

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-897

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA: 20-897

Compound: Ditropan® XL (Oxybutynin Hydrochloride), 5 and 10 mg extended release tablets

Sponsor: ALZA

Type of Submission: Original NDA and amendments

Date of Submission: December 17, 1997
April 30, 1998
September 30, 1998
October 27, 1998

Reviewer: Sam H. Haidar, R.Ph., Ph.D.

I. Synopsis:

NDA 20-897 for Ditropan® XL (Oxybutynin Hydrochloride), 5 and 10 mg extended release tablets was submitted on December 17, 1997, by Alza Corporation. Ditropan® XL extended release tablet is a once-daily, controlled release, oral formulation indicated for the treatment of urge urinary incontinence, urgency, and frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia.

In support of NDA 20-897, the sponsor has submitted the following definitive pharmacokinetic and bioavailability studies:

1. C-96-010 evaluated the pharmacokinetics and safety of oxybutynin following administration of Ditropan® XL 3 x 5 mg every day for 4 days compared with 5 mg Ditropan® (immediate release) administered every 8 hours for 4 days.
2. C-96-068 evaluated the dose proportionality of Ditropan® XL.
3. C-96-074 evaluated the effect of food on the pharmacokinetics and bioavailability of Ditropan® XL relative to Ditropan®.
4. C-97-015 evaluated the bioequivalence of clinical and commercial batches of Ditropan® XL

II. Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-897, submitted on December 17, 1997 and its amendments, dated April 30, September 30, and October 27, 1998. Based on the review of the pharmacokinetic and biopharmaceutics studies submitted, OCPB/DPEII finds this NDA acceptable. However, the reviewer has the following comments to be conveyed to the sponsor:

1. The proposed *in vitro* release specifications for oxybutynin are not acceptable, the recommended specifications are as follows:

Time Interval (hours)	Specification (% of label claim)
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2. Labeling comments as listed in Section VIII, page 18.

/S/

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by Ameeta Parekh, Ph.D., Team Leader AP
FT signed by Ameeta Parekh, Ph.D., Team Leader -

/S/

12/15/98

cc:
NDA 20-897
HFD-870 (M. Chen, A. Parekh, S. Haidar)
HFD-850 (L. Lesko)
HFD-340 (C.T. Viswanathan)
HFD-580 (R. Olmstead, D. Shames)
CDR (Barbara Murphy For Drug)

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III. Background:

Oxybutynin is a tertiary amine which has direct antispasmodic effect on the smooth muscle in addition to anticholinergic effects. It is currently prescribed for the treatment of urge urinary incontinence, urgency and frequency arising from overactivity of the bladder's detrusor muscle. The antimuscarinic activity of oxybutynin is considered to be the drug's primary mechanism of action in the treatment of urinary incontinence. Oxybutynin has been marketed in the United States for over 20 years as an immediate-release tablet (Ditropan[®]). The starting dose is usually 5 mg twice daily, and maybe titrated to 20 mg daily. Following oral administration, oxybutynin undergoes extensive first pass effect by cytochrome P450 3A4. The major metabolite (N-desethyl oxybutynin) has pharmacological activity similar to the parent drug. The structures of oxybutynin and its major metabolite are shown in Figure 1 (a) and (b), respectively.

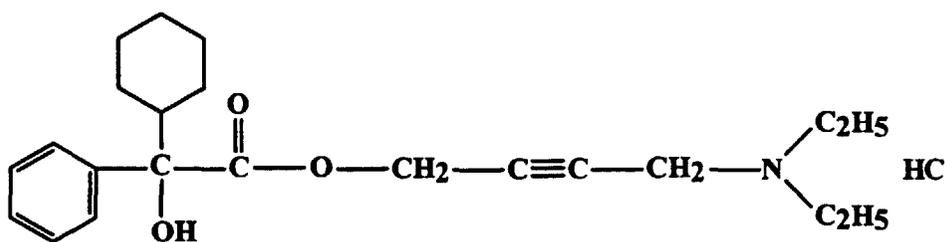


Figure 1(a). Oxybutynin Hydrochloride

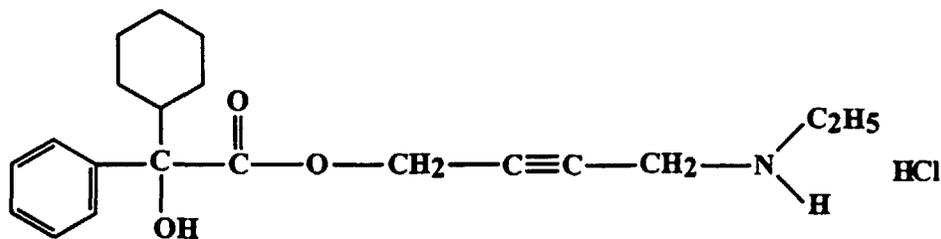


Figure 1(b). N-desethyloxybutynin

Ditropan[®] XL (oxybutynin chloride) was developed using Alza Corporation's controlled-release technology for drug delivery via the gastrointestinal (GI) tract. The delivery system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. In an aqueous environment, such as the GI tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and push the layer to expand. This expansion pushes the drug out through a precision laser-drilled orifice. The semipermeable membrane controls the rate at which water permeates into the tablet core, which in turn controls the rate of drug delivery. Other marketed drugs with similar delivery systems include Procardia[®] XL (nifedipine) and Glucotrol[®] XL (glipizide) extended release tablets.

IV. Formulation

The formulation components of Ditropan® XL are listed in Table I. An illustration of the release system is shown in Figure 2.

Table I. Components of Ditropan® XL (5 mg and 10 mg) tablets.

Component	Ref.	Role	5 mg	10 mg
Drug Layer: 92 mg				
Oxybutynin chloride (unmilled)	USP			
Sodium chloride (powder)	USP			
Polyethylene oxide,	NF			
Hydroxypropyl methylcellulose,	USP			
Magnesium stearate	NF			
Butylated hydroxytoluene	FCC			
Iron oxide,				
	NF			
Push Layer: 92 mg				
Polyethylene oxide,	NF			
Sodium chloride (powder)	USP			
Hydroxypropyl methylcellulose,	USP			
Iron Oxide,				
Magnesium stearate	NF			
Butylated hydroxytoluene				
Membrane: 15-20 mg^{1,2}				
Cellulose acetate	NF			
Polyethylene glycol	NF			
Color Overcoat:				

¹ Membrane weight measured in-process.

² Membrane weight may vary to achieve target release rate.

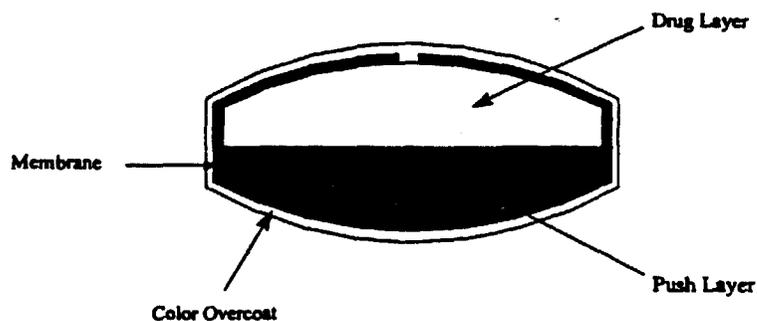


Figure 2. Illustration of Ditropan® XL tablet.

Reviewer Comment

The clinically tested formulation and the "to be marketed" formulation were linked by a bioequivalence study (Study No. C-97-015).

V. *In Vitro* Drug Dissolution

The *in vitro* release methodology and the proposed specifications for Ditropan® XL tablets are presented in Table II. Tables III and IV provide *in vitro* release data for the clinically tested batches.

Table II. Proposed Drug Release Method and Release Rate Specifications.

Apparatus Type	USP Type VII Apparatus.	
Media	Artificial Gastric Fluid, without enzyme (37.0 ±0.5°C)	
Volume	50 mL	
Frequency/Amplitude	30 cycles/minute cm	
Sampling Times	hours.	
Proposed Specifications*	Time Intervals (hours)	Specification (% of label claim)
Cumulative amount released per tablet over a time interval		

Table III. *In vitro* release profiles of clinically tested batches (5 mg system).

Batch Number	Clinical Study No.	Percent label claim released [mean (±SD)] n = 12			
		Time (hours)	0-4	0-10	0-24
790894	C94010 C95031		8.6 (2.6)	46 (6.4)	91 (2.8)
838796	C95049 C96074		10 (0.6)	42 (3.4)	89 (5.4)
888896	C96070		12 (1.4)	46 (4.0)	81 (4.6)
MV9620003	C96070		13 (1.2)	42 (3.0)	82 (4.0)
MV9720193	C96068		12 (2.0)	51 (4.8)	89 (2.6)

Table IV. *In vitro* release profiles of clinically tested batches (10 mg system).

Batch Number	Clinical Study No.	Percent label claim released [mean (\pm SD)]			
		Time (hours)	0-4	0-10	0-24
			n = 12		
889696	C96070 C96074 C97015		12 (0.9)	47 (3.2)	86 (1.9)
889796	C96070		9.2 (0.9)	41 (2.4)	83 (1.4)
MV9720201	C96068		12 (1.6)	50 (4.2)	91 (1.3)
MV9720209	C97015		12 (1.4)	47 (3.9)	88 (1.2)

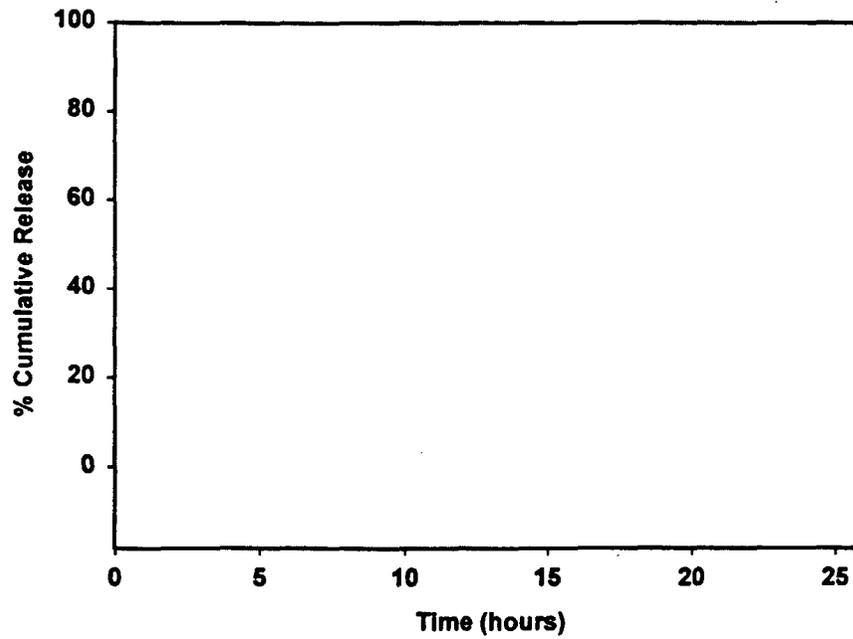


Figure 3. *In vitro* release profile for oxybutynin (Batch No. 790894).

Reviewer Comments

1. The proposed *in vitro* dissolution methods are acceptable.
2. The proposed *in vitro* release specifications for oxybutynin are not acceptable, the recommended specifications are as follows:

**Time Interval
(hours)**

**Specification
(% of label claim)**

VI. Analytical Methodology

Reviewer Comment

1. The analytical methods and validation for the estimation of oxybutynin and desethyloxybutynin concentrations in plasma are acceptable.

VII. Clinical Pharmacology and Biopharmaceutics Studies

Table VII. Summary of clinical studies.

Study Type	Study No.	Study Design	Dosage Form	Study Population
Single and multiple dose	C-94-010	Open label, randomized, two-way crossover,	Ditropan XL and immediate release (IR) oxybutynin	Healthy (H) females (n=13)
Dose proportionality	C-96-068	Open-label, single dose, randomized 3-treatment, 3-period, 2-sequence crossover	Ditropan XL 5 mg, Ditropan XL 10 mg.	H males (n=18); H females (n=18)
Bioequivalence	C-97-015	Randomized, single dose, 2-treatment, 2-period crossover	Ditropan XL 10 mg (clinical) Ditropan XL 10 mg (to be marketed formulation)	H males (n=32); H females (n=22)
Food Effect	C-96-074	Randomized, open-label, 4-treatment, 4-period, 6-sequence crossover	Ditropan XL 5 mg, Ditropan XL 10 mg.	H males (n=21); H females (n=27)

1. Pharmacokinetics:

a) *Single and Multiple Dose*

The single and repeat dose pharmacokinetics of Ditropan XL were evaluated in Studies C-94-010 and C-96-074. Following administration, plasma oxybutynin and desethyl-

oxybutynin concentrations increased over 4-6 hours, then maintained steady state levels for up to 24 hours. Steady state is achieved by Day 3 of dosing. In contrast, when immediate release oxybutynin was administered, plasma levels of oxybutynin and desethyloxybutynin increased rapidly, achieving C_{max} within an hour, then declined rapidly in a biexponential manner. Table VIII summarizes the first day and steady state pharmacokinetic parameters for oxybutynin and desethyloxybutynin following the daily administration of 3 x 5 mg Ditropan XL (single dose). Figures 4 and 5 illustrate mean (SD) plasma profiles for oxybutynin and desethyloxybutynin, respectively.

Table VIII. Summary of pharmacokinetic parameters (mean \pm SD), for oxybutynin and desethyloxybutynin following a single dose and daily (x 4 days) administration of Ditropan XL (3 x 5 mg).

Parameter	Single Dose (Study C-94-010)	Single Dose (Study C-96-074)	Multiple Dose (Study C-94-010)
<i>Oxybutynin</i>			
C_{max} (ng/mL)	4.2 (1.6)	4.2 (1.4)	6.7 (2.1)
T_{max} (hr)	13.2 (6.9)	12.7 (5.4)	5.2 (3.7)
$AUC_{0-\infty}$ (ng.hr/mL)	117 (49.7)	91.2 (33.4)	109 (42.5)
$T_{1/2}$ (hr)	-----	13.2 (1.4)	13.8 (2.9)
<i>Desethyloxybutynin</i>			
C_{max} (ng/mL)	13.9 (6.6)	22.1 (8.9)	22.5 (13.6)
T_{max} (hr)	15.0 (5.8)	10.3 (3.8)	7.1 (4.2)
$AUC_{0-\infty}$ (ng.hr/mL)	310 (184)	463 (142)	304 (145)
$T_{1/2}$ (hr)	-----	10.5 (5.5)	8.3 (2.5)

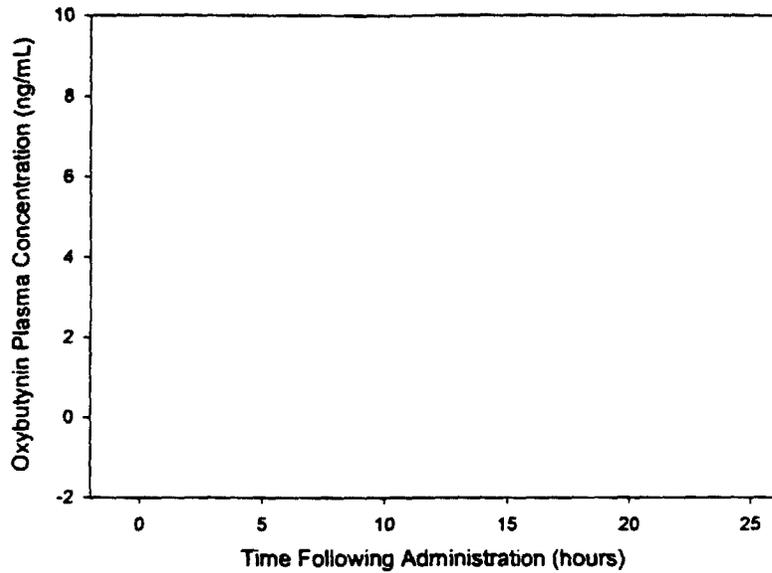


Figure 4. Mean (SD) oxybutynin plasma concentrations following administration of a single dose (*Day 1*) and daily dosing of 3 x 5 mg Ditropan XL for four days (*Day 4*).

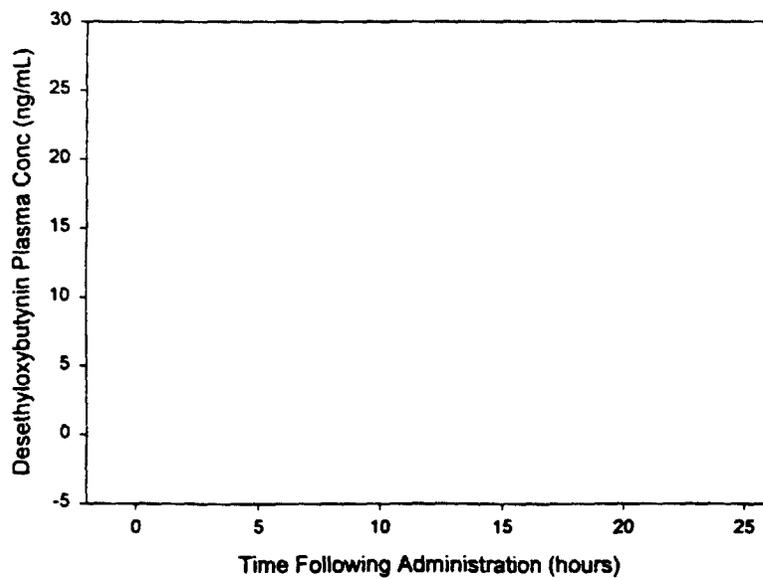


Figure 5. Mean (SD) desethyloxybutynin plasma concentrations following administration of a single dose (*Day 1*) and daily dosing of 3 x 5 mg Ditropan XL for four days (*Day 4*).

Reviewer Comments:

1. Steady state plasma levels were achieved for oxybutynin by Day 3 of dosing.
2. Multiple dosing of Ditropan XL resulted in no accumulation of oxybutynin or desethyloxybutynin.

2. Bioavailability/Bioequivalence:

a) *Absolute/Relative Bioavailability*

The absolute bioavailability of oxybutynin was not determined for this NDA; however, Douchamps *et al.*, 1988, report an absolute bioavailability of about 6% for oxybutynin IR. The bioavailability of oxybutynin and desethyloxybutynin following Ditropan XL administration relative to that following immediate release Ditropan was evaluated in Studies C-94-010 and C-96-074. The results are listed in Table IX. Figures 6 and 7 show plasma concentration profiles for oxybutynin and desethyloxybutynin, respectively, following TID (three times daily) dosing with immediate release (IR) oxybutynin, or a single dose (3 x 5 mg) of Ditropan XL.

Table IX. Mean (SD) 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)

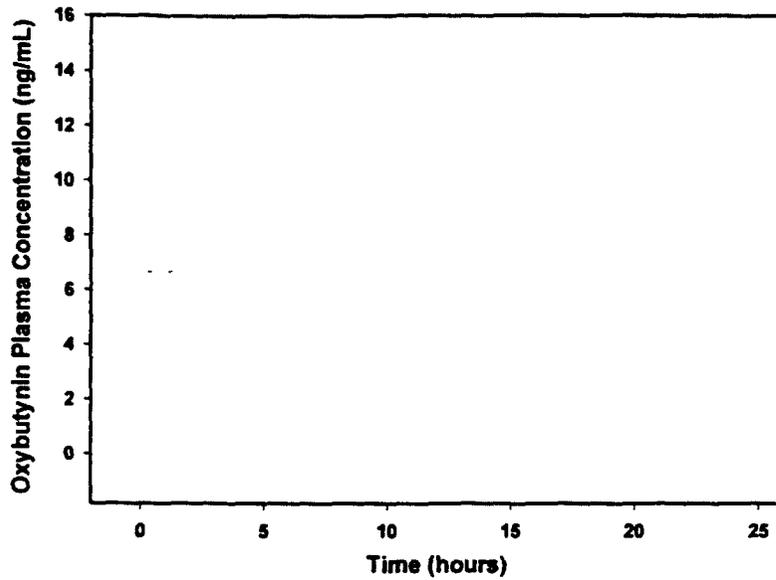


Figure 6. Mean (SD) oxybutynin plasma concentrations following TID dosing of 5 mg immediate release (IR) oxybutynin and a single dose administration of 3 x 5 mg Ditropan XL.

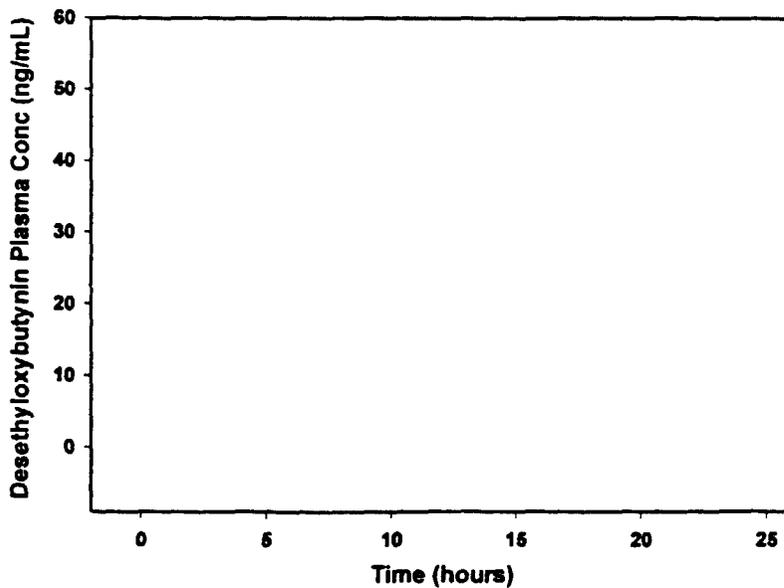


Figure 7. Mean (SD) desethyloxybutynin plasma concentrations following TID dosing of 5 mg immediate release (IR) oxybutynin and a single dose administration of 3 x 5 mg Ditropan XL.

Reviewer Comments:

1. The oxybutynin bioavailability of Ditropan XL appears to be greater (153%) than that of immediate release oxybutynin. The bioavailability of desethyloxybutynin is lower (69%) with Ditropan XL. R/S ratio of oxybutynin and desethyloxybutynin were not significantly different between Ditropan XL and oxybutynin IR.
2. According to the sponsor, the greater bioavailability of oxybutynin and lower bioavailability of desethyloxybutynin seen with Ditropan XL may be the result of decreased metabolism by the GI flora. Relative to immediate release oxybutynin, Ditropan XL releases more drug lower in the GI tract, where metabolizing bacteria are fewer in number, therefore, resulting in decreased GI first pass effect.

b) Bioequivalence

The bioequivalence of clinical and commercial scale batches was evaluated in Study C-97-015. Fifty-four healthy volunteers (32 men and 22 women) were enrolled and 52 completed the study. The results (for the 10 mg tablet) are summarized in Table X and Table XI for oxybutynin and desethyloxybutynin, respectively. A bioequivalence comparison was also performed for the 5 mg dose. Two 5 mg tablets of a clinical batch were bioequivalent to a 10 mg tablet of the commercial batch, with regard to C_{max} and AUC of both isomers of oxybutynin, and the S-isomer of desethyloxybutynin. The C_{max} of the R-isomer of desethyloxybutynin fell outside the range required for bioequivalence (78.1-93.1); however, this difference was not deemed clinically significant by the medical officer, Dr. Dan Shames (HFD-580). Commercial and clinical batches differed in size (clinical batch < 10% of commercial batch), and sodium chloride content, which functions as an osmotic agent.

Table X. Mean Oxybutynin Pharmacokinetic Parameters Following Ditropan XL (oxybutynin chloride) treatments.

Parameters (units)	<u>R-oxybutynin</u>		<u>S-oxybutynin</u>	
	Clinical (n=52)	Commercial (n=52)	Clinical (n=52)	Commercial (n=52)
C_{max} (ng/mL)	0.78	0.66	1.5	1.29
$t_{1/2}$ (hr)	18.5	19.6	17.9	15.8
AUC _t (ng·hr/mL)	14.9	14.7	29	28.5
AUC _{inf} (ng·hr/mL)	17.5	17.8	32.9	31.4
90% Confidence Intervals*				
AUC	93.9-111		90.8-106	
C_{max}	83.0-101		83.0-103	

* 90% confidence interval of the reference mean (commercial/clinical supplies) for the log-transformed parameters

Table XI. Mean desethyloxybutynin pharmacokinetic parameters following Ditropan XL (oxybutynin chloride) treatments.

Parameters (units)	R-desethyloxybutynin		S-desethyloxybutynin	
	Clinical (n=52)	Commercial (n=52)	Clinical (n=52)	Commercial (n=52)
C_{max} (ng/mL)	6.33	5.82	4.0	3.66
$t_{1/2}$ (hr)	16.3	14.4	15.7	13.8
AUC_t (ng-hr/mL)	120	122	87.2	87.8
AUC_{inf} (ng-hr/mL)	134	133	89.0	98.3
90% Confidence Intervals*				
AUC	96.1-108		93.2-106	
C_{max}	87.7-102		88.7-104	

* 90% confidence interval of the reference mean (commercial/clinical supplies) for the log-transformed parameters

Reviewer Comments:

1. The commercial scale batches were bioequivalent to the clinically tested batches with regard to oxybutynin as well as desethyloxybutynin plasma levels.

c) Dose Proportionality

Dose proportionality of Ditropan XL over the dose range of 10 to 20 mg was evaluated in Study C-96-068. Thirty five subjects were administered a single dose of 1 x 10 mg, 2 x 5 mg, and 4 x 5 mg tablets of Ditropan XL in a randomized, crossover design. Bioequivalence of the three treatments was evaluated for oxybutynin as well as for desethyloxybutynin. The results demonstrated dose-normalized bioequivalence for the three treatments. The 90% confidence interval for log transformed AUC and C_{max} between all three treatments were within 80-125%, for oxybutynin and desethyl-oxybutynin.

Reviewer Comments:

1. Dose proportionality of Ditropan XL was demonstrated for doses 10 to 20 mg.

3. Food Effect

The effect of food on the pharmacokinetics of oxybutynin and desethyloxybutynin was evaluated in Study C-96-074. Forty-three subjects were given 10 mg Ditropan XL after fasting, and following a standard high-fat breakfast. Mean (SD) pharmacokinetic parameters for oxybutynin and desethyloxybutynin are summarized in Table XII and Table XIII, respectively.

Table XII. Mean (SD) oxybutynin pharmacokinetic parameters following Ditropan XL (10 mg) administration under fed and fasted states.

Parameters (units)	R-oxybutynin		S-oxybutynin	
	Fed (n=43)	Fasted (n=43)	Fed (n=43)	Fasted (n=43)
C _{max} (ng/mL)	0.83 (0.49)	0.97 (0.59)	1.48 (0.88)	1.81 (0.96)
t _{1/2} (hr)	12.7 (5.1)	13.2 (6.2)	12.4 (4.9)	12.4 (6.1)
AUC _t (ng·hr/mL)	16.5 (9.5)	18.4 (10.3)	29.3 (15.1)	34.2 (16.9)
AUC _{inf} (ng·hr/mL)	18.8 (10.6)	21.3 (12.2)	33.4 (17.5)	39.5 (21.2)
*Ratio (%) AUC	89.0		85.0	
*Ratio (%) C _{max}	87.8		80.4	

* Ratio of Fed/Fasted, log-transformed pk parameters

Table XIII. Mean (SD) desethyloxybutynin pharmacokinetic parameters following Ditropan XL (10 mg) administration under fed and fasted states.

Parameters (units)	R-desethyloxybutynin		S-desethyloxybutynin	
	Fed (n=43)	Fasted (n=43)	Fed (n=43)	Fasted (n=43)
C _{max} (ng/mL)	10.9 (4.1)	9.36 (3.73)	5.59 (2.15)	5.36 (2.20)
t _{1/2} (hr)	9.2 (4.81)	10.0 (5.52)	10.1 (5.1)	11.1 (5.8)
AUC _t (ng·hr/mL)	181.9 (79.2)	176.1 (74.6)	103.8 (47.5)	107.0 (49.9)
AUC _{inf} (ng·hr/mL)	192.7 (85.9)	190.5 (85.3)	112.2 (50.9)	118.5 (57.5)
*Ratio (%) AUC	101.7		95.4	
*Ratio (%) C _{max}	116.6		103.8	

* Ratio of Fed/Fasted, log-transformed pk parameters

4. Special Populations

Race and Gender

Using pooled data from different studies, it does not appear that gender or race has a significant effect on the pharmacokinetics of oxybutynin.

Age

Steady state, pre-dose oxybutynin plasma concentrations from two controlled clinical studies were dose normalized and pooled. The data set was divided into two sets: plasma levels from subjects 34-65 years of age (n = 46); and plasma levels from subjects 65-78 years of age (n = 34). Comparison of two data sets indicated no significant differences between the two age groups (n = 34).

5. Metabolism

The metabolism of oxybutynin is well defined and no new studies were needed.

6. Drug Interactions

No studies were done with Ditropan XL to evaluate drug interactions.

7. PK/PD Relationships and Population Pharmacokinetics

Population PK-PD modeling using NONMEM was performed in two clinical studies: Study C-95-031 and C-95-049. The sponsor did a dose/response as well as dose/side-effect analysis. Models which provided good fit of the data were then used to generate dose/response and dose/side-effect profiles for Ditropan XL and IR oxybutynin. The sponsor concluded that based on PK-PD modeling and simulations, Ditropan XL had a greater therapeutic index. Dr. Raymond Miller, acting Director of Pharmacometrics (HFD-850), was consulted by the reviewer to evaluate the PK-PD modeling submitted by the sponsor. Dr. Miller stated that the modeling and simulations appear to be appropriate; however, proper interpretation of the results requires the submission of additional data, including intermediate models used during the modeling process.

Reviewer Comments:

1. The PK-PD simulations show that at equal efficacy, 5 mg Ditropan XL had a lower probability of dry mouth when compared with 7 mg IR oxybutynin (46% vs. 63%, respectively). The clinical significance of the results could not be determined based on the simulations alone.
2. According to the medical officer, Dr. Dan Shames (HFD-580), and the statistician, Sonia Castillo (HFD-715), the results of the clinical studies do not support a

superiority claim (Ditropan XL over Ditropan IR). Therefore, although the PK-PD simulations show a trend for decreased side effects (dry mouth) for Ditropan XL relative to Ditropan IR, results of the clinical studies failed to confirm these results in a clinically significant manner.

VIII. Labeling

The sponsor's proposed labeling is included in Attachment A.

Reviewer comment:

The recommended labeling changes are listed below:

Attachment A

NDA 20-897

Proposed Labeling

Redacted 13

pages of trade

secret and/or

confidential

commercial

information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-897

ADMINISTRATIVE DOCUMENTS

NDA 20-897
Ditropan® XL (oxybutinin chloride)
Alza Corporation

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

Group Leader Memorandum

DEC 14 1998

NDA: 20-897

Drug : Ditropan-XL™
Oxybutynin Chloride as an extended release formulation

Sponsor: Alza Corporation

Dose Formulation: 5 and 10 mg capsules which allow controlled-release delivery

Doses Proposed: 5 mg daily up to a maximum of 30 mg daily

Proposed Indication: Treatment of patients with overactive bladder with the symptoms of urinary frequency, urgency, and urge incontinence

NDA Submitted: 12/17/97
NDA Received: 12/19/97
Review Completed: 12/14/97

I. Background

Two anticholinergic medications are currently available for the treatment of urinary incontinence: oxybutynin (Ditropan®) and tolterodine (Detrol®). Both are produced as immediate release formulations to be taken several times per day.

Oxybutynin (Ditropan®) has been available as an immediate release formulation since its approval in 1975. It is available as both a tablet and a syrup formulation, with the suggested usual dose being 5 mg taken two to three times a day, and the maximum suggested dose being 5 mg taken four times a day (20 mg maximum daily dose). Alza Corporation now submits their NDA for an extended release formulation of oxybutynin that can be taken once daily. The sponsor proposed approval of both a 5 and 10 mg capsule, to be taken once daily at a dose not to exceed 30 mg/day.

Anticholinergic side effects are common problems with these medications. In particular, dry mouth can be very bothersome, and causes patients to either accept a lower dose with less than optimal efficacy or to discontinue therapy altogether. In theory, if dry mouth is associated with high peak serum levels of oxybutynin, the extended-release formulation might be superior to the immediate release formulation. Another theory is that the extended-release formulation has different metabolites (based on its more distal colonic absorption), and that these differences result in less dry mouth. The sponsor examined dry mouth in the pivotal trials, and proposes that the results support the claim of less dry mouth for the extended release formulation.

II. Clinical Studies

Three controlled clinical trials were performed to support this NDA and are summarized. For the purposes of this review, the following abbreviations will be used:

Ditropan® immediate release formulation: "IR"
Ditropan XL™ extended release formulation: "XL"
Placebo: "P"

Trial C-95-031

This trial was a multicenter, randomized, double-blind, double-dummy, fixed dose-escalation, controlled trial which compared five treatment arms. Of the five arms, three were relevant to the NDA and included

IR (n=32), XL (n=34) and P (n=16). Patients were enrolled and began taking 5 mg of study drug, increasing to a maximum dose of 15 mg by week 6. The primary endpoint analyzed was the difference in mean number of urinary incontinence episodes per week from baseline to week 6.

Results revealed that, for the ITT population, mean urinary incontinence episodes went from 25.3 to 5.1 (IR), from 15.9 to 1.5 (XL), and from 20.9 to 10.3 (P). Due to baseline imbalances in incontinence, adjustments to this analysis were made. Comparisons between active drugs and placebo revealed that the improvements in incontinence episodes noted with IR and XL were significantly better than those achieved with placebo. Thus, this trial demonstrated that both IR and XL formulations of Ditropan were superior to placebo.

Tolerability of IR and XL formulations was comparable. There were no serious adverse events or deaths in this trial. Dry mouth occurred in 100% of IR subjects compared to 85% of XL subjects; moderate to severe dry mouth occurred in 53% of each active arm. Other common anticholinergic side effects included somnolence (18.8% IR vs 38.2% XL), constipation (31.3% IR vs 29.4% XL), blurred vision (25.1% IR vs 23.5% XL) and nausea (25.0% IR vs 20.6% XL).

Trial C-95-049-05

This was a randomized, multicenter, double-blind, double-dummy, parallel-group, dose-titration study comparing XL (n=53) to IR (n=52). Enrolled subjects were randomized to start at a dose of 5 mg of IR or XL, and were increased in increments of 5 mg every 5-7 days. Doses were increased until patients reached either a minimum effective dose, a maximum tolerated dose, or a maximum allowed dose (which was 20 mg/day for IR and 30 mg/day for XL). Once the final dose was reached, patients were continued at one week of therapy at this "optimal" dosage level, and if dose appeared correct, they then entered a one week maintenance period at the established dose. The primary endpoint was the difference in mean urinary incontinence episodes per week from baseline to the end of the study. Once these differences were calculated, the difference between treatment arms would be determined. If the 95% CI around the changes noted between treatment arms revealed that they were within 4 episodes of one another, then equivalence would be established.

An evaluable patient analysis revealed that baseline incontinence episodes decreased from 27.4 to 4.8 in the XL arm (n=46), compared to a decrease from 23.4 to 3.1 in the IR arm (n=47). Thus, the absolute difference between the changes (-22.6 in XL arm versus -20.3 in the IR arm) was 2.3, in favor of the XL arm. Again, however, due to baseline imbalances in the primary endpoint, an adjustment was made. The adjusted change from baseline was -20.7 in the XL arm versus -21.6 in the IR arm, resulting in an absolute between arm difference of 0.9, in favor of the IR arm. The 95% CI around this difference was calculated by the sponsor (-2.8, 4.6), and was recalculated by the FDA statistician (-2.93, 6.35). Neither of these analyses supported a determination of equivalence since the 95% CI in each case exceeded 4.

Tolerability of the IR and XL formulations was similar. The medical officer review examined side effects by dose, and concluded that the proposed dosage range of XL up to 30 mg once daily was acceptable. Anticholinergic side effects were common, overall, in both treatment arms. Dry mouth was reported in 87% of the IR patients versus 68% of the XL patients (p=0.035); moderate or severe dry mouth was reported by 46.2% of IR versus 24.5% of XL patients (p=0.025). There are several important concerns, however, which preclude the conclusion that the XL formulation is superior. These include:

- Equivalence was not established between the XL and IR formulations.
- Patients were not allowed to reach a true steady state level of therapeutic efficacy. One week of therapy on the maintenance dose is too short to reflect patient tolerability on a medication which is taken chronically. A maintenance period of 8 to 12 weeks is suggested to confirm that patients have truly reached an optimal dose, and to assure that optimal doses of each formulation are being compared for their respective tolerability.
- Information from patients taking antihistamines has shown that tolerance to dry mouth can develop over time; this again supports the need for a longer duration on maintenance therapy.

- Study drug discontinuations were similar between arms. A longer trial may reveal that more patients on IR discontinued due to dry mouth. Such a result, even if just a trend, would clearly be supportive of a claim of superiority regarding dry mouth. The lack of such a finding in this trial is concerning.
- Other anticholinergic side effects were very balanced between treatment arms. If the XL formulation were truly superior regarding dry mouth, one would expect at least a trend favoring XL regarding other anticholinergic side effects.
- Dry mouth was not a prespecified primary endpoint of this study, and adjustments were not made for multiple comparisons.

Trial C-97-020-03

This was a randomized, multicenter, double-dummy, double-blind, parallel-group, dose-titration trial designed to compare the difference in dry mouth in patients with urge urinary incontinence. The study enrolled 226 patients and randomized them to XL (n=111) or IR (n=115). Patients were enrolled and underwent dose titration to the most effective dose. Dose titration lasted up to four weeks. The maximum dose allowed of XL or IR was 20 mg/day. Following dose titration, patients were maintained on their dosage for two additional weeks.

There were two co-primary endpoints in this trial: one was the patient's report of moderate or severe dry mouth during the study period, and the second was the reduction in weekly episodes of urinary incontinence.

Results from this study showed that for the ITT population, the mean number of weekly urge incontinence episodes went from 18.6 to 2.9 (XL arm) versus 19.8 to 4.4 (IR arm). Thus, the XL treatment arm changed by -15.6 episodes, which was quite comparable to the -15.4 change noted in the IR arm. An analysis that adjusted for baseline imbalances confirmed that the XL formulation met the prespecified definition of equivalence to the IR formulation. It is notable that the larger sample size of this trial minimized the baseline treatment imbalances noted in the previous studies; a sample size of at least 200 subjects should probably be suggested for these trials.

The proportion of XL patients reporting moderate to severe dry mouth during the study was 17.1% in the XL arm compared to 26.1% in the IR arm. The difference between treatment arms was therefore -9%, with a 95% CI of (-20.0%, 1.8%). Thus, superiority of the XL formulation over the IR formulation was not demonstrated. In addition to the previously mentioned concerns about the claim for dry mouth, there were several additional concerns raised by this study design:

- Baseline symptoms of dry mouth were not assessed, and the sample size for this trial was relatively small. Since baseline differences can occur (even in randomized trial designs, as was noted with the incontinence episodes), this is a significant concern.
- The scale used by the sponsor to determine "moderate to severe" dry mouth has not been validated. A visual analogue scale is recommended. Meaningful differences between treatment arms using such a scale should be specified prospectively, and should be supported with data or literature references.
- Some of the same patients were enrolled in the three pivotal trials. To support a claim of dry mouth, the pivotal trials should clearly enroll different populations of patients. Otherwise the "confirmatory" role of the second trial is rendered moot.
- Patients in the XL arm were not allowed to progress in dosing beyond 20 mg/day, yet the sponsor intends to obtain an indication for doses up to 30 mg/day. Since the pharmacokinetics of the XL and IR formulations do not correlate dose for dose, the appropriate study design for a dry mouth claim of superiority should clearly allow each patient to reach the maximum recommended dose, if this is tolerable.

III. Conclusions

The sponsor has demonstrated superiority of the XL formulation over placebo, and in one of their comparative trials they demonstrated equivalence to the IR formulation for the management of incontinence. This is sufficient for the approval of the XL formulation for the desired indication.

Claims of superiority regarding dry mouth for the XL formulation are not supported by the data in this application. Numerous deficiencies (see bulleted points in this review, as well as the primary medical officer review) need to be addressed in future clinical trials in order to adequately support a superiority claim regarding dry mouth. I concur with the medical officer that Ditropan XL be approved.

/S/

Marianne Mann, M.D., Deputy Director

cc:

Rarick/Director/HFD-580

Shames/MO/HFD-580

Olmstead/PM/HFD-580

NDA 20-897/Division File

NDA 20-897
Ditropan® XL (oxybutinin chloride)
Alza Corporation

Safety Update Review

Included in Medical Officer review dated December 14, 1998.

NDA 20-897
Ditropan® XL (oxybutinin chloride)
Alza Corporation

Microbiology Review

Oral dose, no microbiology review is required.

NDA 20-897
Ditropan® XL (oxybutinin chloride)
Alza Corporation

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 20-897
Ditropan® XL (oxybutinin chloride)
Alza Corporation

Federal Register Notices

This application was not the subject of any Federal Register Notices.

NDA 20-897
Ditropan® XL (oxybutinin chloride)
Alza Corporation

Advertising Material

No advertising material has been submitted.

PATENT DECLARATION

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of OROS® (oxybutynin chloride). This product is the subject of this application for which approval is being sought.

<u>PATENT NO.</u>	<u>TYPE</u>	<u>EXPIRATION</u>	<u>PATENT OWNER</u>
5,674,895	Formulation	05/22/2015	ALZA Corporation
5,082,668	Formulation	09/16/2003	ALZA Corporation
4,783,337	Formulation and Method of Use	09/16/2003	ALZA Corporation
4,612,008	Formulation	09/16/2007	ALZA Corporation
4,519,801	Formulation	05/28/2002	ALZA Corporation
4,327,725	Formulation	05/04/1999	ALZA Corporation

ALZA Corporation



Peter D. Staple
Vice President and General Counsel
Dated: November 11, 1997

Original NDA No. 20-897: OROS® (oxybutynin chloride)

SECTION 14. PATENT CERTIFICATION

Not applicable for 505 (b) (1) NDA.

DEC 16 1998

Memo to the Record

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

Date: December 16, 1998
To: HFD-580
From: Sam H. Haidar, R.Ph., Ph.D.
RE: NDA 20-897

The recommended *in vitro* dissolution specification for Ditropan XL, as listed in the Clinical Pharmacology and Biopharmaceutics review of NDA 20-897, has been accepted by the sponsor.

/S/

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

cc:
NDA 20-897
HFD-870 (M. Chen, A. Parekh, S. Haidar)
HFD-580 (R. Olmstead, D. Shames)
CDR (Barbara Murphy For Drug)

EXCLUSIVITY SUMMARY for NDA # 20-897

Trade Name: Ditropan® XL Generic Name: oxybutinin chloride
Applicant Name: Alza Corporation

Approval Date December 16, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?

YES / X / NO / /

b) Is it an effectiveness supplement?

YES / / NO / X /

If yes, what type? (SE1, SE2, etc.)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES / / NO / /

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 17-577 Ditropan (oxybutinin chloride)

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain:

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # C-95-031

Investigation #2, Study # C-95-049

Investigation #3, Study # C-97-020

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
 NDA # _____ Study #
 NDA # _____ Study #

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
 NDA # _____ Study #
 NDA # _____ Study #

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # C-95-031

Investigation #2, Study # C-95-049

Investigation #3, Study # C-97-020

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND: YES / / NO / / Explain

Investigation #2

IND: YES / / NO / / Explain:

Investigation #3

IND YES / / NO / / Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / / Explain _____ NO / / Explain _____

Investigation #2

YES / / Explain _____ NO / / Explain _____

- (c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / /

NO / X /

If yes, explain: _____

Signature

Date 12.16.98

Title: *Project Manager*

Signature of Division Director

Date 12.16.98

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

PLA/PMA # 20-897 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-580 Trade and generic names/dosage form: Ditropan[®] XL (oxybutinin chloride) 5mg, 10mg Action: AP AE NA

Applicant Alza Corporation Therapeutic Class 3S

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate inadequate

Proposed indication in this application: Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- c. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, attach memo describing status of discussions.
- d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
5. PEDIATRIC LABELING MAY NOT BE ADEQUATE.
- a. Pediatric studies are needed.
- b. Pediatric studies may not be needed but a pediatric supplement is needed.
6. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? Yes No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

ISI Project Manager
Signature of Preparer and Title

12.16.98
Date

cc: Orig NDA/PLA/PMA #20-897
HFD-580/Div File
NDA/PLA Action Package
HFD-006/ KRoberts

(revised 9/15/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

SECTION 16. DEBARMENT STATEMENT

ALZA hereby certifies, in accordance with the Federal Food, Drug and Cosmetic Act [FDC Act § 306(k)], that it has not utilized the services of any firm or person(s) debarred in the preparation of information for this NDA as described in Section 306(e) of the Federal Food, Drug, and Cosmetic Act, as Amended.

 20 Nov 97

Janne Wissel

Date

Vice President
Regulatory & Quality Management

ORIGINAL

Memorandum

To: NDA 20-897, Ditropan XL (oxybutynin chloride extended release tablet)
Through: Moo-Jhong Rhee, Ph.D. *MJR 7/31/98*
From: David Lin, Ph.D. *DL 7/31/98*
Date: July 31, 1998
Re: Review of Labeling Amendment (June 30, 1998) to Original NDA

This amendment contains revised proposed labels for both the 100 count and 500 count immediate container bottles. The middle four digits of the ten digit NDC numbers for the 5 mg and 10 mg products will be revised from "9220" and "9221" to "8500" and "8501", respectively. The statement "Caution: Federal law prohibits dispensing without prescription" will be revised to "Rx only". These two proposals are acceptable.

The third revision involves a change in the logo format for the product name, Ditropan[®] XL. The letter "O" in DITROPAN now contains a blue color crescent shading that covers the bottom third of the letter. This modification changes the letter "O" to a symbol, which changes the DITROPAN trademark. This is unacceptable.

All other components of the label are acceptable, except for the storage conditions statement. The statement "Store at controlled room temperature" should be changed to "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]."

cc:
Orig. NDA #20-897
HFD-580/Division File
HFD-580/ROlmstead
HFD-580/MRhee/DLin

Filename: nda20897mem.lab (doc)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-897

CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-897

NOV 13 1998

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

Dear Dr. Ketchum:

Please refer to your pending December 17, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ditropan XL (oxybutynin chloride extended release tablets).

We also refer to your submission dated December 17, 1997, April 30, 1998, June 30, 1998, August 6, 1998, and September 30, 1998.

We have completed our review of the Chemistry section(s) of your submission and have the following comments and information requests:

1. In the release testing of the bulk drug substance, the methods used for determining methanol content and particle size should be provided.
2. Please provide the updated batch formula describing the 5 mg strength tablet utilizing the new yellow color overcoat.
3. The Certificate of Analysis for _____ should be provided.
4. There is no data provided on the drug product manufactured at the _____ . A listing is provided on page 73 (vol. 1.5) of the equipment used in the manufacturing of the drug product at _____ . Although the same equipment is being used at both facilities, accelerated stability data and comparative dissolution data for the drug product tablets manufactured at _____ facility are needed; otherwise, this facility should be excluded from this NDA.
5. The recentering process via a membrane weight adjustment is unclear. Please provide information on the following: a) when is the cumulative release data reviewed to determine whether adjustments are necessary (the NDA states "periodically"), and b) whether the target membrane weight is adjusted during the manufacturing process or after the current batch is finished.

6. The in-process controls section contains a discrepancy in the acceptance limit for the moisture content of the active dried granulation as reported in the description section (vol. 1.5, pg. 61) and in the master batch record (vol. 1.5, pg. 83). Please clarify which acceptance limit is correct, $\leq 1.5\%$ as reported in the description section or $\leq 1.0\%$ as reported in the master batch record. This is also the case for the osmotic (push) granulation.
7. There is a statement in Volume 1.1 of the NDA that the nominal release rate of the 5mg and 10 mg tablets is 0.3 mg/h and 0.6 mg/h, respectively. Please explain how these release rates are measured and whether these rates correlate with cumulative release data presented in the NDA.
8. The impurities specifications need to be tightened for both tablet strengths. Based on the submitted stability data, the limits should be: Total Impurities %, Cyclohexylphenylglycolic acid (CPA) %. The limit for individual unspecified impurities is unchanged.
9. The following information should be provided for the head space analysis method: a) method analysis time, b) injection volumes of the samples and standards, and c) the number of injections used to conduct the system suitability study. In addition, please explain the discrepancies between the headspace injector programs on pages 232 (vol. 1.5) and 203 (vol. 1.6). Please explain why there is such a large analyst to analyst variability.
10. The actual print on the tablet should be included in the drug product appearance specification. In the analysis of the appearance of the tablet, the word should be quantitatively defined.
11. No cotton is used in the bottles. Please justify how the tablets are prevented from being broken when the bottles are shaken, especially during shipping.
12. The photostability studies conducted on the 5 mg blister packs are unclear. Please clarify whether two separate stability studies were performed on the same product lot in Stability Study # SS2026.
13. In the graphical analysis section of the September 30, 1998 amendment (appendix 7, vol. 6.3, pg. 230-231), the graphs do not appear to reflect the data from the primary stability studies. For example, the graphs for oxybutynin and CPA are plotted to eight months, but there are twelve months of controlled room temperature data presented in tabular form. Please comment.
14. The words ' in statement #4 of the stability commitment should be revised to read
15. There appears to be an error in the target weight of magnesium stearate in the push layer of the formulation of the 5 mg system, Alza code AA-06216. The weight probably should be mg and not mg. Please comment.
16. In the package insert, the word in parenthesis should be added to the chemical name as follows:

17. Please change the storage statement on the container and blister pack labels to read

18. Please provide copies of the final proposed container and blister pack labels.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely,

JSI 11/10/98

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

NDA 20-897

Page 4

cc:

Archival NDA 20-897

HFD-580/Div. Files

HFD-580/Rarick/Mann/Shames/Jordan/Rhee/Lin

HFD-715 / Castillo

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: rco/November 2, 1998

Initialed by: rumble 11.5.98/ Lin 11.9.98/Rhee 11.9.98

final: Olmstead 11.10.98

filename: CMC11-2-98.doc

INFORMATION REQUEST (IR)





Food and Drug Administration
Rockville MD 20857

NDA 20-897

DEC 31 1997

Alza Corp.
Attention: Ms. Janne Wissel
Vice President, Regulatory Affairs
1010 Joaquin Road, P.O. Box 7210
Mountain View, CA 94039-7210

Dear Ms. Wissel:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Ditropan XL (oxybutinin chloride) Extended Release Tablets
Therapeutic Classification: Standard
Date of Application: December 17, 1997
Date of Receipt: December 19, 1997
Our Reference Number: 20-897

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 17, 1998, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Randy Olmstead, Technical Information Specialist, at 301-827-4260.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

IS/
12/30/97
Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-897
Page 2

cc:

Original NDA 20-897
HFD-580/Div. Files
HFD-580/CSO/RO
HFD-580/Jolson, Jordan Rhee, Dorantes, Shames
DISTRICT OFFICE

Drafted by: ROlmstead/December 30, 1997/N20897AK.001
Final:

ACKNOWLEDGEMENT (AC)

① 12/30/97



December 11, 1998

NDA Number 20-897
Volume 13.1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Subject: **Amendment to Pending New Drug Application 20-897
for Ditropan[®] XL (oxybutynin chloride) Extended Release Tablets:
Responses to Agency's 12/8/98 and 12/10/98 Labeling and Chemistry
Comments**

Dear Dr. Rarick:

Please find enclosed to this submission ALZA Corporation's (ALZA's) responses to the Agency's labeling and chemistry comments communicated by facsimile and/or telephone on December 8th and 10th, 1998. A more detailed description of the specific documents contained in this amendment is provided in the Amendment Overview section of this submission. Diskette copies of the revised physician insert are provided only in the Archival, Clinical, Statistical, and desk copies of this submission.

In accordance with 21 CFR 314.50 (l)(3), ALZA hereby certifies that the field copy of this submission is a true copy of that contained in the archival and review copies of the submission.

If you have any questions regarding this submission, please contact me at 650-962-4282 or Susan Rinne, Vice President of Regulatory Affairs, at 650-237-2523 (or either of us by facsimile at 650-237-2581).

Sincerely,

Janne Wissel
Senior Vice President
Operations

(Enclosures)

Copies: Archival (1)
Reviewer (7) for: Chemistry, Clinical, Pharm/Tox, PK/Biopharm, Stats, Field Chemistry
Desk (2) for: Randy Olmstead, Project Manager, DRUDP, HFD-580

BC

ORIGINAL



ORIG AMENDMENT



December 7, 1998

NDA Number 20-897
Volume 12.1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Subject: **Amendment to Pending New Drug Application 20-897
for Ditropan® XL (oxybutynin chloride) Extended Release Tablets:
Response to December 7th, 1998 Information Request Letter**

Dear Dr. Rarick:

Please refer to the Agency's letter dated December 7th, 1998. A complete response to the chemistry comments and information requests in that letter are provided in Section 1 of this submission.

In accordance with 21 CFR 314.50 (l)(3), ALZA Corporation hereby certifies that the field copy of this submission is a true copy of that contained in the archival and review copies of the submission.

If you have any questions regarding this submission, please contact me at 650-962-4282 or Susan Rinne, Vice President of Regulatory Affairs, at 650-237-2523 (or either of us by facsimile at 650-237-2581).

Sincerely,

Janne Wissel
Senior Vice President
Operations

(Enclosures)

Copies: Archival (1)
Review (3) for: Chemistry, Field Chemistry, and Pharmacokinetics
Desk (2) for: Randy Olmstead, Project Manager

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE



December 4, 1998

NDA Number 20-897
Volume 11.1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Subject: Amendment to Pending New Drug Application 20-897
for Ditropan® XL (oxybutynin chloride) Extended Release Tablets:
Response to Request for Information

Dear Dr. Rarick:

Please find enclosed to this submission ALZA Corporation's (ALZA's) response to a pharmacokinetic data-related request from the Agency. The specific contents of this response are discussed in the Amendment Overview section of this submission.

If you have any questions regarding this submission, please contact me at 650-962-4282 or Susan Rinne, Vice President of Regulatory Affairs, at 650-237-2523 (or either of us by facsimile at 650-237-2581).

Sincerely,

A handwritten signature in cursive script, appearing to read "Susan Rinne for".

Janne Wissel
Senior Vice President
Operations

(Enclosures)

Copies: Archival (1)
Desk (2) for: Randy Olmstead, Project Manager, DRUDP, HFD-580

ORIGINAL

BC

No clinical data
discuss
12/1/98

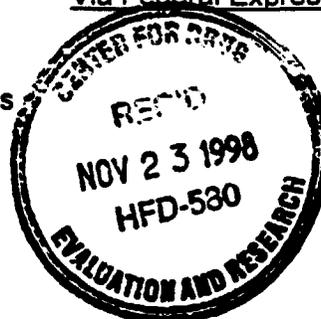


NDA 20-897: Volumes 10.1 - 10.2

November 20, 1998

Via Federal Express

Lisa Rarick, MD
Director, Division of Reproductive and Urologic Drug Products
(HFD-580), Document Control Room 17B-20
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
5600 Fishers Lane
Rockville MD 20857



Subject: Amendment to Pending NDA 20-897 for Ditropan® XL (oxybutynin chloride) Extended Release Tablets: 1) Supporting Information in Response to Discussions Held During the November 17, 1998 and November 20, 1998 Teleconferences Between the Division and ALZA and 2) Response to November 10, 1998 Information Request Letter

Dear Dr. Rarick:

In response to the teleconferences held between the Division and ALZA Corporation (ALZA) on November 17 and 20, 1998, ALZA is providing supporting information in Section I (Volume 1) of this submission.

Please refer to the Agency's letter dated November 10, 1998. A complete response to the chemistry comments and information requests in that letter are provided in Section II (Volume 2) of this submission.

In accordance with 21 CFR § 314.50 (l)(3), ALZA hereby certifies that the field copy of this submission is a true copy of that contained in the archival and review copies of the submission.

Please feel free to contact me by phone at (650) 962-4282 or Sue Rinne, Vice President of Regulatory Affairs, at 650-237-2523 if you have further questions or comments. We share the same facsimile number, (650) 237-2581.

Sincerely,

Janne Wissel
Senior Vice President

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

BL



ORIGINAL

November 16, 1998

NDA Number 20-897
Volume 9.1

AJ 11/29/98



*will review
have desktop
DTC
11/24/98*

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Subject: **Amendment to Pending New Drug Application 20-897
for Ditropan® XL (oxybutynin chloride) Extended Release Tablets:**

Response to FDA's 10/30/98 Comments on the Proposed Physician Insert

Dear Dr. Rarick:

Please find enclosed to this submission ALZA Corporation's (ALZA's) revised proposed physician insert in response to the Agency's comments communicated by facsimile on October 30th, 1998. This revised labeling replaces the version enclosed to ALZA's NDA Amendment submitted on September 30th, 1998 (in Volume 6.1, on Pages 26-38). A more detailed description of the specific documents contained in this amendment is provided in the Amendment Overview section of this submission.

If you have any questions regarding this submission, please contact me at 650-962-4282 or Susan Rinne, Vice President of Regulatory Affairs, at 650-237-2523 (or either of us by facsimile at 650-237-2581).

Sincerely,

Susan Rinne for

Janne Wissel
Senior Vice President
Operations

*will review
have desktop
DTC
11/24/98*

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
<input type="checkbox"/> MEMO	
CSO INITIALS	DATE

11-30-98

(Enclosures)

Copies: Archival (1)
Reviewer (5) for: Medical, Chemistry, Pharmacology, Pharmacokinetics, Statistics
Desk (3) for: Randy Olmstead, Project Manager, DRUDP, HFD-580



October 30, 1998

NDA Number 20-897
Volume 8.1

ORIGINAL

ORIG AMENDMENT

*DOS
11/6/98
Review*



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Subject: Amendment to Pending New Drug Application 20-897
for Ditropan[®] XL (oxybutynin chloride) Extended Release Tablets:
Revised Proposed Labeling (Physician Sample Blister Pack) for Review

Dear Dr. Rarick:

Please find enclosed to this submission revised proposed labeling for the physician sample blister pack for the 5 mg dosage strength of Ditropan[®] XL. This revised labeling replaces the version enclosed to the original NDA (in Volume 1.1, on Page 97), and ALZA Corporation (ALZA) hereby requests that the Division review this physician sample blister pack labeling so that agreement can be reached on the final texts for these items. ALZA would appreciate receiving the Agency's comments on this physician sample labeling by Wednesday, November 11th.

This submission also contains the agreed upon copies of the immediate container labels; as discussed in the Amendment Overview section of this submission, ALZA has incorporated the Agency's requested revisions to these labels.

If you have any questions regarding this submission, please contact me at 650-962-4282 or Susan Rinne, Vice President of Regulatory Affairs, at 650-237-2523 (or either of us by facsimile at 650-237-2581).

Sincerely,

Janne Wissel
Senior Vice President
Operations

(Enclosures)

Copies: Archival (1)
Reviewer (2) for: Medical and Chemistry Reviewers
Desk (2) for: Randy Olmstead, Project Manager, DRUDP, HFD-580



October 27, 1998

ORIG AMENDMENT
BB

NDA Number 20-897
Volume 7.1



ORIGINAL

Will review
desk copy
Sam H. Hinder
11-13-98

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Subject: Amendment to Pending New Drug Application 20-897
for Ditropan® XL (oxybutynin chloride) Extended Release Tablets:
Response to Request for Information

Dear Dr. Rarick:

Please find enclosed to this submission ALZA Corporation's (ALZA's) response to a request from the Biopharm Reviewer which was communicated by telephone earlier today. The specific contents of this response are discussed in the Amendment Overview section of this submission.

For administrative purposes, this submission also contains copies of three facsimiles which ALZA previously sent to the Chemistry, Medical, and Biopharm Reviewers in response to their respective verbal requests for information in conjunction with their review of our pending NDA 20-897.

If you have any questions regarding this submission, please contact me at 650-962-4282 or Susan Rinne, Vice President of Regulatory Affairs, at 650-237-2523 (or either of us by facsimile at 650-237-2581).

Sincerely,

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED		
CSO ACTION		
<input type="checkbox"/> INTERVIEW	<input checked="" type="checkbox"/> FINAL	<input type="checkbox"/> MEMO
CSO Initials: <i>[Signature]</i>		DATE: 11-6-98

(Enclosures)

Copies: Archival (1)
Reviewer (1) for: PK/Biopharm Reviewer
Desk (1) for: Randy Olmstead, Project Manager, DRUDP, HFD-580



ORIGINAL

September 30, 1998

NDA Number 20-897
Volumes 6.1 - 6.3

ORIG AMENDMENT



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Subject: **Amendment to Pending New Drug Application 20-897
for Ditropan® XL (oxybutynin chloride) Extended Release Tablets:**

**Revised Labeling (Physician Insert)
Updated Chemistry, Manufacturing and Controls Information**

Dear Dr. Rarick:

Pursuant to 21 CFR 314.60(a), ALZA Corporation (ALZA) is hereby submitting an amendment to our pending NDA 20-897 for Ditropan® XL (oxybutynin chloride) Extended Release Tablets which was submitted on December 17, 1997. Please find enclosed to this submission the revised proposed Physician Insert for Ditropan® XL, and an updated stability report that includes additional data on primary registration lots and supporting studies. A more detailed description of the specific documents contained in this amendment is provided in the Amendment Overview section of this submission.

We look forward to our continued interactions as the review of this NDA proceeds. Please feel free to contact me with any questions regarding this submission at 650-962-4282, or via facsimile at 650-237-2581. In the event you are unable to contact me, please contact Steve Ketchum, PhD, Director of Regulatory Affairs, at 650-237-2510. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED	
CSD ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
<input type="checkbox"/> MEMO	
CSD INITIALS	DATE

10-22-98



ORIGINAL

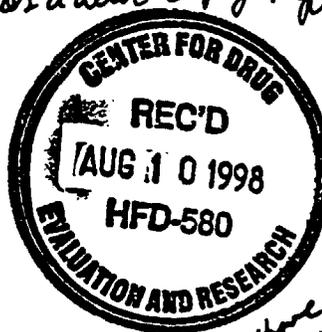
*Under review by
Sonia Castillo - she
has a desk copy. Lia Kammanna
10/6/98*

August 6, 1998

**NDA Number 20-897
Volumes 4.1 - 4.40**

ORIG AMENDMENT

5U



*I have the
desk copy
made from*

*DSS
10/6/98*

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: **Amendment to Pending New Drug Application (NDA) 20-897
for Ditropan® XL (oxybutynin chloride) Extended Release Tablets:
Chemistry, Manufacturing and Controls Information
Safety Update Report**

Dear Dr. Rarick:

Pursuant to 21 CFR 314.50 (d)(5)(vi)(b) and 314.60 (a), ALZA Corporation (ALZA) is hereby submitting an amendment to our pending NDA 20-897 for Ditropan® XL (oxybutynin chloride) Extended Release Tablets which was submitted on December 17, 1997. The enclosed Chemistry, Manufacturing and Controls information provides an updated stability report that includes additional data on primary registration lots and supporting studies. And further to the agreement reached at the FDA/ALZA meeting on June 24, 1998, the Safety Update provided in this amendment includes the final data from clinical study C-97-020. A more detailed description of the specific documents contained in this amendment is provided in the Amendment Overview section of this submission.

We look forward to our continued interactions as the review of this NDA proceeds. Please feel free to contact me with any questions regarding this submission at (650) 962-4282, or via facsimile at (650) 237-2581. In the event you are unable to contact me, please contact Steve Ketchum, PhD, Associate Director of Regulatory Affairs, at (650) 237-2510. We share the same facsimile number.

Sincerely,

Janne Wissel for

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE



ORIGINAL

July 30, 1998
NDA Number 20-897

ORIG AMENDMENT

BC

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED	
CSO	
<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> MEMO	
CSO INITIALS	DATE

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: General Correspondence to Pending New Drug Application 20-897
for Ditropan® XL (oxybutynin chloride) Extended Release Tablets:
Chemistry Information (Request for Review of Revised Proposed Labeling)

Dear Dr Rarick:

Further to a request yesterday (July 29, 1998) from Dr. David Lin (Chemistry Reviewer), please find enclosed a full copy of a facsimile which ALZA Corporation (ALZA) sent to the Division on July 27, 1998 in follow-up to our request for review of several revised proposed labeling materials. A more detailed description of the specific revisions to the labeling materials is provided in the enclosed facsimile.

If you have any questions regarding this submission, please contact me at 650-962-4282, or via facsimile at 650-237-2581. In the event you are unable to contact me, please contact Steve Ketchum, PhD, Associate Director, Regulatory Affairs at 650-237-2510. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

(Enclosures)

Copies: Archival (1)
Reviewer (1) for: Chemistry Reviewer
Desk (2) for: Randy Olmstead, Project Manager, DRUDP, HFD-580
David Lin, PhD, Chemistry Reviewer, c/o DRUDP, HFD-580



ORIGINAL



June 30, 1998

NDA Number 20-897
Volume 3.1

BZ
ORIG AMENDMENT



Handwritten: 7/2/98 [Signature]

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: Amendment to Pending New Drug Application 20-897
for Ditropan® XL (oxybutynin chloride) Extended Release Tablets:
Request for Review of Revised Proposed Labeling

Dear Dr Rarick:

Please find enclosed to this submission revised proposed labeling for the 100 count and 500 count bottles of the 5 mg and 10 mg dosage strengths of Ditropan® XL. These revised samples replace the versions of the labeling which were enclosed to the original NDA (in Volume 1.1, Pages 84-95).

ALZA Corporation (ALZA) requests that the Division review the enclosed materials so that agreement can be reached on the final text for these labeling items. ALZA is planning to contact Mr. Randy Olmstead the week of July 13, 1998 to elicit the Division's comments on the enclosed proposed labeling. A more detailed description of the specific revisions to the labeling materials contained in this amendment is provided in the Amendment Overview section of this submission.

If you have any questions regarding this submission, please contact me at 650-962-4282, or via facsimile at 650-237-2581. In the event you are unable to contact me, please contact Steve Ketchum, PhD, Associate Director, Regulatory Affairs at 650-237-2510. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

(Enclosures)

Copies: Archival (1)
Reviewer (2) for: Medical and Chemistry Reviewers
Desk (2) for: Randy Olmstead, Project Manager, DRUDP, HFD-580

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE



ORIGINAL

April 30, 1998

NDA Number 20-897
Volumes 2.1 - 2.46

REVIEWS COMPLETED
CSO ACTION: <input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

ORIG AMENDMENT

32

BY 6/4/98



will review
Dish
copy

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: Amendment to Pending New Drug Application 20-897
for Ditropan® XL (oxybutynin chloride) Extended Release Tablets

Chemistry, Manufacturing and Controls Information
4-Month Safety Update Report

Dear Dr. Rarick:

Reference is made to ALZA Corporation's (ALZA) New Drug Application (NDA) 20-897 for Ditropan® XL (oxybutynin chloride) Extended Release Tablets submitted on December 17, 1997.

Pursuant to 21 CFR 314.50 (d)(5)(vi)(b) and 314.60 (a), ALZA is submitting an amendment to pending NDA 20-897. Provided herewith, in 46 volumes (archival copy), is updated Chemistry, Manufacturing and Controls information, and a 4-month Safety Update Report. This amendment provides the following information.

- The original NDA requests approval for Ditropan® XL 5 mg and 10 mg tablets. The Chemistry, Manufacturing and Controls update provided in this amendment (1 volume total) includes the following: (1) a change in ownership of the drug substance supplier, (2) the deletion of an inert ingredient from the composition of the 5 mg tablet overcoat, (3) a revised product assay method, and (4) a corrected method validation report.



**Amendment to Pending NDA 20-897
Ditropan® XL (oxybutynin chloride) Extended Release Tablets**

**April 30, 1998
Page 2**

- The original NDA includes interim results from open-label, uncontrolled efficacy and safety study C-96-070 which was ongoing at the time of the submission. ALZA received concurrence from the Division on January 27, 1997 and July 8, 1997 to submit the final safety data from this study in the planned 4-month safety update to the application. Accordingly, this Safety Update Report (44 volumes total) includes the following information: (1) a revised Integrated Summary of Safety, including all safety results from study C-96-070, (2) the final report for study C-96-070 (42 volumes total), including case report forms, and case report form tabulations (in 27 volumes), (3) the electronic data set from study C-96-070, and (4) a blinded interim safety report from ongoing study
- The draft annotated labeling for Ditropan® XL has been revised to reflect the new Chemistry, Manufacturing and Controls information, and the final results from study C-96-070, as provided in this amendment.

A more detailed description of the specific Chemistry, Manufacturing and Controls information and Safety Update Report documents contained in this amendment is provided in the Amendment Overview section of this submission.

The clinical development program for Ditropan® XL was discussed with consideration of the extensive (over 20 years) commercial safety and efficacy experience with the immediate release formulation of Ditropan® (oxybutynin chloride). Please note that the ownership and all applicant rights and responsibilities for Ditropan® Tablets (5 mg) NDA 17-577 and Ditropan® Syrup (5 mg/5 mL) NDA 18-211 were administratively transferred from Hoechst Marion-Roussel to ALZA on March 9, 1998.

ALZA has appreciated the Division's guidance on the development of this new product. We believe that the information contained in this application clearly supports the efficacy and safety of Ditropan® XL for the proposed indication.

We look forward to our continued interactions as the review of this NDA proceeds. Please feel free to contact me with any questions regarding this submission at (650) 962-4282, or via facsimile at (650) 237-2581. In the event you are unable to contact me, please contact Steve Ketchum, PhD, Associate Director, Regulatory Affairs at (650) 237-2510. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations



December 17, 1997

NDA Number 20-897
Volumes 1.1 - 1.198

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: **Submission of New Drug Application 20-897**
for Ditropan® XL (oxybutynin chloride) Extended Release Tablets

Dear Dr. Rarick:

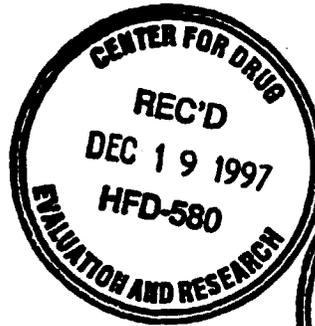
In accordance with Section 505(b) of the Federal Food, Drug and Cosmetic Act, and with the provisions of 21 CFR Section 314.50, ALZA Corporation (ALZA) hereby submits, in 198 volumes (archival copy), a New Drug Application for a once-daily controlled release Oral Osmotic System [OROS®] formulation of oxybutynin chloride.

The proposed tradename is Ditropan® XL (oxybutynin chloride) Extended Release Tablets. The FDA Labeling and Nomenclature Committee (LNC) reviewed the tradename (which was submitted to IND

at their meeting of October 28, 1997. ALZA was notified by Mr. Alvis Dunson on November 20, 1997, of the LNC's favorable recommendation on the proposed tradename.

Ditropan® XL was developed under IND for the treatment of urge urinary incontinence, urgency and frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia. This application requests approval for two dosage strengths of once-daily oxybutynin chloride: 5 mg and 10 mg tablets.

Seven new clinical investigations were conducted with Ditropan® XL in a total of 594 patients and healthy subjects. The efficacy and safety of Ditropan® XL was evaluated in two well-controlled studies (C-95-031 and C-95-049) and in one ongoing, open-label,





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Ditropan® XL (oxybutynin chloride)
Extended Release Tablets**

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uncontrolled study. An interim report for study is provided in this submission; the remaining safety data from this study will be submitted in the planned 4-month Safety Update to the application. In addition, four clinical pharmacology studies (C-94-010, C-96-068, C-96-074 and C-97-015) were conducted to evaluate the pharmacokinetics of the controlled release dosage form. Because ALZA conducted significant new clinical investigations that are essential to approval this application, we are requesting exclusivity under 21 CFR Section 314.108.

This NDA was developed in consultation with the FDA Division of Reproductive and Urologic Drug Products. A copy of the FDA minutes from the ALZA/FDA meetings on January 29, 1997, February 28, 1997, and July 8, 1997 to discuss the development program are provided in Section 3.1 of this application.

The clinical development program for Ditropan® XL was discussed with consideration of the extensive (over 20 years) commercial safety and efficacy experience with the immediate release formulation of Ditropan® (oxybutynin chloride) [Ditropan® tablets, Hoechst Marion-Roussel, NDA No. 17-577]. ALZA recently acquired the rights to the Ditropan® product and trademark in the United States from Hoechst Marion-Roussel.

ALZA appreciates the Division's guidance on the development of this new product. We believe that the information contained in this application clearly supports the efficacy and safety of Ditropan® XL for the treatment of urge urinary incontinence, urgency and frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia.

We look forward to our continued interactions as the review of this NDA proceeds. Please feel free to contact me with any questions or comments at (650) 962-4282, or via facsimile at (650) 237-2581. In the event you are unable to reach me, please contact Ray Lubecki, Manager, Regulatory Affairs at (650) 237-2528. We share the same facsimile number.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Wissel'.

**Janne Wissel
Vice President
Quality Management
and Regulatory Affairs**