number of U-UI episodes per week from baseline (Off-medication Run-in period just prior to randomization) to the end of the study as recorded in the Patient Urinary Diary (PUD). Patients recorded events in their PUD at the time of each incontinence episode (they were instructed to differentiate between stress and urge), and each voluntary void. Other variables that were analyzed from the PUD included: the proportion of patients achieving elimination of urge urinary

incontinence, the total number of urge incontinence episodes, the proportion of patients achieving total urinary incontinence and the total void frequency (the number of normal micturitions plus the number of incontinence episodes).
Other measurements were post-void residual (determined by bladder ultrasound within 15 minutes of voiding) and volume voided. These were determined at screening, end of the study and if the patient complained of severe urinary hesitancy.

Reviewer's comment: Comparison of volume voided and post-void residual from screening (on previous medication) to the end of the study will not provide meaningful information regarding the pharmacological action of the drug tested. Changes in volume voided from baseline to endpoint may provide supportive evidence.

Two tools were used to evaluate the patient's subjective assessment of treatment. They were the Subjective Assessment of Urinary Symptom Severity (SAUSS) and the Patient Satisfaction and Overall Rating (PSOR). The SUASS used a 5-point scale (0-4) for the patients to assess the severity of various symptoms. The PSOR asked the global question; "Are you satisfied with the treatment?" and further asked the patients to rate the positive or negative effect of their treatment on a 5 point scale where 1 was "very negative" and 5 was "very positive".

At each study visit, during the treatment and maintenance periods, patients completed the Anticholinergic Effects Assessment (ACEA) questionnaire. The ACEA consisted of three parts. Parts one and two listed approximately ten symptoms possibly related to anticholinergic effects (i.e. dry mouth, blurred vision, constipation etc.) that the patient graded on a four point ordinal scale (0=none, 1=mild, 2=moderate, and 3=severe). Part 1 of the ACEA asked the patient to rate these events during the last dosing interval (4-7 days), while Part 2 asked the patient to rate the symptoms several hours after taking the last dose of medication. When the patient reported an anticholinergic effect as grade 3, the study physician performed a directed examination to determine whether the patient was experiencing an acute anticholinergic toxicity. The physician then recorded this event in the ACEA. Any event reported in the ACEAS was reported as an adverse event. In addition other adverse events were recorded on the adverse event CRF at each visit and when volunteered by the patient in the routine fashion.

Pre and post-dose vital signs were obtained with the patient supine and standing in order to detect orthostasis. These measurements were obtained with each in-clinic dose and at the end of the study. Orthostatic hypotension (decrease in Systolic BP of $\geq$ 20 mm Hg or increase in HR of $\geq$10 per minute) was recorded as an adverse event. EKG, routine blood work, urinalysis and urine for drug screen were obtained at screening and at the end of the study. Blood collections were obtained at various times during the study to assess plasma concentration of R and S oxybutynin and desethyloxybutynin.

5.2 Study Population: There were 105 randomized patients enrolled in 13 study centers. There were 53 in the Ditropan XL group and 52 in the IR oxybutynin group.

Baseline Demographics were similar between the two groups. Most of the patients in both groups were female (≥90%). The mean age was 59.2 years in the Ditropan XL group, and 59.6 years in the IR oxybutynin group. Forty of 53 (75%) patients were Caucasian, seven (13%) were black and 5 (9%) were Hispanic in the Ditropan XL group. This compared to 47 of 52 (90%) patients that were Caucasian, two (4%) African American and 2 Hispanic in the IR oxybutynin group. In both groups, mean weight was about 79 kg with a mean height of 163 cm.

More than 40% of patients in both groups had a history of incontinence for more than 5 years. Approximately 90% of all patients had been incontinent for at least a year. Use of tissues or pads in the undergarments was the primary method of incontinence management, being used by over 70% of the patients.

Withdrawals and Compliance: Seven of 53 (13.2%) patients in the Ditropan XL group discontinued before the end of the study. One left for a personal reason (schedule conflict) and one because of misrepresentation of age. Five left because of adverse events: three urinary tract infections and two anticholinergic adverse events (blurred vision, dyspepsia).

Six of 52 (11.5%) patients in the IR oxybutynin group discontinued before the end of the study. Five left because of adverse events; one for personal reasons (illness in family). The adverse events included a subdural hematoma in one patient, urinary tract infection in three patients and an anticholinergic effect (dry mouth) in one.

Medication compliance was assessed from data in the diaries and medication counts during clinic visits. Median compliance rate was 98% for both treatment groups. No individual had a compliance rate less than 80%.

5.3 Protocol Violations and Deviations: Two patients in the Ditropan XL group did not meet the inclusion criteria of at least six urge incontinence episodes during the baseline period. Of these, one patient had no urge incontinence episodes and one had two episodes. Nine patients in the Ditropan XL group had a positive urine drug screen. However only one had a positive retest and that was for pseudoephedrine. Six patients in the IR oxybutynin group had a positive blood screen but all were negative on retest.

5.5 Efficacy analysis

5.51 Statistical Methods: For the evaluation of the primary and secondary efficacy parameters, the analysis included all randomized patients with available baseline and endpoint data. All patients that received study medication were included in the safety analysis. For patients with missing data, Patient Urinary Diary measurements were normalized to 7 days to derive baseline and endpoint values.

A two way ANOVA or ANCOVA model was prospectively specified for the analysis of the primary efficacy variable. The two-way ANOVA model included treatment, center and treatment, and center interactions that were used in the comparison of the baseline measurements. The two-way ANCOVA model analyzed treatment, center and treatment and center interaction, using the number of urge urinary incontinence episodes per week during the baseline period as the covariant. The least squares estimate of the mean difference between the two treatments, including the 95% confidence interval, are presented. Prospectively planned two-way ANOVA/ANCOVA models were used to analyze the secondary efficacy parameters. One–way ANOVA/ANCOVA models were used in the analysis of voided volume, post-void residual and total bladder volume.

The primary hypothesis to be tested was that the difference between the change in mean number of urge urinary incontinence episodes per week from baseline to end of study between the Ditropan XL and IR oxybutynin group would be zero. The revised objective of the study was to demonstrate the therapeutic equivalence of Ditropan XL and IR oxybutynin. It was agreed during a teleconference on 28 Feb. 1997 that Ditropan XL and IR oxybutynin would be considered therapeutically equivalent if the 95% confidence interval of the difference between Ditropan XL and IR in the reduction of mean urge urinary incontinence episodes did not exceed 4 episodes in favor of IR. Secondary parameters analyzed included the total incontinence episodes, mean voided volumes, post void residuals and quality of life measurements.

5.52 Efficacy Results: The number of patients on each dose at the end of the study is described in Table 7

Table 7
Number of patients by dose at end of Study C-95-049-05

	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Ditropan XL (n=46)	**10**	**8**	**12**	**4**	**6**	**6**
IR Oxybutynin (n=47)	**13**	**14**	**12**	**8**	**NA**	**NA**

Reviewer's comment: There is a fairly even distribution of the number of patients at their final titrated dose. This supports dose titration as an appropriate mode of administration for these drugs.

The unadjusted mean number of urge incontinence episodes improved significantly in both arms of the study (Table 8).

Table 8
Mean Number of Urge Urinary Incontinence Episodes per week (unadjusted)
Study C-95-049-05

	Ditropan XL (n=46)	IR Oxybutynin (N=47)
Baseline	27.4	23.4
Endpoint	4.8	3.1

Because the sponsor believed that the baseline number of urge incontinence episodes was a significant covariant, the ANOVA/ANCOVA model was used for the analysis (Table 9)

Table 9

Mean Number of Urge Urinary Incontinence Episodes per week *
(Adjusted with ANCOVA/ANOVA models)
Study C-95-049-05

	Ditropan XL (n=46)	IR Oxybutynin (n=47)
Baseline (adjusted)	25.4	25.4
Endpoint (adjusted)	4.6	3.7
Change from Baseline	-20.7	-21.6
Ditropan XL vs. IR Oxybutynin (95% C.I.)	.9 (-2,8, 4.6)	
P value	0.636	

***Sponsor's calculations**

The sponsor believes that the changes in mean number of weekly episodes of urge incontinence were similar between the Ditropan XL and IR oxybutynin group (-20.7 vs. -21.6). As previously mentioned, it was agreed that the two drugs would be considered to have comparable efficacy if the upper boundary of the 95% confidence interval for the between group difference (Ditropan XL minus IR oxybutynin) would not be greater than 4 urge urinary incontinence episodes.

Reviewer's comment: The upper boundary of the 95 % confidence interval for the between group difference exceeds 4 urge urinary incontinence episodes. Therefore, by the predetermined parameters, this study has not demonstrated that the drugs are equivalent. In addition, The Division's statistical reviewer recalculated the 95% confidence intervals using an intent-to-treat population rather than an evaluable population and found them to be –2.93 and 6.35.

The unadjusted mean weekly void frequency was similar at baseline in the two groups (Ditropan XL; 77.6, IR oxybutynin; 77.8). However, the end-of-study values were significantly different ($p<0.001$) between the groups. Ditropan XL was 73.6 and Ditropan was 60.7. Thus, the change from baseline to end-of-study in terms of mean weekly void frequency was -3.9 for Ditropan XL and –17.1 for IR oxybutynin ($p<0.001$).

Reviewer's comment: In this study, the IR oxybutynin performed significantly better than Ditropan XL in reducing urinary frequency, an important symptom in patients with overactive bladder.

The unadjusted baseline means for the volume per void were 134.2 cc for the Ditropan XL group and 161.2 cc for the IR oxybutynin group. Both drugs increased volume voided by the end-of study. The Ditropan XL patients increased by approximately 43 cc per void and the IR oxybutynin group increased 33 cc per void. The sponsor's analysis revealed no significant difference between the two groups in this parameter.

Reviewer's comment: It is unclear why the volume voided which often indicates anticholinergic effect, was similar between the two groups while weekly void frequency demonstrated a significant difference between the groups.

5.6 Safety Analysis

Deaths: There were no deaths reported in this study.

Serious Adverse Events: There was one serious adverse event in this study. An 74 year old man taking IR oxybutynin developed a subdural hematoma. On the tenth day of treatment he experienced dizziness, the medication was discontinued and the symptoms worsened with progressive neurologic symptoms. The condition was diagnosed, treated with evacuation and the patient recovered fully. The patient reported that he had fallen the week before the event (while he was on study drug) but does not remember if he hit his head.

Reviewer's comment: This event may have been indirectly related to the study drug if the patient fell because of dizziness caused by the medication.

All Adverse Events: There were 53 Ditropan XL patients and 52 IR oxybutynin patients in the safety population. The large majority of adverse events reported in this trial were consistent with anticholinergic effects. Eighty- six percent of the patients in the Ditropan XL group and 94 % of the patients in the IR oxybutynin group reported at least one event that was consistent with an anticholinergic effect. The proportion of patients that

experienced at least one moderate or severe anticholinergic adverse event was 24/53 (45.3%) in the Ditropan XL patients and 30/52 (58%) in the IR oxybutynin group. These difference was not statistically significant.

The most common anticholinergic effect reported was dry mouth (68% of the Ditropan XL patients, 87% of the IR oxybutynin patients, p=0.035). Moderate or severe dry mouth was reported by 13/53(24.5 %) of the Ditropan XL patients and 24/52(46.2%) of the IR oxybutynin patients (p=0.025).

Reviewer's comment: Because Ditropan XL and IR oxybutynin were not equivalent for efficacy in this study claims of superiority for dry mouth are inappropriate.

Somnolence (37.7%, 40.3%,), constipation (30.1%, 30.7%,), blurred vision (28.3%, 17.3%), dizziness (28.3%, 38.4%), impaired urination (24.5%, 28.8%), nervousness (24.5%, 23%) and nausea (18.8%, 17.3%) were the next most frequently reported adverse events in the Ditropan XL and IR oxybutynin groups respectively. The frequencies of these events reported by patients in the two groups were not significantly different from each other.

Reviewer's comment: The common adverse events experienced by patients were not different between the groups in a clinically meaningful way.

Laboratory and Clinical Safety Parameters: Clinical laboratory parameters were measured at baseline and end-of-study. There were no clinically significant overall trends or patterns in mean laboratory parameters from baseline to end-of-study, and there were no significant differences between the treatment groups. There were some individual abnormalities in laboratory parameters (decreased platelets, decreased Hgb. and increased eosinophil count) but upon review of the patients' synopses, there did not appear to be a pattern and relationship to study drug is uncertain.

Blood pressure and heart rate were measured at baseline and end of study. There were no differences in mean blood pressure and heart rate from baseline to end of study for any of the treatment groups, and there were no differences between the groups.

Electrocardiograms (ECG's) were obtained at baseline and end-of-study. No statistically significant differences were observed within or between treatment groups for PR, QRS, or QT intervals from baseline to the end of the study.

Thirteen of 53 (25%) of the patients treated with Ditropan XL and 8/52(15%) patients treated with IR oxybutynin had ECG changes at the end of the study. The most frequent finding was sinus bradycardia, which occurred in 10% of the Ditropan XL group and 2% of the IR oxybutynin group. Six percent of the Ditropan XL patients developed first degree AV block compared to 2 % in the IR oxybutynin group. Patients in the active treatment group also developed such abnormalities such as premature atrial contractions, atrial fibrillation, premature ventricular contractions and others.

Reviewer's comment: While probably not statistically significant, there appeared to be a slightly higher incidence of EKG changes in the Ditropan XL arm, especially sinus bradycardia. These EKG changes did not cause patients to develop clinical symptoms. In addition, the changes noted of sinus bradycardia and first degree heart block would not be expected as an anticholinergic side effect.

5.7 Evaluation of Safety and Efficacy: The sponsor's major conclusions from this study were:

1. Ditropan XL and IR oxybutynin were comparably efficacious in reducing the number of urge urinary incontinence episodes over the course of the study.

2. Ditropan XL and IR oxybutynin were both well tolerated and have comparable safety profiles except that fewer patients reported dry mouth in the Ditropan XL group compared to the IR oxybutynin group.

The reviewer believes that neither the statistical or clinical equivalence of Ditropan XL to IR oxybutynin was demonstrated in this study. Since there was no placebo arm in this study, the sponsor is unable to claim based on this study that Ditropan XL is efficacious in reducing incontinence episodes in patients with urge incontinence. In addition, IR oxybutynin performed significantly better than Ditropan XL in reducing urinary frequency, an important symptom in patients with overactive bladder.

Any statements regarding the superiority of Ditropan XL with respect to anticholinergic effects and more specifically dry mouth are not supported by this trial. There are several reasons why this trial does not support a claim for superior tolerability of Ditropan XL compared to IR oxybutynin. First, the trial did not demonstrate equivalence of efficacy between Ditropan XL and IR oxybutynin, and therefore comparative statements regarding adverse events cannot be fairly made. In addition, the trial design had several flaws: the study was not long enough, dry mouth was evaluated throughout the study rather then at the end, and the measurement of dry mouth was not well defined (see Reviewer's overall assessment of Safety and Efficacy).

The evidence reported by the sponsor does not adequately support the claim of superior tolerability. The sponsor states (V.1.58/117) that "Significantly fewer patients reported dry mouth with Ditropan XL compared to IR oxybutynin (68% vs. 87%, p=0.035). Also, significantly fewer patients reported moderate or severe dry mouth (25% vs.46%), p=0.025)." Even with an ideal trial design and demonstration of equivalent efficacy, the there is no evidence that these differences are clinically meaningful and perceptible by the patients. In addition, the proportion of patients that dropped out because of adverse events was essentially the same in both groups (9.4% Ditropan XL and 9.6% IR oxybutynin). The reviewer believes that if there was a clinically meaningful difference in tolerability between Ditropan XL and IR oxybutynin then there would be a difference in dropout rates between the two groups.

The reviewer concludes that this study has not demonstrated the efficacy of Ditropan XL for reducing urge incontinence episodes in patients with overactive bladder. The study does not support clinical equivalence of Ditropan XL to IR oxybutynin, nor does it demonstrate superior tolerability of Ditropan XL compared to IR oxybutynin. The study does, however, demonstrate that Ditropan XL is safe for its intended use.

6.0 Clinical Trial C-97-020-03

6.1 Design and Conduct of the Trial: This was a randomized, multicenter (20 US), double-dummy, double-blind, parallel-group, dose-titration trial designed to compare the difference in dry mouth in patients with urge urinary incontinence treated with Ditropan XL and IR oxybutynin. In addition, the study compared the efficacy, quality of life, patient satisfaction and safety of the two comparators. Two hundred and twenty-six male and female patients ages 40-75 years were enrolled in the study. The first patient was enrolled in the study on December 3, 1997 the last patient completed the study on May 18, 1998.

Three categories of patients were included in this trial:

- Patients who had been taking IR oxybutynin, Levsin®, or Pro-Banthine® or any other anticholinergic medications for the treatment of urge incontinence.

- Patients who had previously been on anti-cholinergic medications and discontinued because of reasons other than lack of efficacy.

- Patients who had never taken the above drugs for urge incontinence but who were demonstrated to be responsive to oxybutynin in a Therapeutic Responder Screening Trial (described on page 28)

The study was divided into three periods: Run-in, Dose-titration and Maintenance (see Figure 5). During the Run-in Period (2 weeks), the patients received no medication for urge incontinence. During week 1 of this period, all the medications for incontinence were discontinued. During the second week, a placebo (single-blind) was administered and baseline assessments were obtained. The baseline assessments included recording data in a Patient Urinary Diary (PUD), filling out a study medication card, and completing the Urge-Incontinence Impact Questionnaire (U-IIQ) during the clinic visit at the end of the week.

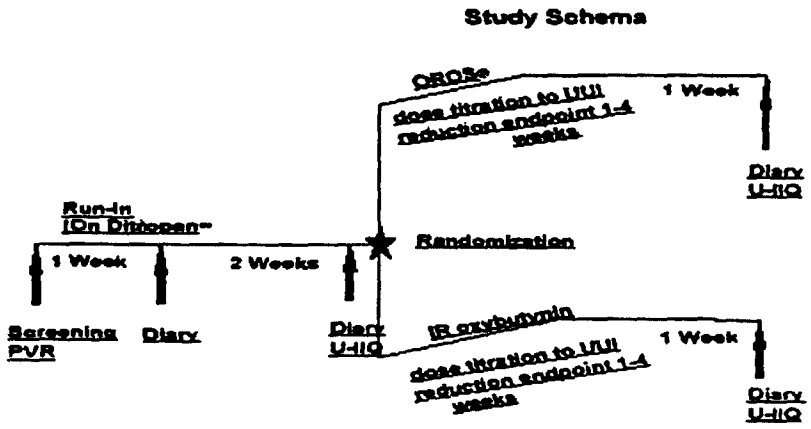


FIGURE 5 (FROM V.4.6/39)
OROS is a previous name for Ditropan XL

The **Dose-Titration Period** lasted up to four weeks. Patients made one to four clinic visits at intervals of approximately 7 days for dose titration after randomization. At the first visit during this period, the patients were randomized to the Ditropan XL or the IR oxybutynin arm. Patients began at the 5-mg/day dose in both arms. During the subsequent visits patient doses were escalated up to 20 mg/day using the following criteria:

- The patient achieved a target efficacy endpoint of no urge urinary incontinence episodes for the last three days of the period.

- The patient received the maximum allowable dose (20 mg/day).

- The patient reported a tolerable anticholinergic effect but believed that the symptom would be intolerable if the medication were increased. In this case, the patient entered the Maintenance Period at the present dose.

- The patient experienced an intolerable anticholinergic effect. In this case, the dose was decreased to the next lower dose or the patient was discontinued from the study at the discretion of the study physician.

Patients who achieved any of the above conditions entered into the **Maintenance Period** for one week. During this period, the patients completed a Patient Urinary Diary (PUD), filled out the medication card, and responded to the patient satisfaction questionnaire and U-IIQ during the clinic visit at the end of the week.

Ditropan XL, IR oxybutynin and placebo were overencapsulated (for blinding) and packaged on dosing cards. All capsules appeared identical. Dose escalation occurred as described in Table 10.

Daily Dose Composition and Times

Daily Dose Level	OROS® Oxybutynin	IR oxybutynin
5 mg	One 5-mg OROS Oxybutynin system at 0700*	One 5-mg IR oxybutynin tablet at 0700*
10 mg	Two 5-mg OROS Oxybutynin systems at 0700*	One 5-mg IR oxybutynin tablet and one placebo capsule at 0700*
	One placebo capsule at 1900*	One 5-mg IR oxybutynin tablet at 0700*
15 mg	Three 5-mg OROS Oxybutynin systems at 0700*	One 5-mg IR oxybutynin tablet and two placebo capsules at 0700*
	One placebo capsule at 1300*	One 5-mg IR oxybutynin tablet at 1300*
	One placebo capsule at 1900*	One 5-mg IR oxybutynin tablet at 1900*
20 mg	Four 5-mg OROS Oxybutynin systems at 0700*	One 5-mg IR oxybutynin tablet and three placebo capsules at 0700*
	One placebo capsule at 1200*	One 5-mg IR oxybutynin tablet at 1200*
	One placebo capsule at 1700*	One 5-mg IR oxybutynin tablet at 1700*
	One placebo capsule at 2200*	One 5-mg IR oxybutynin tablet at 2200*

* All times listed are approximate

TABLE 10 (FROM V.4.6/50)
OROS is a previous name for Ditropan XL

Randomization was stratified according to the number of urge urinary incontinence episodes per week during week 2 of the Run-in period. The strata were 7 to21 (mild) and more than 21 (severe) urinary incontinence.

Patients who would have otherwise qualified for the study but had not been previously treated with anticholinergic medication were allowed to enter a **Therapeutic Responder Trial.** During this period, the patient took 5 mg bid or tid of IR oxybutynin, if the investigator believed that the patient was responsive to the treatment, the patient was entered into the Run-in Period and was involved in the study in the same manner as all other patients.

Patients were included in the study if they were male or female, 40 to 75 years of age with clinically defined urge or mixed incontinence in which stress incontinence was not the predominant factor. They were to have had 7 to 42 episodes of urge incontinence at baseline as recorded in the PUD and could not have a total of 3 or more days with no urge urinary incontinence during that one week period. Patients were in good general health and females who had childbearing potential agreed to use a medically acceptable form of birth control.

Patients were excluded from the study if they had a known treatable genitourinary condition that caused incontinence, or had a post-void residual more than 100 ml. Patients with evidence of urinary tract infection, or a history of drug or alcohol abuse were excluded from the study. Patients who had been enrolled in study C-95-031-08, C-95-049 and C-96-070 (open label extension) could be enrolled in this study.
Reviewer's comment: About 20% of the patients in this study had been previously enrolled in other studies.

Patient compliance was monitored by examining returned used and unused dose cards and examining the daily dosing record in the case report forms. During the dose titration period, patients that missed three or more doses during the last 72 hours of the interval were continued on the same dose of medication for three more days and their appointment was rescheduled.

The co-primary parameter measured in this trial was the patient's report of moderate or severe dry mouth during the treatment period recorded on the adverse event form.

Reviewer's comment: During meetings on March 11 and December 17, 1997, The Division suggested that the measurement of dry mouth during the Maintenance Period would be more appropriate for the comparative purposes of this study. This is because anticholinergic effects of other medications are known to disappear or lessen over time (see Reviewer's Overall Assessment of Safety and Efficacy). The sponsor does present "final dose " dry mouth data in the submission.

The investigator actively solicited adverse events at each visit or when otherwise volunteered by the patients. Patients who reported dry mouth were asked to assess severity according to the following criteria:

- Mild dry mouth: "Dry mouth relieved with increase in fluid or hard candy"

- Moderate dry mouth: "Dry mouth and throat but no difficulty swallowing solid foods (e.g., you can eat a cracker without water)."

- Severe dry mouth: "Very dry mouth and throat, difficulty swallowing solid foods without water (e.g. you could not eat a cracker without water)."

Reviewer's Comment: A visual analogue scale is the preferred method of measuring dry mouth in the context of a comparative trial (see Reviewer's Overall Assessment of Safety and Efficacy).

The co-primary variable in this trial was the reduction in weekly episode of urge urinary incontinence episodes from baseline to end of study as measured in the Patient Urinary Diary (PUD). Patients recorded events in their PUD at the time of each incontinence episode (they were instructed to differentiate between stress and urge), and each voluntary void. Other variables that were analyzed from the PUD included reduction in weekly urinary incontinence (total urinary incontinence) episodes from baseline to end of study, and reduction of weekly voids from baseline to end of study.

Reviewer's comment: PVR was only measured at screening and volume voided was not measured at all. Volume voided measured at baseline and endpoint can be an important supportive measure.

The Urge-Incontinence Impact Questionnaire (U-IIQ) was completed at Baseline and Endpoint. This is a 32-item self-report instrument that has been validated in various populations. The instrument included assessments of the impact of urinary incontinence on seven domains. These included: "Activities, travel, physical activities, feelings, relationships, sexual functioning and night bladder control. Summary domain and total scores were used in the analysis of the data from this instrument.

A single general Patient Satisfaction Question was completed at baseline and end of study. The question was administered before the U-IIQ described above. The question was: "In the past 7 days, how satisfied were you with the treatment for your urinary leakage and/or bladder problems. The patients scored this on a 7 point visual analogue scale with 1 being "not satisfied at all" and 7 being "completely satisfied". A mean score was derived and reported.

Vital signs were obtained after the patient had been sitting for five minutes. These measurements were obtained with each in-clinic dose and at the end of the study. EKG, routine blood work, urinalysis and urine for drug screen were obtained at screening and at the end of the study. When the patient reported an anticholinergic effect as severe or intolerable, the study physician performed a directed examination to determine whether the patient was experiencing an acute anticholinergic toxicity. The physician then recorded this event in the Physician's Anticholinergic Effects Assessment (P-ACEA). Any event reported in the P-ACEA was reported as an adverse event. In addition other adverse events were recorded on the adverse event CRF at each visit and when volunteered by the patient in the routine fashion.

6.2 Study Population: There were 226 randomized patients enrolled in 19 centers (one center did not enroll any patients). There were 111 in the Ditropan XL and 115 in the IR oxybutynin group.

Baseline Demographics were similar between the two groups. Most of the patients in both groups were female. Ninety-eight of 111(88%) of the Ditropan XL patients were female and 104 of 115 (90%) IR oxybutynin patients were female. The mean age was 58.8 years in the Ditropan XL group and 59.6 years in the IR oxybutynin group. Ninety-six of 111 (87%) of patients were Caucasian, six (5%) were African American and six (5%) were Hispanic in the Ditropan XL group. This compared to 104 of 115 (90%) patients that were Caucasian, 4 (4%) African American and 4(4%) Hispanic in the IR oxybutynin group. In both groups, mean weight was about 79 kg with a mean height of 164 cm.

More than 45% of patients in both groups had incontinence for more than 5 years. Approximately 95% of the patients had been incontinent for at least a year. Use of tissues or pads in the undergarments was the primary method of incontinence management and was utilized by over 70% of the patients in both groups.

Withdrawals and Compliance: Seven of 111 (6%) of the patients in the Ditropan XL group discontinued before the end of the study: three patients left because of adverse events; one (1%) each because of lack of efficacy, lost to follow-up, and personal reasons. One patient was discontinued because of a protocol violation (<6 urge urinary episodes per week at baseline).

Ten of 115 (9%) of patients in the IR oxybutynin group discontinued the study: Seven left because of adverse events; two left because of lack of efficacy; one left for personal reasons.

Medication compliance was assessed from data in the diaries and medication counts during clinic visits. Median compliance rate was 98% for the Ditropan XL group and 96% for the IR oxybutynin group. Mean compliance rate was greater than 95% for each dose (5-20 mg/day).

Reviewer's comment: Compliance and withdrawals are supportive measures in assessing the tolerability of a drug. These data suggest comparative tolerability between XL and IR.

6.3 Protocol violations and deviations: The protocol violations included such categories as the patients experienced a severe anticholinergic AE but it was not recorded in the P-ACEA (13), patients that were included in the Therapeutic Responder Trial who had previously taken anticholinergic medication (3), a patient was placed in incorrect incontinence strata (1), patients took an extra dose of medication on one occasion (3), a patient placed on maintenance prematurely (1) and patients not having all the end of study procedures (8).

Reviewer's comment: The reviewer does not believe that these deviations substantially affected the outcome of the study.

6.5 Data Analysis (dry mouth and efficacy analyses)

6.51 Statistical Methods: The first of the two **co-primary hypotheses** to be tested in this study was that the difference between Ditropan XL and IR oxybutynin is equal to zero in the proportion of patients who reported moderate to severe dry mouth throughout study treatment. This and all statistical tests for efficacy and safety were performed at the $\alpha <$ 0.05 significance level. The statistical tests used for analysis of baseline data were at the 0.10 significance level. All tests were two-sided.

The **second co-primary hypothesis** was that the reduction in weekly urge urinary incontinence episodes from baseline to end of study was different. For this parameter a 95% confidence interval was constructed. If the lower bound of the 95% confidence interval for urge urinary incontinence was not less than 25% of the mean reduction of weekly urge incontinence episodes in the IR oxybutynin group, the Ditropan XL was considered therapeutically equivalent to IR oxybutynin. A two-way ANOVA model or ANOCVA model was used to analyze the efficacy parameters. The ANOVA model included the treatment factors and the ANCOVA included baseline number on incontinence episodes per week as a covariant. The least squares estimate of the mean difference between the two treatments and the 95% confidence interval were presented.

Reviewer's comment: This analysis assumes a mean change of 16 incontinence episodes per week from baseline to endpoint. Therefore the lower bound of the confidence interval should not exceed 4. It is unclear, however, whether a difference of 4 incontinence episodes per week is perceivable by patients.

Other important parameters that were analyzed by the sponsor were: reduction in the number of weekly voids from baseline to the end of the study, patient's satisfaction with the study treatment at the end of the maintenance period, and analysis of the Urge-Incontinence Impact Questionnaire (U-IIQ).

The sponsor offered a post-hoc survival analysis of several of the important parameters to support the claim that Ditropan XL is equally effective as IR oxybutynin yet causes less dry mouth and therefor more "satisfaction" and improved quality of life. In essence, the sponsor believes that the original analysis, that compares the drugs at their final titrated dose, is not appropriate and the analysis should be performed comparing the drugs at the same dosage level.
Reviewers comment:

1. **The titration approach used in this trial is similar to what is done in actual practice. The drugs should be compared at the final dose reached after titration in order to compare both efficacy and tolerability.**

2. **The survival analysis approach done by the sponsor was done post-hoc. This should have been suggested and discussed with The Division prospectively in order to support a superiority claim.**

6.52 Efficacy Results (Includes Dry Mouth Analysis): The proportion of patients reporting moderate or severe dry mouth at any time during randomization (the original proposed analysis) revealed that the was no statistically significant difference between Ditropan XL an IR oxybutynin (see Table 11).

TABLE 11*
The Proportion of Patients Reporting Moderate or Severe Dry Mouth at Any Time During the Dose Titration and Maintenance Portion of the Study.

	Ditropan XL (n=111)	IR oxybutynin (n=115)	Difference (XL-IR)	p-value
Moderate or Severe Dry Mouth	19 (17.1%)	30 (26.1%)	-9%	0.102
95% C.I.	(10.1%, 24.1%)	(18.1%, 34.1%)	(-20%, 1.8%)	

***Sponsor's calculation**
Reviewer's comment: Even if the difference were statistically significant, it is unclear whether this would be clinically meaningful since it is comparing dry mouth as patients are being titrated and not after they have reached their ultimate effective dose.

The reduction in weekly urge incontinence episodes from baseline to end of study was similar between Ditropan XL and IR oxybutynin (see Table 12).

TABLE 12*
Mean Number of Weekly Urge Incontinence Episodes (Adjusted)

	Ditropan XL (n=103)	IR oxybutynin (n=105)	Difference (XL-IR)	P value
Baseline	18.2	19.2	-1.1	0.59
End of Study	3.3	4.6	-1.3	0.210
Change	-14.9	-14.7	-0.2	0.924
95 % C.I.			(-4.1, 3.7)	

Sponsor's calculation
Reviewer's comment: The efficacy of Ditropan XL compared to IR oxybutynin regarding reduction of incontinence episodes appears to be similar.

Other analyses performed by the sponsor revealed that the proportion of continent patients reporting moderate or severe dry mouth at the end of the study were not statistically different between the Ditropan XL and IR oxybutynin groups. When results from all patients were analyzed at the end of study, there was no difference between the two groups in any of the eight domains (including the overall index) of the U-IIQ (urgency incontinence impact questionnaire). In addition, comparison of the responses to

the Global Question (In the past 7 days how satisfied were you with your treatment for your ...bladder problem? 1= not satisfied, 7 =completely satisfied) were essentially identical. The score was 3.91 for the Ditropan XL group and 3.85 in the IR oxybutynin group (p=1.000).

Reviewer's comment: The above data support the hypothesis that Ditropan XL and IR oxybutynin are similarly tolerated at equally efficacious doses as titrated in this trial.

6.6 Safety Analysis:

Deaths: There were no deaths reported in this study.

Serious Adverse Events: There was one serious adverse event in this study. The patient, a 75-year-old man, was on IR oxybutynin and developed a small bowel obstruction. He was being treated with 10 mg/ day and developed abdominal pain, nausea, and vomiting after six days on the medication. The patient had a history of left colon resection for diverticulitis. The study medication was discontinued on the day of admission and he was treated with nasogastric decompression and a rectal tube improving in 24 hours. The patient recovered and was discharged four days after admission.

Reviewer's comment: The anticholinergic effects of oxybutynin could have contributed to this event.

All Adverse Events: There were 111 Ditropan XL and 115 IR oxybutynin patients in the safety population. The large majority of adverse events reported in this trial were consistent with anticholinergic effects. Fifty-seven percent of the patients in the Ditropan XL group and 70% of the patients in the IR oxybutynin group reported at least one event that was consistent with an anticholinergic effect. The most common anticholinergic effect reported was dry mouth (48% of the Ditropan XL patients, 59% of the IR oxybutynin patients). Seventeen percent of the Ditropan XL patients and 26% of the IR oxybutynin patients reported moderate or severe dry mouth. The differences in dry mouth were not statistically significant.

Reviewer's comment: The proportion of patients that experienced at least one anticholinergic adverse event was 70% in the Ditropan XL patients and 57% in the IR oxybutynin group. This difference was not statistically significant, but this clearly gives little support to the sponsor's claim of enhanced tolerance of XL regarding dry mouth.

Headache (9.0%, 8.7%), Constipation (9.9%, 7.0%), nausea (4.5%, 5.2%) and upper respiratory infection (7.2%, 7.0%) were the next most frequently reported adverse events in the Ditropan XL and IR oxybutynin groups respectively. The frequencies of these events reported by patients in the two groups were not significantly different from each other.

Reviewer's comment: The common adverse events experienced by patients were not different between the groups in a clinically meaningful way.

Laboratory and Clinical Safety Parameters: Clinical laboratory parameters were measured at baseline and end-of-study. There were no clinically significant overall trends or patterns in mean laboratory parameters from baseline to end-of-study. There were some individual abnormalities in these parameters but upon review of the patients' synopses, they did not appear significant.

Blood pressure and heart rate were measured at baseline and end of study. There were no differences in mean blood pressure and heart rate from baseline to end of study for any of the treatment groups. There were no differences between the groups.

Electrocardiograms (EKG's) were obtained at baseline and end-of-study.
Three patients (3%) in the Ditropan XL group and one patient (1%) in the IR oxybutynin group developed EKG changes from baseline to end of study. There were two cases of sinus bradycardia in the Ditropan XL group and one in the IR oxybutynin group.

Reviewer's comment: In this study, there again appeared to be a slightly higher incidence of EKG changes in the Ditropan XL arm, especially sinus bradycardia.

6.7 Evaluation of Safety and Efficacy: The sponsor's major conclusions from this study were:

3. Ditropan XL and IR oxybutynin were comparably efficacious in reducing the number of urge urinary incontinence episodes over the course of the study.

4. Ditropan XL and IR oxybutynin are both well tolerated and have comparable safety profiles except that fewer patients reported dry mouth in the Ditropan XL group compared to the IR oxybutynin group.

The reviewer believes that the sponsor has demonstrated similar efficacy between IR oxybutynin and Ditropan XL in reducing episodes of urge urinary incontinence in patients with overactive bladder in this trial.

Any statements regarding the superiority of Ditropan XL with respect to anticholinergic effects and more specifically dry mouth are not supported by this trial. There are two reasons why this trial does not support a claim for superior tolerability of Ditropan XL compared to IR oxybutynin. The first is that the trial was inadequately designed to demonstrate this superiority. The study was not long enough and the sponsor's primary analysis was a measurement of dry mouth throughout the study rather than at the end (see Reviewer's overall assessment of Safety and Efficacy).

The second reason why the trial does not support the claim of superior tolerability of Ditropan XL compared to IR oxybutynin is that the evidence reported by the sponsor does

not support the claim. The sponsor's own primary analysis fails to demonstrate a statistically significant difference between Ditropan XL and IR oxybutynin in the proportion of patients reporting moderate or severe dry mouth during the Dose Titration or Maintenance periods. The reviewing statistician calculated the proportion of patients that reported moderate or severe mouth at the end of the study and found that there was no statistical difference between the Ditropan XL and IR oxybutynin groups (see Table 13)

Table 13
The Division's Calculation of the Proportion of Patient's with Moderate of Severe Dry Mouth at the End of the Study.

	XL	IR	XL-IR	P value
N(dry mouth)	12	22		
N (total)	111	115		
proportion	.108	.191		
			-0.083	
				0.118

Other analyses performed by the sponsor revealed that the proportion of continent patients reporting moderate or severe dry mouth at the end of the study were not statistically different between the Ditropan XL and IR oxybutynin groups. When results from all patients were analyzed at the end of study, there was no difference between the two groups in any of the eight domains (including the overall index) of the U-IIQ (urgency incontinence impact questionnaire). In addition, comparison of the responses to the Global Question were essentially identical. The score was 3.91 for the Ditropan XL group and 3.85 in the IR oxybutynin group (p=1.000).

The reviewer concludes that, in this study, the sponsor has demonstrated that the efficacy of Ditropan XL for reducing urge incontinence episodes in patients with overactive bladder is comparable to IR oxybutynin. The sponsor has not demonstrated superior tolerability of Ditropan XL compared to IR oxybutynin. The sponsor has demonstrated that Ditropan XL is safe for its intended use.

7.0 Overall Assessment of Safety and Efficacy
Efficacy: The sponsor submitted three controlled trials in support of the efficacy of Ditropan XL for the treatment of overactive bladder. They were:

4. **C-95-031**, a double-blind, placebo and active-controlled (IR oxybutynin), forced dose-escalation trial involving 82 women.

5. **C-95-049-05**, a double-blind, active-controlled (IR oxybutynin), dose-titration study involving 105 men and women with overactive bladder.

6. **C-97-020-03**, a double-blind, active–controlled (IR oxybutynin) trial, dose-titration trial involving 226 men and women.

It is important to note, that in all three of these trials, the patient populations were "enriched" because many of the patients were individuals known to be responsive to anticholinergic medications. Two of the studies (C-95-049-05, C-97-020-03), utilized a "Therapeutic Responder Trial" as an enrollment criteria. In this segment of the trials, patients were eliminated who did not "respond " to oxybutynin. For example, in trial C-97-020-03, of the 180 patients that were "screened" in the Therapeutic Responder Trial, 62 were "failures" and 118 proceeded to randomization. The reviewer believes that this form of enrichment does not invalidate the comparative efficacy results demonstrated in these trials. However, the absolute and relative changes in urinary incontinence episodes, continence rates and many other parameters reported in these trials may not reflect values observed in the "unenriched" incontinence population visiting a physician's office.

In all three studies, the primary efficacy parameter was the mean number of weekly episodes of urge urinary incontinence. In trial C-95-031, the sponsor demonstrated that Ditropan XL was statistically better than placebo in reducing the mean number of weekly urge incontinence episodes from baseline to the end of the study. In trial C-95-049-05, the efficacy of Ditropan XL and IR oxybutynin tended toward comparability. However, they were not statistically equivalent. In trial C-97-020-03, Ditropan XL and IR oxybutynin were statistically equivalent. **The evidence presented in the submission support the hypothesis that Ditropan XL is efficacious for the treatment of overactive bladder.**

Safety and Dry Mouth Issues: This safety review was based on the updated Integrated Summary of Safety submitted to the Agency August 6, 1998 as well as the clinical data in the December 17, 1997 New Drug Application submission. Eight studies were conducted with Ditropan XL in a total of 670 patients and 151 healthy subjects. Study C-95-031 had a forced dose escalation design to 15mg/day. Studies C-95-049 and C-97-020 incorporated individual dose adjustment designs, reflecting current clinical practice, escalating dosage to a maximum of 30mg/day. Study C-96-070, an uncontrolled, open-label trial encompassed 256 patients treated with Ditropan XL for up to 23 weeks. Efficacy and tolerability were adjusted to a maximum dose of 30mg/day. Four clinical pharmacology studies in 151 healthy subjects treated for 1-4 days were also evaluated.

No deaths and 2 serious adverse events occurred in the controlled studies, both in patients treated with immediate release oxybutynin. One patient suffered a fall and subdural hematoma. The other was diagnosed with a small bowel obstruction 6 days after starting medication. It resolved with nonoperative management. . There were 18 patients in the uncontrolled study with serious adverse events. The one death in the uncontrolled Ditropan XL study involved a woman with a history of cardiac disease who developed a myocardial infarction, thought by the investigator to be unrelated to the study medication. Two events, both related to gastroesophageal reflux, were considered by the investigator to be possibly related to the study drug. One patient experienced serious exacerbation of

known gastroesophageal reflux. The other patient, a 73 year old women with diverticulitis and osteoporosis, developed epigastric pain, nausea, and vomiting, ultimately diagnosed as gastritis, gastroesophageal reflux, and gastric dysmotility. It is unclear whether Fosamax may have also contributed to the symptoms. The remaining 15 serious adverse events were classified by the investigator as unrelated to the study drug. All original case report forms were examined by this reviewer who concurs that aside from the two patients who experienced gastroesophageal reflux, the serious adverse events were not plausibly related to the use of Ditropan XL.

Adverse events culminating in discontinuation of study medication occurred in similar percentages of Ditropan XL and immediate release oxybutynin treated patients (6.2% vs 7%). Dry mouth (1.1%), nausea (1.8%) dyspepsia (0.9%), and somnolence (0.9%) accounted for the majority of Ditropan XL dropouts.

In the controlled studies, 79.8% of patients taking Ditropan XL experienced at least one adverse event vs 86.3% in the uncontrolled study. Reviewing all studies, at least one anticholinergic adverse event was reported by 68.9% of patients taking Ditropan XL. Dry mouth (59%), constipation (12.6%), somnolence (11.5%), nausea (8.4%), blurred vision (7.3%), dyspepsia (6.4%), asthenia (6.4%), and dizziness (5.9%) predominated. At titration levels of 5-30mg/day, impaired urination occurred in 4.4% of patients, insomnia in 4.6%, and confusion in 2.4%. Studies in which dosing tried to balance tolerability with efficacy, (C-95-049 and C-97-020), resulted in dry mouth in 51.8% of Ditropan XL patients. This was classified as moderate or severe in 19.5% of patients. Similar percentages (58.6% and 23%) were identified in the uncontrolled study of similar design. Overall, moderate or severe anticholinergic events were reported in 31.5% of patients taking Ditropan XL.

The reviewer concludes that there are no major safety concerns with Ditropan XL. Immediate release oxybutynin chloride has been widely used for over 20 years, and the safety profile is well established. Ditropan XL employs a capsule design shown to be safe and reliable when used to deliver a variety of other pharmaceutical agents. An osmotically active bilayer core surrounded by a semipermeable membrane perforated by laser-drilled holes releases suspended drug at a controlled rate. The reviewed does not reveal any additional safety concerns over and above those well known and reported with immediate release oxybutynin chloride. A review of blood chemistries, hematology data, and electrocardiogram data shows no significant changes in these parameters that would constitute a safety concern.

The sponsor attempts to prove with data from the three controlled trials that Ditropan XL has increased tolerability in terms of dry mouth compared to IR oxybutynin at equally efficacious doses. The sponsor fails in this attempt primarily because the data from the controlled trials does not demonstrate that there is a statistical or clinically meaningful difference in incidence of dry mouth between Ditropan XL and IR oxybutynin. In addition, there are significant design flaws within the trials that inhibit the ability of the trial to accurately reflect the differential incidence of dry mouth.

The "maintenance period" for a trial that accurately assesses the incidence of dry mouth should be longer than the average of one week in the controlled trials submitted in this NDA. A period of 6-12 weeks would be more appropriate. Oxybutynin is a chronically administered drug and thus a longer "maintenance period" would more appropriately reflect clinical practice, and allow for more accurate assessment of withdrawals and "quality of life" issues. In addition, anticholinergic adverse events are known to lessen in severity or even disappear in some patients over time[6]. Because of a possible change over time in anticholinergic events, it would be optimal to measure dry mouth at the end of an appropriately long (6-12 week) "maintenance period".

A validated visual analogue scale would be a more accurate method to measure a subjective end point such as dry mouth rather than the more vague and ill-defined approaches used in the submitted trials. In addition, the sponsor should propose and support the difference in dry mouth that would be clinically meaningful. The clinically meaningful difference for this type of endpoint should be determined in a trial separate from the efficacy trial.

The reviewer concludes that Ditropan XL is safe and effective for treatment of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence. Increased tolerability of Ditropan XL compared to immediate release oxybutynin with respect to dry mouth was not demonstrated.

8.0 Recommendation of Regulatory Action: The reviewer recommends that Ditropan XL be approved for the indication described above.
9.0 Labeling Revisions: At the of the completion of this review, labeling revisions were still being negotiated

/S/

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CC/
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