CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-897/S-002

Name: Ditropan XL
Extended Release Tablets

Generic Name: oxybutynin chloride

Sponsor: ALZA Corporation

Approval Date: 06/22/1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-897/S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-897/S-002

APPROVAL LETTER

JUN 22 1999

NDA 20-897/S-002

ALZA Corporation
Attention: Janne Wissel
Senior Vice President, Operations
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Dear Ms. Wissel:

Please refer to your supplemental new drug application dated December 22, 1998, received December 28, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ditropan® XL (oxybutynin chloride) Extended Release Tablets.

We acknowledge receipt of your submissions dated April 28, May 6 and June 15, 1999.

This supplemental new drug application provides for the addition of a 15 mg tablet.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental 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 22, 1998).

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 supplement NDA 20-897/S-002." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

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

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-897
HFD-580/Div. Files
HFD-580/K.Colangelo
HFD-580/Rarick/Mann/Rhee/Lin/Rumble
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

APPEARS THIS WAY
ON ORIGINAL

Drafted by: kmc/June 20, 1999
Initialed by: Rarick,6.21.99/Lin,6.21.99/Rhee,6.21.99/Haidar,6.21.99/Rumble,6.21.99
final: 6.22.99
filename: c:\mydocs\nda\20-897\s002ap.doc

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-897/S-002

FINAL PRINTED LABELING

2.1 Physician Insert

The proposed Physician Insert for 5, 10, and 15 mg Ditropan® XL tablets is provided on the following pages. As previously noted in the original NDA for the 5 and 10 mg tablets, the 15 mg dosage strength will initially be launched in only the 100 count bottle. Therefore, only the 100 count bottle is listed in the HOW SUPPLIED section of the proposed insert. ALZA has provided data for, and is requesting approval of, a 500 count bottle, to be implemented when marketing volumes justify its use. The NDC number for the 500 count bottle will be added to the insert when the package size is placed into use.

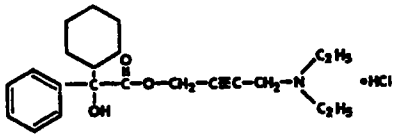
Ditropan® XL
(oxybutynin chloride)
Extended Release Tablets

DESCRIPTION

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

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

Its structural formula is:



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

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

System Components and Performance

DITROPAN® XL uses osmotic pressure to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice in the semipermeable membrane on the drug-layer side of the tablet. In an aqueous environment, such as the

gastrointestinal tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and the push layer to expand. This expansion pushes the suspended drug out through the orifice. The semipermeable membrane controls the rate at which water permeates into the tablet core, which in turn controls the rate of drug delivery. The controlled rate of drug delivery into the gastrointestinal lumen is thus independent of pH or gastrointestinal motility. The function of DITROPAN® XL depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract. Since the osmotic gradient remains constant, drug delivery remains essentially constant. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

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

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

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

Pharmacokinetics

Absorption

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

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

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

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

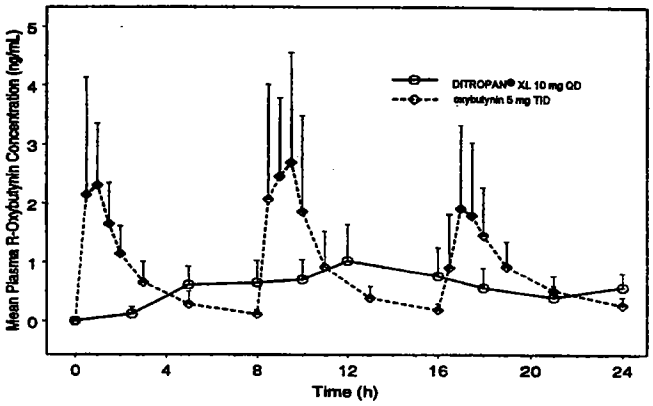


Figure 1. Mean R-oxybutynin plasma concentrations following a single dose of DITROPAN® XL 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment).

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

Food Effects

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

Distribution

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

Metabolism

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

Excretion

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

Dose Proportionality

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

Special Populations

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

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

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

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

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

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

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

Clinical Studies

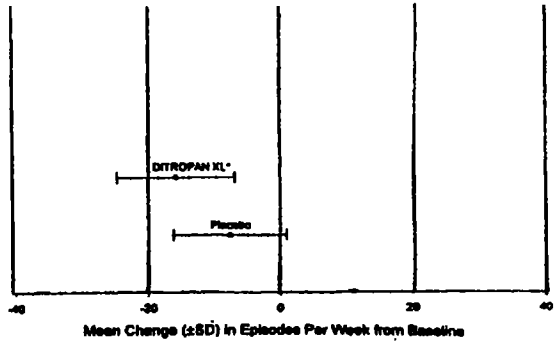
DITROPAN® XL was evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (89.0%) and female (91.9%) with a mean age of 59 years (range,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

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

Number of Urge Urinary Incontinence Episodes Per Week

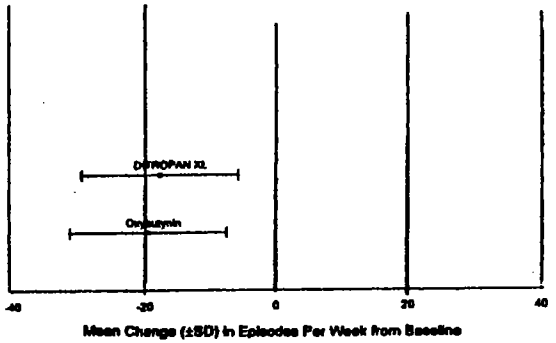
Study 1	N	DITROPAN® XL	N	Placebo
Mean Baseline	34	15.9	16	20.9
Mean (SD) Change from Baseline†	34	-15.8 (8.9)	16	-7.6 (8.6)
95% Confidence Interval for Difference (DITROPAN® XL – Placebo)		(-13.6, -2.8)*		

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



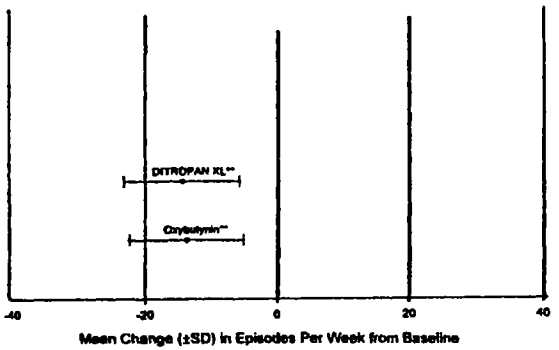
Study 2	N	DITROPAN® XL	N	oxybutynin
Mean Baseline	53	27.6	52	23.0
Mean (SD) Change from Baseline†	53	-17.6 (11.9)	52	-19.4 (11.9)
95% Confidence Interval for Difference (DITROPAN® XL – oxybutynin)		(-2.8, 6.5)		

† Covariate adjusted mean with missing observations set to baseline values



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

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



INDICATIONS AND USAGE

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

CONTRAINDICATIONS

DITROPAN® XL is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

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

PRECAUTIONS

General

DITROPAN® XL should be used with caution in patients with hepatic or renal impairment.

Urinary Retention:

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

Gastrointestinal Disorders:

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

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

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

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

Information for Patients

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

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

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

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

Drug Interactions

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

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

Pharmacokinetic studies with patients concomitantly receiving cytochrome P450 enzyme inhibitors, such as antimycotic agents (e.g. ketoconazole, itraconazole, and miconazole) or macrolide antibiotics (e.g. erythromycin and clarithromycin), have not been performed.

No specific drug-drug interaction studies have been performed with DITROPAN® XL.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Pregnancy: Teratogenic Effects
Pregnancy Category B

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

Adverse Events with DITROPAN® XL

The safety and efficacy of DITROPAN® XL was evaluated in a total of 580 participants who received DITROPAN® XL in clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5-30 mg/day for up to 4.5 months. Safety information is provided for 429 patients from three controlled clinical studies and one open label study (Table 2). The adverse events are reported regardless of causality.

Table 2
Incidence (%) of Adverse Events Reported by ≥ 5% of Patients Using DITROPAN® XL (5-30 mg/day)

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

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

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

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

Adverse Events with Oxybutynin Chloride

Other adverse events have been reported with oxybutynin chloride: tachycardia, hallucinations, cycloplegia, mydriasis, impotence, and suppression of lactation.

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

DITROPAN® XL may be administered with or without food.

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

HOW SUPPLIED

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

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

Storage

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

Rx only.

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

Manufactured, distributed, and marketed by
ALZA Corporation, Palo Alto, CA 94304.

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

Edition: 12/98

[ALZA Logo]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-897/S-002

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 20-897/SCS-002
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 22-DEC-1998
   Stampdate: 28-DEC-1998
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate: 28-APR-1999, 06-MAY-1999
   Stampdate: 29-APR-1999, 07-MAY-1999
5. **RECEIVED BY CHEMIST:** 04-JAN-1999

6. **APPLICANT NAME AND ADDRESS:**
   Alza Corp.
   1010 Joaquin Road
   P.O. Box 7210
   Mountain View, CA 94039-7210

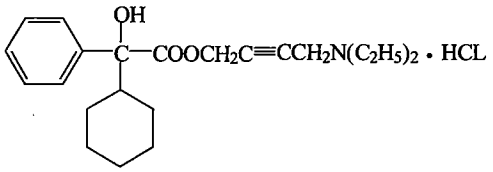
7. **NAME OF DRUG:**
   Ditropan XL Tablets

8. **NONPROPRIETARY NAME:**
   Oxybutynin chloride

9. **CHEMICAL NAME/STRUCTURE:**

a. benzeneacetic acid, α-cyclohexyl-α-hydroxy-,4-(diethylamino)-2-butynyl ester hydrochloride

b. 4-(diethylamino)-2-butynyl α-phenylcyclohexaneglycolate hydrochloride



10. **DOSAGE FORM(S):**
    Tablet

11. **POTENCY:**
    5, 10 , **15** mg

12. **PHARMACOLOGICAL CATEGORY:**
    Anticholinergic/Treatment of urge urinary incontinence, urgency and frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia

13. **HOW DISPENSED:**
    RX

14. **RECORDS & REPORTS CURRENT:**
    Yes

15. RELATED IND/NDA/DMF:
None

16. SUPPLEMENT PROVIDES FOR:
Addition of a 15 mg dosage strength tablet.

17. COMMENTS
Oxybutynin chloride is an anticholinergic agent used in the treatment of urge urinary incontinence, urgency and frequency arising from overactivity of the bladder's detrusor muscle. The original NDA was approved on December 17, 1998 for the 5 mg and 10 mg strength tablets, with the trademark of Ditropan XL. This prior approval supplement has been submitted for a 15 mg strength tablet manufactured at Vacaville, CA.
The Division of Biopharmaceutics was consulted for the drug release specifications. In addition, a food effect study and a bioequivalence study were evaluated. Dr. Sam H. Haidar has determined the data submitted is adequate to support this supplement (see Biopharm. Rev. dated 4/5/99). The drug release specifications are the same as in the approved NDA and are satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS:
This Supplement may be approved. **Issue an approval letter with the following comments.**

- The 24 month expiry dating for the 15 mg strength tablet is acceptable.
- When the [ ] count packaging configuration is listed in the "How Supplied" section of the label, this change can be reported in an Annual Report (21 CFR 314.70 (d)(2)).
- The sponsor should be informed that in order to manufacture the 15 mg strength drug product at the Mountain View site, a supplement will need to be submitted (see the SUPAC-MR guidance).
- The data provided in this supplement do not justify the /% API overage. However, at this time there are not enough data from batches manufactured at the full commercial scale to ascertain whether this overage can be justified. This issue will be evaluated in the future after more data from commercial scale batches are obtained.

19. REVIEWER NAME	**SIGNATURE**	**DATE COMPLETED**
David T. Lin, Ph.D. Review Chemist		21-MAY-1999

cc: Original: NDA 20-897/SCS-002
HFD-580/Division File
HFD-580/KColangelo
HFD-580/MRhee/DLin

INIT by MJ Rhee

Filename: S20897.002 (doc)

Redacted 18 page(s)

of trade secret and/or

confidential commercial

information from

Chemistry Review

CHEMIST REVIEW
OF **SUPPLEMENT**
Addendum #1

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 20-897/SCS-002
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 22-DEC-1998
   Stampdate: 28-DEC-1998
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate: 15-JUN-1999
   Stampdate: 17-JUN-1999
5. **RECEIVED BY CHEMIST:** 04-JAN-1999

6. **APPLICANT NAME AND ADDRESS:**
   Alza Corp.
   1010 Joaquin Road
   P.O. Box 7210
   Mountain View, CA 94039-7210

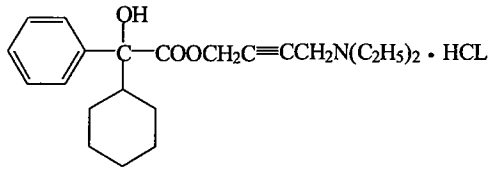
7. **NAME OF DRUG:**
   Ditropan XL Tablets

8. **NONPROPRIETARY NAME:**
   Oxybutynin chloride

9. **CHEMICAL NAME/STRUCTURE:**

a. benzeneacetic acid, α-cyclohexyl-α-hydroxy-,4-(diethylamino)-2-butynyl ester hydrochloride

b. 4-(diethylamino)-2-butynyl α-phenylcyclohexaneglycolate hydrochloride



10. **DOSAGE FORM(S):**
    Tablet

11. **POTENCY:**
    5, 10 , **15** mg

12. **PHARMACOLOGICAL CATEGORY:**
    Anticholinergic/Treatment of urge urinary incontinence, urgency and frequency in unstable bladder conditions associated with detrusor instability or hyperreflexia

13. **HOW DISPENSED:**
    RX

14. **RECORDS & REPORTS CURRENT:**
    Yes

15. RELATED IND/NDA/DMF:
None

16. SUPPLEMENT PROVIDES FOR:
Addition of a 15 mg dosage strength tablet.

17. COMMENTS
Although the conclusion in the first chemistry review of this supplement was an approval with comments, the comments were conveyed to the sponsor in a teleconference on June 14, 1999. In attendance at the telecon were Kim Colangelo and I from the FDA, and Betty Clark and Susan Rinne from Alza (see telecon meeting minutes). All the comments in the first chemistry review were conveyed to then sponsor.
In response to the telecon, the June 15, 1999 amendment addresses the issue of the /% overage in the drug product (see the Review Notes section for further discussion).

18. CONCLUSIONS AND RECOMMENDATIONS:
This Supplement may be approved. **Issue an approval letter.**

19. REVIEWER NAME	**SIGNATURE**	**DATE COMPLETED**
David T. Lin, Ph.D. Review Chemist		17-JUN-1999

cc: Original: NDA 20-897/SCS-002
HFD-580/Division File
HFD-580/KColangelo
HFD-580/MRhee/DLin

INIT by MJ Rhee

Filename: S20897a.002 (doc)

SUPPORTING DOCUMENTS:

See Chemistry Review dated May 21, 1999.

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

Chemistry Review. Addendum #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-897/S-002

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA:	**20-897, Supplement 002**
Compound:	Ditropan® XL (Oxybutynin Hydrochloride), 15 mg extended release tablets
Sponsor:	ALZA
Type of Submission:	NDA Supplement for a new strength
Date of Submission:	December 22, 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 approved on December 19, 1998. The sponsor for this NDA is 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. On December 22, 1998, Alza Corp. submitted Supplement 002 seeking the approval of a new dosage strength (15 mg). Ditropan XL® tablets at dosages of up to 30 mg per day were tested and approved for NDA 20-897. According to the sponsor:

> "The 5, 10, and 15 mg dosage forms are extended release oral tablets incorporating the OROS® push-pull technology. The compositions of the three dosage strengths are qualitatively similar and utilize the same mechanism for drug release. All three tablets are the same size and shape; the different dosage strengths are achieved by the proportion of drug in the drug layer of the bilayer tablet core. In vitro drug release is proportionally similar for the three dosage strengths."

It should be noted that the 5 mg tablet is manufactured in Mountain View, California, while the 15 mg tablet is manufactured in Vacaville, California.

In support of NDA 20-897 Supplement 002, the sponsor has submitted Study C-98-014, which evaluated the effect of food on the pharmacokinetics of 15 mg OROS® (oxybutynin chloride) and the bioequivalence of three 5 mg OROS® tablets and one 15 mg OROS® tablet.

Summary of Study C-98-014

Study C-98-014 was a single-dose, randomized, three-treatment, three-period, six-sequence, 3-week, crossover study. Fifty four healthy volunteers (30 women and 24 men) aged 18 to 45 years were enrolled to ensure 48 evaluable subjects. Treatments were administered at approximately the

same time (0800) in each treatment period. There was a washout period of 5 to 7 days between treatments. Each subject received the three treatments listed below:

A. Three 5 mg tablets qd, fasting
B. One 15 mg tablet qd, fasting
C. One 15 mg tablet qd, after a high-fat breakfast

Blood samples were collected and analyzed for the R and S isomers of oxybutynin (parent drug) and the R and S isomers of desethyloxybutynin (major active metabolite).

Effect of food was evaluated using the 70%-143% criteria for C_{max} and 80%-125% criteria for AUC.

Bioequivalence between 3 x 5 mg tablets and 1 x 15 mg tablet was evaluated by determining if the 90% confidence intervals for the ratios of all the pharmacokinetic parameters (log transformed AUC_{0-24}, $AUC_{0-\infty}$, C_{max} and T_{max}) for all four analytes were within the 80%-125% bioequivalence criteria. The results are shown in Tables V to VIII.

II. Analytical Methodology

Plasma concentrations of the enantiomers of oxybutynin and desethyloxybutynin were determined by High Performance Liquid Chromatography with Multiple Reaction (LC-MS/MS). Assay validation data are presented in Tables I to IV. Sample preparation prior to assay included solid phase extraction.

Table I. Assay validation for R-oxybutynin (n = 18).

	Nominal Oxybutynin Concentrations (ng/mL)			
	0.050	0.150	1.50	7.5
Mean	0.051	0.143	1.33	7.61
Accuracy (%)	100	95.3	89.7	101
Intra-assay Precision (%CV)	7.98	2.40	3.29	2.14
Inter-assay Precision (%CV)	13.0	4.87	4.06	3.08

*The lower limit of quantitation was 0.050 ng/mL.

Table II. Assay validation for S-oxybutynin (n = 18).

	Nominal Oxybutynin Concentrations (ng/mL)			
	0.050	0.150	1.50	7.5
Mean	0.050	0.145	1.34	7.71
Accuracy (%)	100	96.7	89.3	102.8
Intra-assay Precision (%CV)	8.68	2.90	2.84	3.27
Inter-assay Precision (%CV)	7.98	10.4	4.32	4.10

*The lower limit of quantitation was 0.050 ng/mL.

Table III. Assay validation for R-desethyloxybutynin (n =18).

	Nominal Desethyloxybutynin Concentrations (ng/mL)			
	0.25	0.75	5.00	20.0
Mean	0.231	0.650	4.48	19.3
Accuracy (%)	92.2	86.7	89.6	96.4
Intra-assay Precision (%CV)	4.28	1.60	5.01	3.30
Inter-assay Precision (%CV)	4.83	1.88	3.82	2.79

*The lower limit of quantitation was 0.25ng/mL.

Table IV. Assay validation for S-desethyloxybutynin (n =18).

	Nominal Desethyloxybutynin Concentrations (ng/mL)			
	0.25	0.75	5.00	20.0
Mean	0.230	0.663	4.51	19.4
Accuracy (%)	92.2	88.4	90.2	97.0
Intra-assay Precision (%CV)	4.28	1.60	5.01	3.30
Inter-assay Precision (%CV)	6.32	3.54	4.26	3.15

*The lower limit of quantitation was 0.25ng/mL.

Reviewer Comment

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

III. Results of bioequivalence study comparing 3 x 5 mg OROS® tablets to 1 x 15 mg OROS® tablet:

Table V. Mean (±SD) Oxybutynin Pharmacokinetic Parameters Following 3 x 5 mg OROS® (oxybutynin chloride) tablets and 1 x 15 mg OROS® tablet (fasted conditions).

Parameters (units)	R-oxybutynin		S-oxybutynin	
	OROS® 3 x 5 mg (n=50)	OROS® 1 x15 mg (n=50)	OROS® 3 x 5 mg (n=50)	OROS® 1 x15 mg (n=50)
C_{max} (ng/mL)	2.79(1.3)	2.78(1.5)	4.95(2.0)	5.05(2.5)
$t_{1/2}$ (hr)	17.1(4.7)	17.1(5.2)	15.1(4.4)	14.6(4.6)
AUC_{0-24} (ng·hr/mL)	35.9(15)	35.0(18)	65.3(27)	65.3(33)
AUC_{0-inf} (ng·hr/mL)	61.3(25.0)	61.3(28.0)	113(51)	114(57)
90% Confidence Intervals* Treatment B/Treatment A				
C_{max}	91-107		92-107	
AUC_{0-24}	90-103		92-104	
AUC_{0-inf}	93-106		93-107	

* 90% confidence interval of log-transformed parameters.

Table VI. Mean (±SD) Desethyloxybutynin Pharmacokinetic Parameters Following 3 x 5 mg OROS® (oxybutynin chloride) tablets and 1 x 15 mg OROS® tablet (fasted conditions).

Parameters (units)	R-Desethyloxybutynin		S-Desethyloxybutynin	
	OROS® 3 x 5 mg (n=50)	OROS® 1 x15 mg (n=50)	OROS® 3 x 5 mg (n=50)	OROS® 1 x15 mg (n=50)
C_{max} (ng/mL)	26.5(10.7)	24.5(8.4)	14.8(5.3)	14.0(5.7)
$t_{1/2}$ (hr)	11.1(4.1)	10.3(4.6)	12.2(4.8)	13.4(12.2)
AUC_{0-24} (ng·hr/mL)	370(156)	344(125)	219(86.3)	210(98.1)
AUC_{0-inf} (ng·hr/mL)	513(228)	491(185)	333(167)	335(179)
90% Confidence Intervals* Treatment B/Treatment A				
C_{max}	87-101		93-105	
AUC_{0-24}	89-101		89-100	
AUC_{0-inf}	92-102		93-107	

* 90% confidence interval of log-transformed parameters.

IV. Results of the study evaluating the effect of food on 1 x 15 mg OROS® tablet:

Table VII. Mean (±SD) Oxybutynin pharmacokinetic parameters following the administration of 1 x 15 mg OROS® tablet (oxybutynin chloride) under fasted and fed conditions.

Parameters (units)	R-oxybutynin		S-oxybutynin	
	1 x 15 mg (fasted) (n=50)	1 x 15 mg (fed) (n=50)	1 x 15 mg (fasted) (n=50)	1 x 15 mg (fed) (n=50)
C_{max} (ng/mL)	2.78(1.5)	2.65(1.5)	5.05(2.5)	4.32(2.1)
$t_{1/2}$ (hr)	17.1(5.2)	18.3(5.3)	14.6(4.6)	15.3(5.8)
AUC_{0-24} (ng·hr/mL)	35.0(18)	34.1(17.7)	65.3(33)	57.5(27.3)
AUC_{0-inf} (ng·hr/mL)	61.3(28.0)	56.6(26.8)	114(57)	97.2(47)
90% Confidence Intervals* Treatment C/Treatment B				
C_{max}	87-103		81-94	
AUC_{0-24}	91-103		84-95	
AUC_{0-inf}	87-99		81-93	

* 90% confidence interval of log-transformed parameters.

Table VIII. Mean (±SD) Desethyloxybutynin pharmacokinetic parameters following the administration of 1 x 15 mg OROS® tablet (oxybutynin chloride) under fasted and fed conditions.

Parameters (units)	R-Desethyloxybutynin		S-Desethyloxybutynin	
	1 x 15 mg (fasted) (n=50)	1 x 15 mg (fed) (n=50)	1 x 15 mg (fasted) (n=50)	1 x 15 mg (fed) (n=50)
C_{max} (ng/mL)	24.5(8.4)	32.6(16)	14.0(5.7)	16.4(6.3)
$t_{1/2}$ (hr)	10.3(4.6)	11.4(5.6)	13.4(12.2)	13.8(8.4)
AUC_{0-24} (ng·hr/mL)	344(125)	425(216)	210(98.1)	227(93.3)
AUC_{0-inf} (ng·hr/mL)	491(185)	558(273)	335(179)	329(154)
90% Confidence Intervals* Treatment C/Treatment B				
C_{max}	119-139		110-127	
AUC_{0-24}	111-126		103-115	
AUC_{0-inf}	105-117		96-107	

* 90% confidence interval of log-transformed parameters.

Reviewer Comments:

1. Tablets (3 x 5 mg) of OROS® manufactured in Mountain View, California, appear to be bioequivalent to 1 x 15 mg tablet, manufactured in Vacaville, California. Bioequivalence was shown for both enantiomers of the parent drug (oxybutynin) as well as the active metabolite (desethyloxybutynin).
2. Food does not appear to alter the pharmacokinetics of OROS® 15 mg tablet, which is consistent with previous studies using lower strengths.

V. Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-897, Supplement 002, submitted on December 22, 1998 by Alza Corporation. Based on the criteria set forth in CFR 21 Part 320.1, OCPB/DPEII finds this NDA Supplement acceptable.

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 _____

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-897/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ORIGINAL

Reviewed. See Chem. Rev. dated 5/20/99. DTC 5/24/99

NEW CORRESP SAC 002 BC

NDA 20-897
Volume 26.1, Amendment to S-002 (15 mg dosage strength)

May 6, 1999

Sent via Fax
Sent 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: NDA 20-897 for Ditropan® XL (oxybutynin chloride) Extended Release Tablets: Amendment to S-002: Response to Request for Letter of Authorization for Printing Ink

Dear Dr. Rarick:

This amendment to S-002 contains an updated letter of authorization from [ ] allowing ALZA to reference their DMF[ ] for information supporting the use of [ ]. This amendment is submitted as requested by FDA in a telephone conversation between Dr. David Lin, FDA, and Betty Clark, ALZA.

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 this submission.

Please feel free to contact me by phone at (650) 237-2519 or Ms Mirka Dunn, Sr. Director of Regulatory Affairs at (650) 237-2524 if you have any questions or comments. We share the same facsimile number, (650) 237-2581.

Sincerely,

Elizabeth A. Clark

Elizabeth (Betty) A. Clark
Director
Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
AMC 5/24/99
CSO INITIALS DATE

ALZA CORPORATION 950 PAGE MILL ROAD P.O. BOX 10950 PALO ALTO CA 94303-0802 PHONE 650.494.5000 http://www.alza.com

ORIGINAL

Reviewed
See Chem Rev.
dated 5/20/99
DTC
5/24/99

NDA SUPP AMEND
S-002-BC

NDA 20-897
Volume 25.1, Amendment to S-002 (15 mg dosage strength)

April 28, 1999

Sent 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: NDA 20-897 for Ditropan® XL (oxybutynin chloride) Extended Release Tablets: Amendment to S-002: Response to Request for Updated Stability Data for the 15 mg Strength

Dear Dr. Rarick:

This amendment to S-002 contains updated stability data for the 15 mg dosage strength tablet. This amendment is submitted as requested by FDA in a telephone conversation between Dr. David Lin, FDA, and Ms. Janne Wissel, ALZA. The enclosed data continue to support a 24 month expiry dating for the 15 mg product.

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 this submission.

Please feel free to contact me by phone at (650) 237-2519 or Ms Mirka Dunn, Sr. Director of Regulatory Affairs at (650) 237-2524 if you have any questions or comments. We share the same facsimile number, (650) 237-2581.

Sincerely,

Elizabeth A. Clark

Elizabeth (Betty) A. Clark
Director
Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-897/S-002

Alza Corporation
950 Page Mill Road P.O. Box 10950
Palo Alto, CA 94303-0802

DEC 30 1998

Attention: Janne Wissel
Senior Vice President

Dear Ms. Wissel:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Ditropan® XL (oxybutynin chloride) Extended Release Tablets
NDA Number:	20-897
Supplement Number:	S-002
Date of Supplement:	December 22, 1998
Date of Receipt:	December 28, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 26, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

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

Sincerely,

Lana Pauls
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-897/S-002
HFD-580/Div. Files
HFD-580/CSO/R. Olmstead

SUPPLEMENT ACKNOWLEDGEMENT

ORIGINAL

NDA NO. 20897 REF. NO. 002
NDA SUPPL FOR SE2

Reviewed
April 5, 1999
Sam H. Haidar

Note 6

NDA 20-897 Volumes 16.1-16.19

reviewed
Sue Chen. Rev.
Started 5/25/99.
Approved.
DTC
5/25/99

4/4/99

December 22, 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: Supplemental New Drug Application (NDA) 20-897 for Ditropan® XL (oxybutynin chloride) Extended Release Tablets – Addition of a 15 mg Dosage Strength

Dear Dr. Rarick:

ALZA Corporation is submitting this supplemental New Drug Application for Ditropan® XL (oxybutynin chloride) Extended Release Tablets to add a new dosage strength. Ditropan® XL tablets, at dosages of up to 30 mg per day, are approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The original NDA 20-897, approved on December 16, 1998, included information on two dosage strengths (5 and 10 mg). This application requests the approval of an additional dosage strength, 15 mg.

The 5, 10, and 15 mg dosage forms are extended release oral tablets incorporating the OROS® push-pull technology. The compositions of the three dosage strengths are qualitatively similar and utilize the same mechanism for drug release. All three tablets are the same size and shape; the different dosage strengths are achieved by the proportion of drug in the drug layer of the bilayer tablet core. In vitro drug release is proportionally similar for the three dosage strengths. Approval of the 15 mg tablet is therefore supported by the information already reviewed and approved for the 5 and 10 mg tablets.

ALZA CORPORATION 950 PAGE MILL ROAD P.O. BOX 10950 PALO ALTO CA 94303-0802 PHONE 650.494.5000 http://www.alza.com

alza

NDA 20-897
Volumea 16.1-16.19

This application contains chemistry, manufacturing, and control information specific to the 15 mg dosage strength, as well as the results of a bioequivalence and food effect study in support of the new dosage strength.

Please feel free to contact me at (650) 962-4282 if you have any questions or comments concerning this supplement. If you cannot reach me directly, please contact Ms. Mirka Dunn, Senior Director, Regulatory Affairs at (650) 237-2524. We share the same facsimile number, (650) 237-2581.

Sincerely,

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS 6/22/04 DATE