CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78-503

Name: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 mg

Sponsor: Osmotica Pharmaceutical Corp.

Approval Date: February 4, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-503

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-503

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-503

Osmotica Pharmaceutical Corp.
Attention: Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs
1205 Culbreth Drive, Suite 200
Wilmington, NC 28405

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 20, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 mg.

Reference is also made to your amendments dated April 24, July 5, August 29, October 19, and December 11, 2007; July 24, November 24, and December 15, 2008; and January 7, and January 13, 2009.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Ditropan XL Extended-release Tablets, 5 mg, 10 mg, and 15 mg, respectively, of Ortho McNeil Janssen Pharmaceutica Products LP. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The "interim" dissolution specifications are as follows:

Dissolution testing should be conducted according to USP 30, in 50 mL of simulated gastric fluid without enzymes at 37°C, using USP apparatus 7, 30 cycles per minute; 2- to 3-

cm amplitude. The test product should meet the following "interim" specifications:

Time (hours)	Percent Dissolved
4	NMT 25
10	40-65
24	NLT 75

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement – Changes Being Effected" if there are no revisions to be made to the "interim" specifications, or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, Ortho McNeil's Ditropan XL Extended-release Tablets, is subject to periods of patent protection. The following patents and their expiration dates (with pediatric exclusivity added) are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
5,674,895 (the '895 patent)	November 22, 2015
5,840,754 (the '754 patent)	November 22, 2015
5,912,268 (the '268 patent)	November 22, 2015
6,262,115 (the '115 patent)	November 22, 2015
6,919,092 (the '092 patent)	November 22, 2015

With respect to each of these patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 mg, under this ANDA. You notified the agency that Osmotica Pharmaceutical Corp. (Osmotica) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of any of these patents was brought against Osmotica within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(2)(B)(iii).

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National

Library of Medicine for public dissemination. For administrative purposes, please designate this submission as ***"Miscellaneous Correspondence - SPL for Approved ANDA 78-503".***

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
2/4/2009 02:45:38 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-503

LABELING

8597

Oxybutynin Chloride Extended-Release Tablets USP

4008597
Rx Only Rev. 02/08

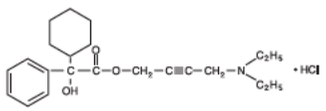
Prescribing Information

DESCRIPTION

Oxybutynin chloride extended- elease tablets a e an antispasmodic, anticholinergic agent. Each Oxybutynin chloride extended-release tablet contains 5 mg, 10 mg, or 15 mg of oxybutynin chloride USP, formulated as a once-a-day extended- elease tablet for oral administ ation. Oxybutynin chloride is administered as a racemate of R- and S-enantiomers.

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

Its structu al formula is:



Oxybutynin chloride is a white crystalline solid wi h a molecular weight of 393 9. It is readily soluble in water and acids, but elatively insoluble in alkalis.

Oxybutynin chloride extended-release tablets also contain the following inert ingredients: anhydrous lactose, lactose monohydrate, mannitol, anhydrous dext ose, tartaric acid, colloidal silicon dioxide, magnesium stearate, cellulose acetate, polyethylene glycol, titanium dioxide, triacetin, black iron oxide, propylene glycol, hypromellose.

System Components and Perfonnance

Oxybutynin chloride extended-release tablets 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 co e surrounded by a semipermeable membrane. The unitary tablet co e is composed of he drug and excipients (including he osmotically active components). There is a precision-laser drilled orifice in he semipermeable membrane on the side of he tablet. In an aqueous environment, such as the gast ointestinal t act, water permeates th ough the memb ane into the tablet core, causing he drug to go into suspension and he osmotic components to expand. This expansion pushes he drug out hrough the orifice. The semipermeable membrane controls the rate at which water permeates into the tablet core, which in tu n controls he rate of drug delivery. The controlled rate of drug delivery into he gastrointestinal lumen is hus independent of pH or gastrointestinal motility. The function of Oxybutynin chloride extended- elease tablets depends on he existence of an osmotic g adient between he contents of he core and the fluid in the gastrointestinal tract. Since the osmotic gradient emains constant, drug delivery remains essentially constant. The biologically inert components of he tablet remain intact du ing gastrointestinal transit and a e eliminated in he feces as an insoluble shell.

CLINICAL PHARMACOLOGY

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

Oxybutynin chloride elaxes bladder smooth muscle. In patients w th conditions characterized by involuntary bladder cont actions, cystometric studies have demonstrated that oxybutynin increases bladder (vesical) capacity, diminishes he frequency of uninhibited cont actions of the detrusor muscle, and delays the initial desire to void. Oxybutynin thus decreases urgency and the f equency of bo h incontinent episodes and voluntary urination.

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

Pharmacokinetics

Absorption

Following the first dose of Oxybutynin chloride extended- elease tablets, oxybutynin plasma concentrations rise for 4 to 6 hours; he eafter steady concent ations a e maintained for up to 24 hou s, minimizing fluctuations between peak and t ough concent ations associated wi h oxybutynin.

The relative bioavailabilities o R- and S-oxybutynin from Oxybutynin chloride extended-release tablets are 156% and 187%, respectively, compa ed w th 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 a e similar in shape; Figure 1 shows he profile for R-oxybutynin.

Table 1
Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following a Single Dose of Oxybutynin chloride extended-release tablets 10 mg (n=43)

Paramete s (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)
$AUC_{(0\text{-}48)}$ (ng•h/mL)	18.4	(10 3)	34.2	(16.9)
AUC_{∞}(ng•h/mL)	21 3	(12 2)	39.5	(21.2)

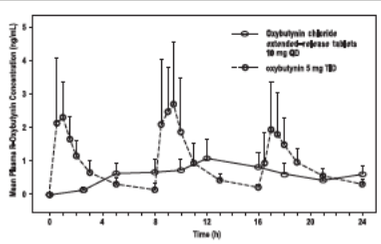


Figure 1. *Mean R-oxybutynin plasma concentrations following a single dose of Oxybutynin chloride extended-release tablets 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment).*

Steady-state oxybutynin plasma concentrations a e achieved by Day 3 of epeated Oxybutynin chloride extended-release tablets dosing, wi h no observed drug accumulation or change in oxybutynin and dese hyloxybutynin pharmacokinetic parame s.

Oxybutynin chloride extended- elease tablets steady-state pharmacokinetics we e studied in 19 children aged 5-15 yea s w th detrusor overactivity associated w th a neu ological condition (e.g., spina bifida). The child en were on Oxybutynin chloride extended-release tablets total daily dose anging f om 5 to 20 mg (0.10 to 0 77 mg/kg). Sparse sampling technique was used to obtain serum samples. When all available data are normalized to an equivalent of 5 mg per day Oxybutynin chloride extended-release tablets, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 2. The plasma-time concentration p ofiles for R- and S-oxybutynin are similar in shape; Figu e 2 shows the profile for R-oxybutynin when all available data a e normalized to an equivalent of 5 mg per day.

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

	R-Oxybutynin	S-Oxybutynin	R-Dese hyloxybutynin	S-Desethyloxybutynin
C_{max} (ng/mL)	0 7 ± 0.4	1.3 ± 0.8	7.8 ± 3.7	4 2 ± 2 3
T_{max} (hr)	5	5	5	5
AUC(ng•hr/mL)	12.8 ± 7 0	23.7 ± 14.4	125 1 ± 66 7	73 6 ± 47 7

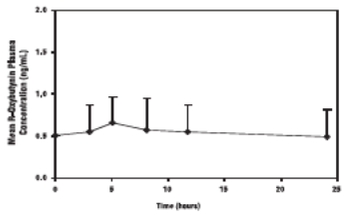


Figure 2. *Mean steady-state (±SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg Oxybutynin chloride extended-release tablets once daily in children aged 5-15. Plot represents all available data normalized to an equivalent of Oxybutynin chloride extended-release tablets 5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

Food Effects

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

Distribution

Plasma concent ations of oxybutynin decline biexponentially following int avenous or oral administ ation. 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 Oxybutynin chloride extended- elease tablets administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, espectively, of concentrations obse ved w th oxybutynin.

Excretion

Oxybutynin is extensively metabolized by the liver, wi h less than 0 1% of the administe ed dose excreted unchanged in the urine. Also, less than 0 1% of the administered dose is excreted as he metabolite desethyloxybutynin.

Dose Proportionality

Pharmacokinetic paramete s of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of 5-20 mg of Oxybutynin chloride extended- elease tablets a e dose proportional.

Special Populations

Geriatric: The pharmacokinetics of Oxybutynin chloride extended-release tablets were similar in all patients studied (up to 78 years of age).

Pediatric: The pharmacokinetics of Oxybutynin chloride extended-release tablets were evaluated in 19 children aged 5-15 years w th detrusor overactivity associated wi h a neu ological condition (e g., spina bifida). The pharmacokinetics of Oxybutynin chloride extended-release tablets in hese pediatric patients were consistent wi h hose eported for adults (see Tables 1 and 2, and Figu es 1 and 2 above).

Gender: There are no significant diffe ences in the pharmacokinetics of oxybutynin in hea thy male and female volunteer s following administ ation of Oxybutynin chloride extended-release tablets.

Race: Available data suggest that there a e no significant differences in the pharmacokinetics of oxybutynin based on ace in heal hy volunteers following administ ation of Oxybutynin chloride extended-release tablets.

Renal Insufficiency: There is no experience wi h he use of Oxybutynin chloride extended-release tablets in patients w th renal insufficiency.

Hepatic Insufficiency: There is no experience w th the use of Oxybutynin chloride extended-release tablets in patients w th hepatic insufficiency.

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

CLINICAL STUDIES

Oxybutynin chloride extended-release tablets we e evaluated for the t eatment of patients with overactive bladder wi h symptoms of urge urinary incontinence, urgency, and f equency in three cont olled studies and one open label study. The majority of patients we e Caucasian (89 0%) and female (91.9%) w th a mean age of 59 years (range, 18 to 98 yea s). Entry criteria required that patients have u ge or mixed incontinence (wi h a p edominance of urge) as evidenced by ≥ 6 urge incontinence episodes per week and ≥ 10 micturitions per day. Study 1 was a fixed 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 imp ovement of incontinence symptoms and tolerability of side effects. Cont olled studies included patients known to be esponsive to oxybutynin or other anticholinergic medications, and hese patients were maintained on a final dose for up to 2 weeks.

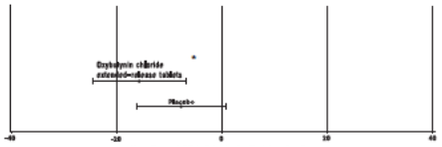
The efficacy results for the th ee cont olled trials are p esented in the following tables and figu es.

Number of Urge Urinary Incontinence Episodes Per Week

Study 1	n	Oxybutynin chloride extended-release tablets	n	Placebo
Mean Baseline Mean (SD) Change	34	15 9	16	20.9
from Baseline†	34	-15.8 (8 9)	16	-7 6 (8 6)
95% Confidence Interval for Diffe ence (Oxybutynin chloride extended-release tablets – Placebo)		(-13 6, -2.8)*		

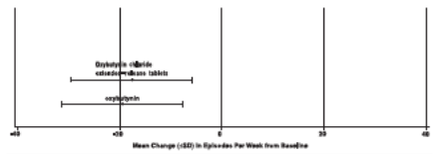
*The diffe ence between Oxybutynin chloride extended-release tablets and placebo was statistically significant.

†Covariate adjusted mean w th missing observations set to baseline values



Study 2	n	Oxybutynin chloride extended-release tablets	n	oxybutynin
Mean Baseline Mean (SD) Change	53	27 6	52	23 0
from Baseline†	53	-17 6 (11 9)	52	-19.4 (11 9)
95% Confidence Inte val for Difference (Oxybutynin chloride extended- release tablets – oxybutynin)		(-2.8, 6 5)		

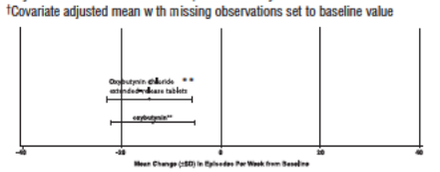
†Covariate adjusted mean wi h missing observations set to baseline values



Study 3	n	Oxybutynin chloride extended-release tablets	n	oxybutynin
Mean Baseline Mean (SD) Change	111	18 9	115	19.5
from Baseline†	111	-14.5 (8 7)	115	-13 8 (8 6)
95% Confidence Inte val for Difference (Oxybutynin chloride extended- release tablets – oxybutynin)		(-3 0, 1.6)**		

**The diffe ence between Oxybutynin chloride extended-release tablets and oxybutynin fulfilled he criteria for comparable efficacy.

†Covariate adjusted mean w th missing observations set to baseline value



INDICATIONS AND USAGE

Oxybutynin chloride extended- elease tablets a e a once-daily extended-release tablet indicated for the t eatment of overactive bladder wi h symptoms of u ge urinary incontinence, u gency, and frequency.

Oxybutynin chloride extended-release tablets a e also indicated in the t eatment of pediatric patients aged 6 yea s and older w th symptoms of detrusor overactivity associated w th a neurological condition (e g., spina bifida).

CONTRAINDICATIONS

Oxybutynin chloride extended- elease tablets a e cont aindicated in patients wi h urinary etention, gastric etention and other severe decreased gast ointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride extended- elease tablets are also cont aindicated in patients who have demonstrated hypersensitivity to he drug substance or other components of the p oduct.

PRECAUTIONS

Central Nervous System Effects

Oxybutynin is associated wi h anticholinergic central nervous system (CNS) effects (See **ADVERSE REACTIONS**). A variety of CNS anticholinergic effects have been reported, including hallucinations, agitation, confusion and somnolence. Patients should be monitored for signs of anticholine gic CNS effects, particularly in the first few months after beginning treatment or increasing he dose. If a patient experiences anticholinergic CNS effects, dose eduction or drug discontinuation should be considered.

Oxybutynin chloride extended- elease tablets should be used with caution in patients wi h p eexisting dementia t eated wi h cholineste ase inhibito s due to the risk of aggravation of symptoms.

General

Oxybutynin chloride extended- elease tablets should be used with caution in patients w th hepatic or enal impairment and in patients w th myasthenia g avis due to he risk of symptom aggravation.

Urinary Retention

Oxybutynin chloride extended-release tablets should be administered w th caution to patients w th clinically significant bladder outflow obstruction because of he risk of urinary etention (see **CONTRAINDICATIONS**).

Gastrointestinal Disorders

Oxybutynin chloride extended-release tablets should be administered w th caution to patients wi h gast ointestinal obstructive diso ders because of he risk of gastric retention (see **CONTRAINDICATIONS**).

Oxybutynin chloride extended-release tablets, like o her anticholinergic drugs, may decrease gastrointestinal motility and should be used wi h caution in patients w th conditions such as ulce ative colitis and intestinal atony.

Oxybutynin chloride extended- elease tablets should be used with caution in patients who have gast oesophageal eflux and/or who are concurrently taking drugs (such as bisphosphonates) hat can cause or exace bate esophagitis.

As wi h any o her nondeformable material, caution should be used when administering Oxybutynin chloride extended-release tablets to patients w th p eexisting severe gast ointestinal nar owing (pathologic or iatrogenic). The e have been are eports of obstructive symptoms in patients w th known strictures in association wi h the ingestion of other drugs in nondeformable extended-release formulations.

Information for Patients

Patients should be informed that heat p ostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride a e administered in the p esence of high envi onmental temperature.

Because anticholinergic agents such as oxybutynin may p oduce 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 Oxybutynin chloride extended-release tablets should be swallowed whole wi h he aid of liquids Patients should not chew, divide, or crush tablets. The medication is contained wi hin a nonabsorbable shell designed to release the drug at a cont olled rate. The tablet shell is eliminated from the body; patients should not be concerned if hey occasionally notice in their stool something that looks like a tablet. Oxybutynin chloride extended- release tablets should be taken at approximately the same time each day.

Drug Interactions

The concomitant use of oxybutynin w th other anticholinergic drugs or w th o her agents which p oduce dry mouth, constipation, somnolence (drowsiness), and/or o her anticholinergic-like effects may increase he frequency and/or severity of such effects. Anticholine gic agents may potentially alter the absorption of some concomitantly administe ed drugs due to anticholinergic effects on gast ointestinal motility. This may be of conce n for drugs w th a narrow herapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 2 fold higher when Oxybutynin chloride extended-release tablets we e administered w th ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of he cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., eryth omycin and clar th omycin), may alter oxybutynin mean pharmacokinetic parameters (i e., C_{max} and AUC). The clinical elevance of such potential interactions is not known. Caution should be used when such drugs are co-administe ed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-mon h study in ats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are app oximately 6, 25, and 50 times he maximum human exposure, based on surface a ea. Oxybutynin chloride showed no inc ease of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems. Reproduction studies wi h oxybutynin chloride in the mouse, rat, hamster, and abbit showed no definite evidence of impaired fertility.

Pregnancy: Teratogenic Effects

Pregnancy Category B

Rep oduction studies w th oxybutynin chloride in he mouse, at, hamster, and abbit showed no definite evidence of impai ed fertility or harm to he animal fetus. The safety of Oxybutynin chloride extended- elease tablets administration to women who a e or who may become p egnant has not been established. Therefo e, Oxybutynin chloride extended-release tablets should not be given to pregnant women unless, in he judgment of he physician, he probable clinical benefits outweigh the possible haza ds.

Nursing Mothers

It is not known whether oxybutynin is exc eted in human milk Because many drugs are excreted in human milk, caution should be exercised when Oxybutynin chloride extended-release tablets are administe ed to a nursing woman.

Pediatric Use

The safety and efficacy of Oxybutynin chloride extended- elease tablets were studied in 60 children in a 24-week, open-label trial. Patients we e aged 6-15 years, all had symptoms of detrusor overactivity in association wi h a neu ological condition (e g., spina bifida), all used clean intermittent ca heterization, and all were cur ent use s of oxybutynin chloride. Study results demonstrated hat administ ation of Oxybutynin chloride extended-release tablets 5 to 20 mg/day was associated w th an increase from baseline in mean u ine volume per catheterization from 108 mL to 136 mL, an inc ease from baseline in mean urine volume after morning awakening from 148 mL to 189 mL, and an inc ease from baseline in he mean pe centage of catheterizations wi hout a leaking episode from 34% to 51%.

Urodynamic results were consistent w th clinical results. Administration of Oxybutynin chloride extended- elease tablets resulted in an inc ease f om baseline in mean maximum cystometric capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor p essu e at maximum cystometric capacity from 44 cm H_2O to 33 cm H_2O, and a eduction in he percentage of patients demonst ating uninhibited detrusor contractions (of at least 15 cm H_2O) f om 60% to 28%.

Oxybutynin chloride extended-release tablets a e not ecommended in pediatric patients who can not swallow the tablet whole w thout chewing, dividing, or crushing, or in children under he age of 6 (See **DOSAGE AND ADMINISTRATION**).

Geriatric Use

The rate and severity of anticholine gic effects eported by patients less han 65 years old and those 65 yea s and older were similar (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**, ***Special Populations:*** *Geriatric*).

ADVERSE REACTIONS

Adverse Events with Oxybutynin chloride extended-release tablets

The safety and efficacy of Oxybutynin chloride extended-release tablets were evaluated in a total of 580 participants who received Oxybutynin chloride extended-release tablets in 4 clinical trials (429 patients) and four pharmacokinetic studies (151 hea thy voluntee s). The 429 patients were treated wi h 5-30 mg/day for up to 4.5 months. Three of the 4 clinical trials allowed dose adjustments based on efficacy and adverse events and one was a fixed dose escalation design. Safety information is provided for 429 patients from these three controlled clinical studies and one open label study in the first column of Table 3 below.

Adve se events from two additional fixed dose, active controlled, 12 week treatment duration, postmarketing studies, in which 576 patients we e treated wi h Oxybutynin chloride extended-release tablets 10 mg/day, a e also listed in Table 3 (second column). The adverse events a e reported rega dless of causality.

Table 3

Incidence (%) of Adverse Events Reported by ≥ 5% of Patients Using Oxybutynin chloride extended-release tablets (5-30 mg/day) and % of Corresponding Adverse Events in Two Fixed Dose (10 mg/day) Studies

Body System	Adverse Event	Oxybutynin chloride extended-release tablets 5-30 mg/day (n=429)	Oxybutynin chloride extended-release tablets 10 mg/day (n=576)
General	headache	10	6
	asthenia	7	3
	pain	7	4
Digestive	dry mouth	61	29
	constipation	13	7
	diar hea	9	7
	nausea	9	2
	dyspepsia	7	5
Ne vous	somnolence	12	2
	dizziness	6	4
Respiratory	hinitis	6	2
Special Senses	blurred vision	8	1
	dry eyes	6	3
Urogenital	urinary tract infection	5	5

The most common adverse events reported by the 429 patients receiving 5-30 mg/day Oxybutynin chloride extended-release tablets we e he expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

The discontinuation rate for all adverse events was 6 8% in the 429 patients from the 4 studies of efficacy and safety who received 5-30 mg/day. The most f equent adve se event causing early discontinuation of study medication was nausea (1 9%), while discontinuation due to dry mou h was 1.2%.

In addition, the following adverse events we e reported by ≥1 to < 5% of all patients who eceived Oxybutynin chloride extended-release tablets in he 6 adjustable and fixed dose efficacy and safety studies. *Infections and infestations:* nasopharyngitis, upper respiratory tract infection, sinusitis, b onchitis, cystitis; *Psychiatric disorders:* insomnia, dep ession, nervousness, confusional state; *Nervous System Disorders:* dysgeusia; *Cardiac disorders:* palpitations; *Vascular disorders:* hypertension; *Respiratory, thoracic and mediastinal disorders:* nasal dryness, cough, pharyngolaryngeal pain, dry throat; *Gastrointestinal Disorders:* gast oesophageal reflux disease, abdominal pain, loose stools, flatulence, vomiting; *Skin and subcutaneous tissue disorders:* dry skin, pruritis; *Musculoskeletal and connective tissue disorders:* back pain, ar hralgia, pain in extremity; *Renal and urinary disorders:* urinary retention, urinary hesitation, dysuria; *General disorders and administration site conditions:* fatigue, edema peripheral, as henia, chest pain; *Investigations:* blood pressu e increased.

Postmarketing Surveillance

Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate heir frequency or establish a causal relationship to drug exposure. The following additional adverse drug reactions have been eported from worldwide postmarketing experience w th Oxybutynin chloride extended-release tablets: *Psychiatric Disorders:* psychotic disorder, agitation, hallucinations; *Nervous System Disorders:* convulsions; *Cardiac Disorders:* ar hythmia; tachycardia; *Vascular Disorders:* flushing; *Skin and Subcutaneous Tissue Disorders:* rash; *Renal and Urinary Disorders:* impotence; *Injury, poisoning and procedural complications:* fall.

Additional adverse events eported wi h some other oxybutynin chloride formulations include: cycloplegia, mydriasis, and supp ession of lactation.

OVERDOSAGE

The continuous release of oxybutynin f om Oxybutynin chloride extended-release tablets should be considered in the t eatment of overdosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. Activated cha coal as well as a ca hartic may be administered.

Ove dosage wi h oxybutynin chloride has been associated w th anticholinergic effects including central nervous system excitation, flushing, fever, dehyd ation, cardiac ar hythmia, vomiting, and urinary retention.

Ingestion of 100 mg oxybutynin chloride in association w th alcoho 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 ar hythmia, and retention of urine. Both patients fully recovered w th symptomatic treatment.

DOSAGE AND ADMINISTRATION

Oxybutynin chloride extended-release tablets must be swallowed whole w th he aid of liquids, and must not be chewed, divided, or crushed. Oxybutynin chloride extended- elease tablets may be administered wi h or w thout food.

Adults: The recommended starting dose of Oxybutynin chloride extended-release tablets is 5 or 10 mg once daily at approximately the same time each day. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tole ability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.

Pediatric patients aged 6 yea s of age and older: The recommended starting dose of Oxybutynin chloride extended-release tablets is 5 mg once daily at approximately the same time each day. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

HOW SUPPLIED

Oxybutynin Chloride Extended Release Tablets USP 5 mg a e round, biconvex, white coated tablets imprinted in black ink w th 270 on one side and K and U on the o her side.

They are supplied as follows:

Bottles of 30 Tablets	NDC 62175-270-32
Bottles of 100 Tablets	NDC 62175-270-37
Bottles of 500 Tablets	NDC 62175-270-41
Bottles of 1000 Tablets	NDC 62175-270-43

Oxybutynin Chloride Extended-Release Tablets USP 10 mg are ound, biconvex, white coated tablets imprinted in black ink w th 271 on one side and K and U on the o her side.

They are supplied as follows:

Bottles of 30 Tablets	NDC 62175-271-32
Bottles of 100 Tablets	NDC 62175-271-37
Bottles of 500 Tablets	NDC 62175-271-41
Bottles of 1000 Tablets	NDC 62175-271-43

Oxybutynin Chloride Extended-Release Tablets USP 15 mg are ound, biconvex, white coated tablets imprinted in black ink w th 272 on one side and K and U on the o her side.

They are supplied as follows:

Bottles of 30 Tablets	NDC 62175-272-32
Bottles of 100 Tablets	NDC 62175-272-37
Bottles of 500 Tablets	NDC 62175-272-41
Bottles of 1000 Tablets	NDC 62175-272-43

Storage

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

For Medical Information

Contact: Medical Affai s Department
Phone: (866) 822-0068
Fax: (770) 970-8859

Distributed by:

KREMERS-URBAN

Kremers Urban, LLC
Seymour, N 47274, USA

for:

Osmotica Pharmaceutical

Wilmington, NC 28405, USA

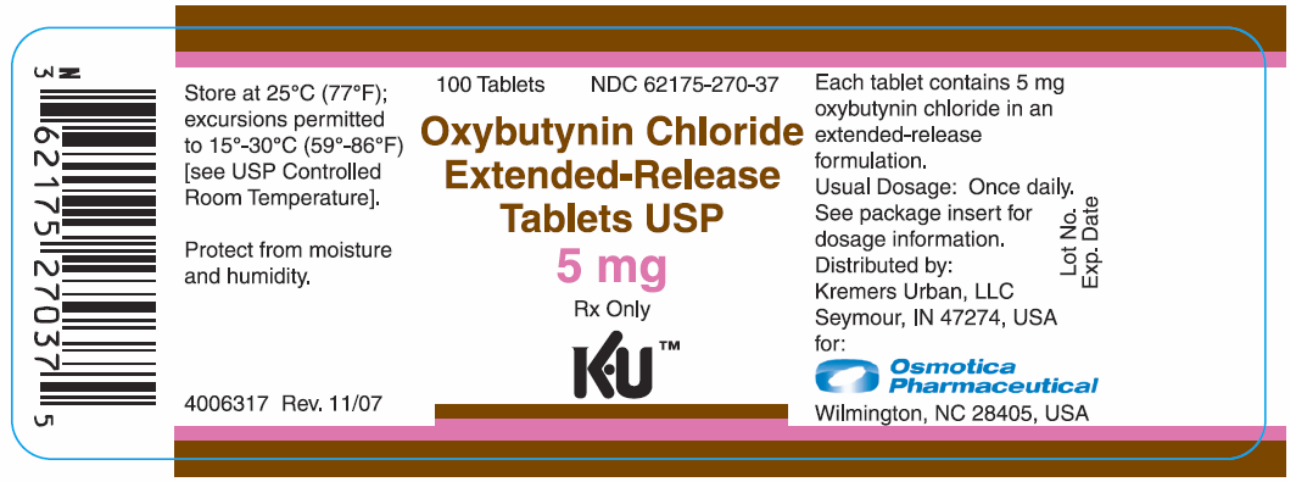
4008597 Rev. 02/08

1.14.2.1 Final Carton or Container Labels

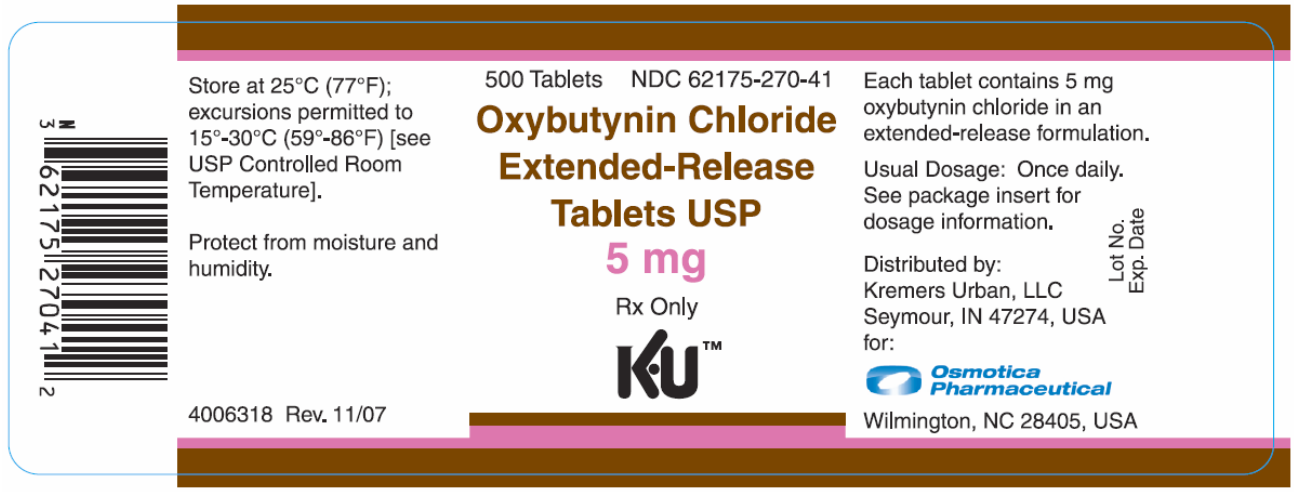
The commercial packaging configurations are 30, 100, 500, and 1,000 tablet counts for each label strength. The Final Printed Labels for the containers (bottles) are provided.

5 mg 30 Tablet Count

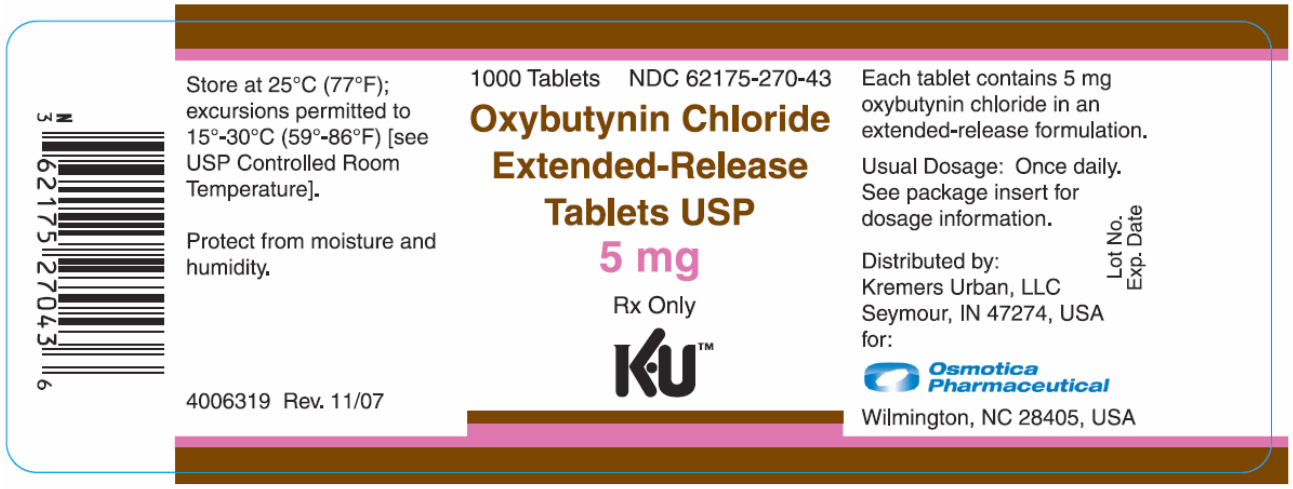
5 mg 100 Tablet Count



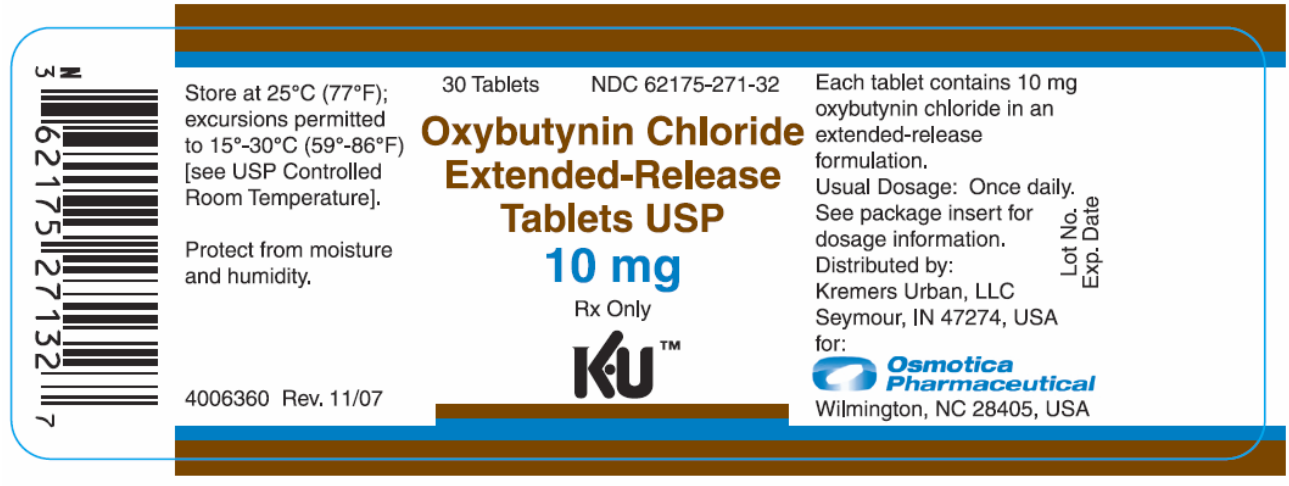
5 mg 500 Tablet Count



5 mg 1000 Tablet Count

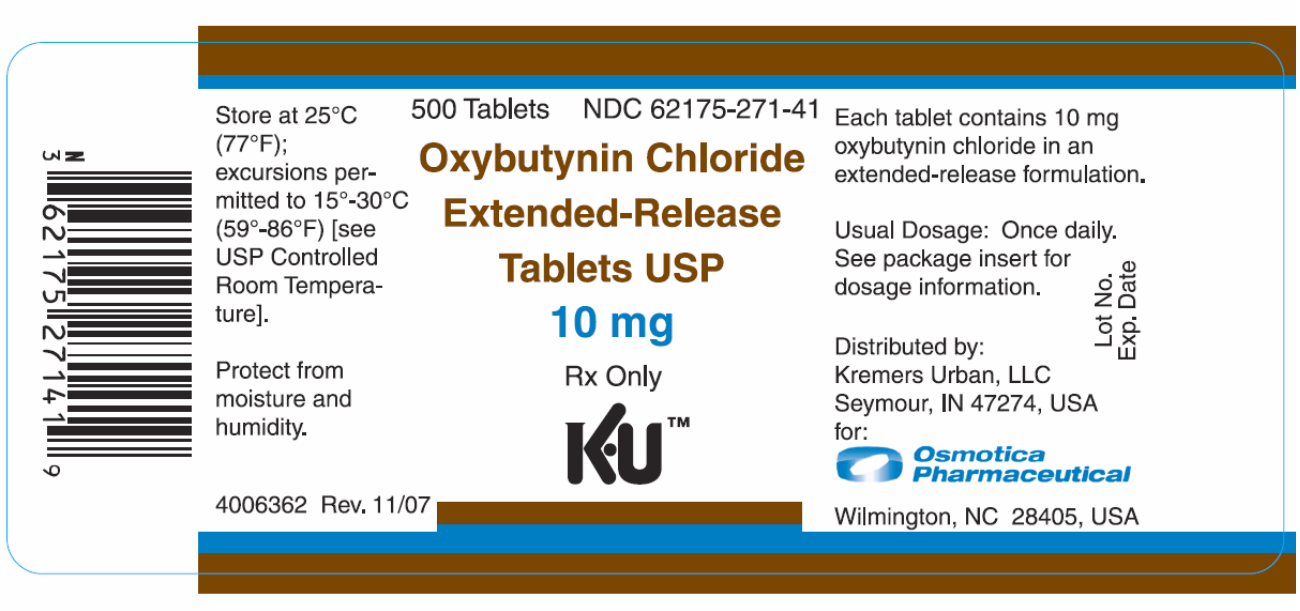


10 mg 30 Tablet Count

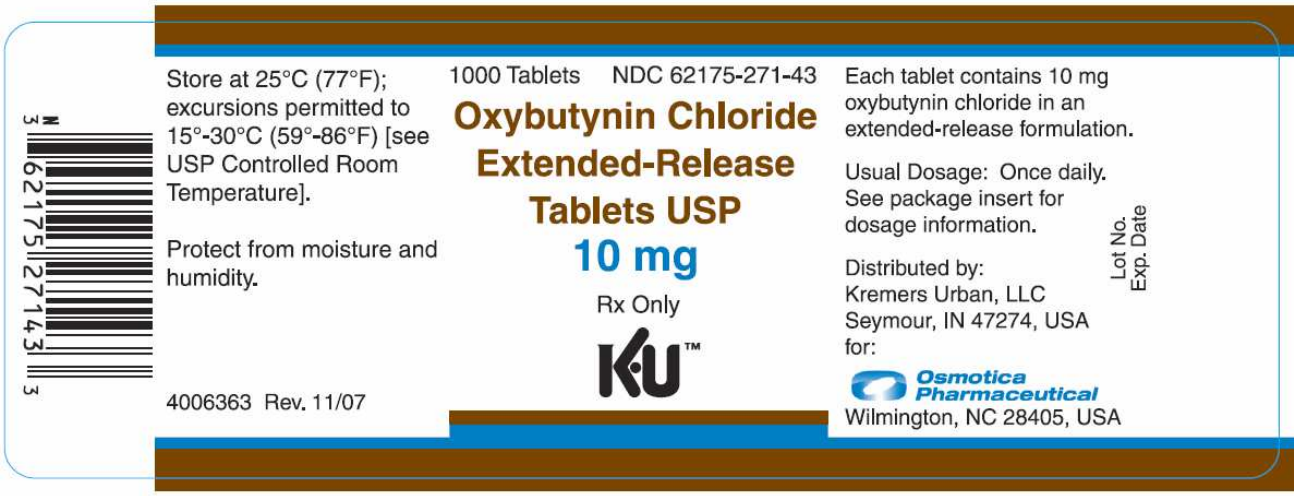


10 mg 100 Tablet Count

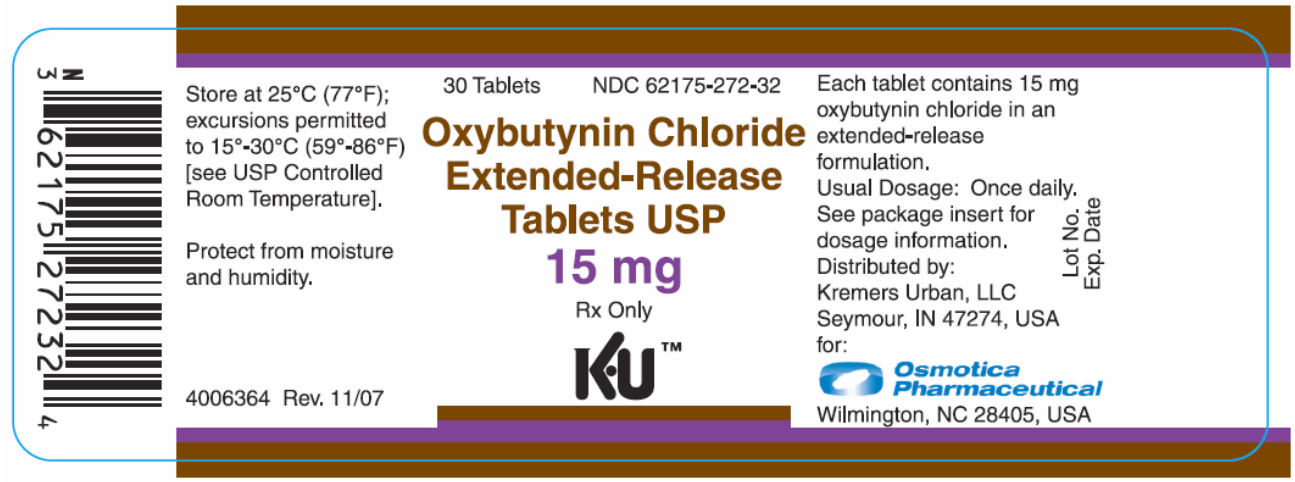
10 mg 500 Tablet Count



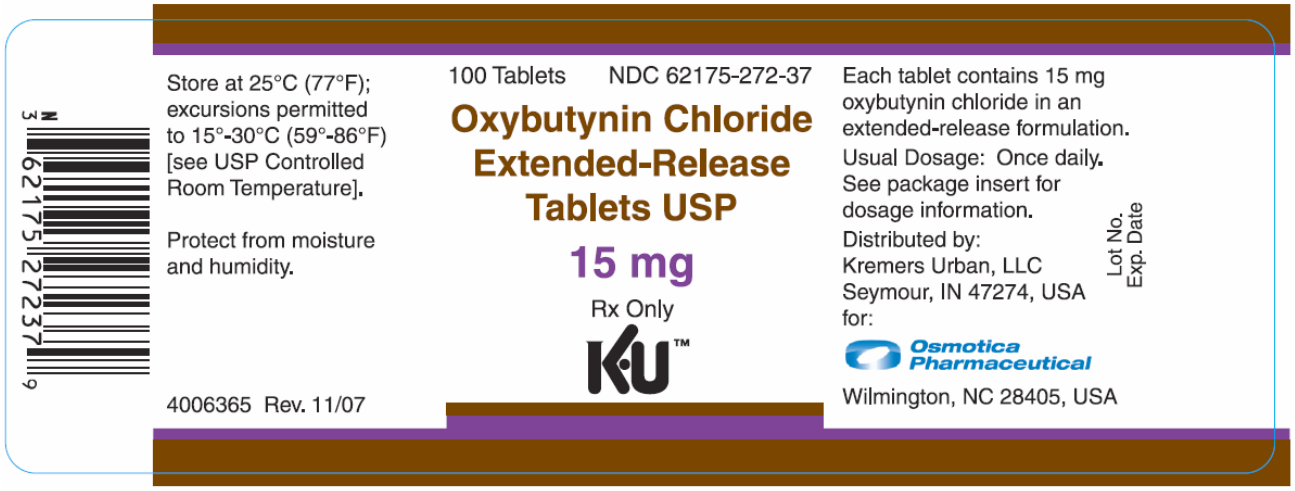
10 mg 1000 Tablet Count



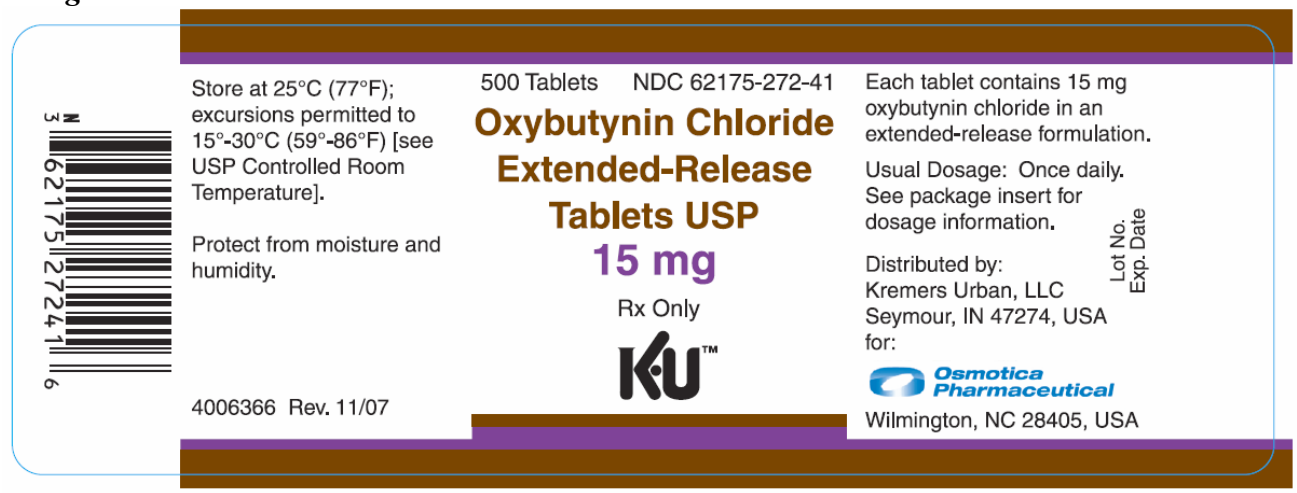
15 mg 30 Tablet Count



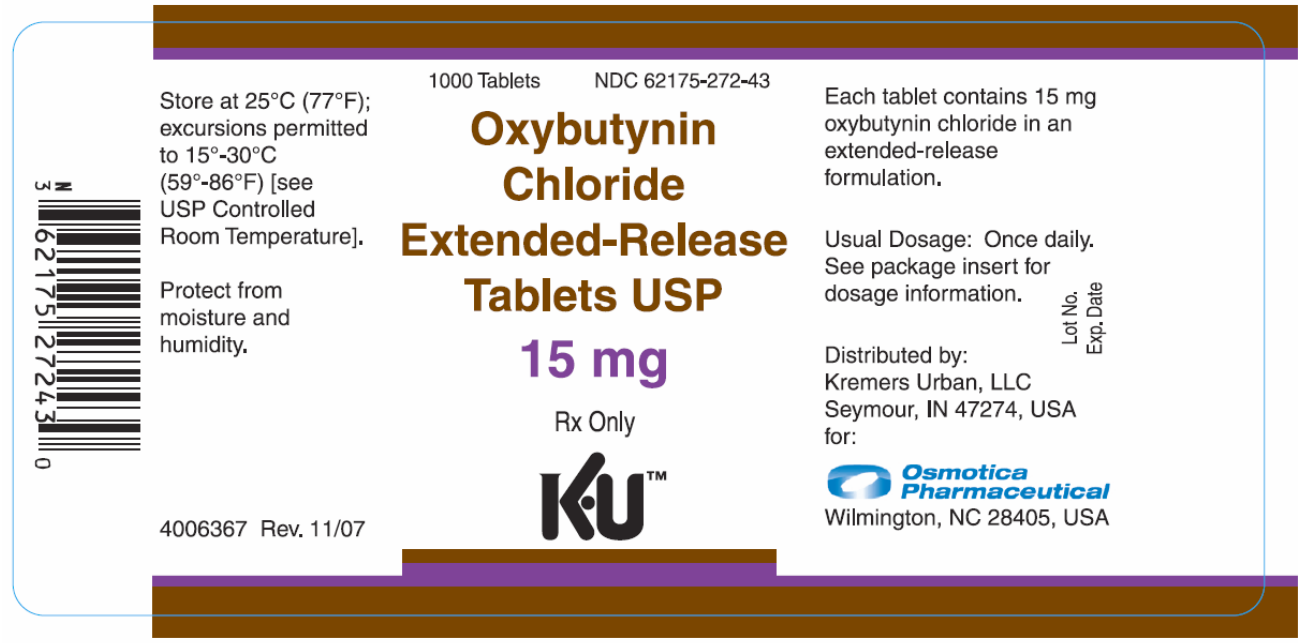
15 mg 100 Tablet Count



15 mg 500 Tablet Count



15 mg 1000 Tablet Count



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-503

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	78-503	Date of Submission:	October 20, 2006
Applicant's Name:	Osmotica Pharmaceutical Corp.		
Established Name:	Oxybutinin Chloride Extended-release Tablets USP, 5 mg, 10 mg and 15 mg		

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1. CONTAINER (All strengths in bottles 30, 100, 500 and 1000)

Satisfactory in draft. We encourage the use of boxing, contrasting colors or other means to differentiate the 10 mg and 15 mg strengths of your product.

2. INSERT

a. In the DESCRIPTION section revise “lactose” to read “anhydrous lactose and lactose monohydrate” and “dextrose” to read “anhydrous dextrose”.
b. Insert the following as inactive ingredients: (b) (4).
c. In the Table 2 of the CLINICAL PHARMACOLOGY section revise “5.0” to read “5”
d. In the CONTRAINDICATIONS section the second sentence should begin a new paragraph.
e. In the first sentence of the second paragraph of the PRECAUTIONS: Drug Interactions subsection revise “was” to read “were”
f. Throughout the insert revise the sentences that read, “Oxybutynin Chloride Extended-release Tablets (oxybutynin chloride) is…” to read “Oxybutynin chloride extended-release tablets are…”

3. GENERAL COMMENT

Revise the established name on all labeling to read “Oxybutynin Chloride Extended-Release Tablets USP”.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

BASIS OF APPROVAL:

APPROVAL SUMMARY
Container Labels: (bottles of 100 and 500)

Professional Package Insert Labeling:
Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Ditropan XL
NDA Number: 18-211
NDA Drug Name: Oxybutinin Extended-release Tablets
NDA Firm: Alza
Date of Approval of NDA Insert and supplement #: June 30, 2004
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:
Other Comments

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:
1. Review based on the labeling of Ditropan XL by Alza approved June 30, 2004 (NDA 20-897/S013).

2. PATENT/ EXCLUSIVITIES

PATENT/ EXCLUSIVITIES

Patent Data –

No	Expiration	Use Code	Use	File
5674895	May 22, 2015			IV
5674895*PED	Nov 22, 2015			
5840754	May 22, 2015			IV
5840754*PED	Nov 22, 2015			
5912268	May 22, 2015			IV
5912268*PED	Nov 22, 2015			
6124355	May 22, 2015	U-378	Method for treating incontinence	IV
6124355*PED	Nov 22, 2015	U-378	Method for treating incontinence	
6262115	May 22, 2015	U-393	Management of incontinence, mgt of hormone replacement therapy, treatment of involuntary incontinence, mgt overactive bladder and increasing compliance in such pt	IV
6262115*PED	Nov 22, 2015	U-393	Management of incontinence, mgt of hormone replacement therapy, treatment of involuntary incontinence, mgt overactive bladder and increasing compliance in such pt	
6919092	May 22, 2015	U-667	Management of incontinence; method for treating incontinence	IV
6919092*PED	Nov 22, 2015			

Exclusivity Data -

There is no unexpired exclusivity.

3. MANUFACTURING FACILITY

The drug product is manufactured, packaged, labeled, and tested by
(b) (4)

4. STORAGE CONDITIONS:

NDA - Store at controlled room temperature 15 ˚to 25 ˚C (59 ˚to 77 ˚F).
ANDA - Store at 25 ˚(77 ˚C) excursions permitted to 15 ˚- 30 ˚C (59 ˚- 86 ˚F) [See USP for Controlled Room Temperature]. Protect from moisture and humidity.
USP- Preserve in tight, light-resistant containers.

5. DISPENSING RECOMMENDATIONS:

NDA - Dispense in a tight, light-resistant container as defined in the USP.
ANDA -

6. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert IS consistent with the listing of inactive ingredients found in the statement of components and composition.

Lactose Anhydrous NF
Mannitol USP (b) (4)
Anhydrous Dextrose USP (b) (4)
Tartaric Acid NF, (b) (4)
Colloidal Silicon Dioxide NF (b) (4)
Magnesium Stearate NF (b) (4)
Cellulose Acetate NF (b) (4)
Polyethylene Glycol (b) (4)
(b) (4)

Non-Compendial
(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) (used only for ANDA batches)
(b) (4)

7. PACKAGING CONFIGURATIONS:

NDA- The 5 mg, 10 mg and 15 mg tablets are packaged in bottles of 100 tablets.

ANDA- The 5 mg, 10 mg and 15 mg tablets will be packaged in bottles of 30, 100, 500 and 1000 tablets.

8. CONTAINER/CLOSURE SYSTEM:

30 count for all three strengths: 50 cc round wide mouth, white opaque HDPE bottle, 33-400 finish, White CRC cap with (b) (4) Liner, 33-400 finish, and 1 gram dual desiccant/charcoal canister

100 count for 5 and 10 mg strengths: 50 cc round wide mouth, white opaque HDPE bottle, 33-400 finish, White Ribbed CT cap with (b) (4) Liner, 33-400 finish, and 1 gram dual desiccant/charcoal canister

100 count for 15 mg strength: 100 cc round white opaque HDPE bottle, 38-400 finish, White Ribbed CT cap with (b) (4) Liner, 38-400 finish, and 1 gram dual desiccant/charcoal canister

500 count
5 mg - 150 cc round wide mouth, white opaque HDPE bottle, 33-400 finish, White Ribbed C/T cap with (b) (4) Liner, 38-400 finish, and 1 gram dual desiccant/charcoal canister (2 per bottle)

10 mg - 225 cc white HDPE bottle, 45-400 finish, White CT cap with (b) (4) Liner, 45-400 finish, and 1 gram dual desiccant/charcoal canister (2 per bottle)

15 mg - 300 cc Round white HDPE bottle, 45-400 finish, White CT cap with (b) (4) Liner, 45-400 finish, and 1 gram dual desiccant/charcoal canister (2 per bottle)

1000 count
5mg - 300 cc white HDPE bottle, 45-400 finish, White CT cap with (b) (4) Liner, 45-400 finish, and 1 gram dual desiccant/charcoal canister (3 per bottle)

10 mg - 500 cc round, wide mouth white HDPE bottle, 53-400 finish, White Ribbed C/T cap with (b) (4) Liner, 53-400 finish, and 1 gram dual desiccant/charcoal canister (3 per bottle)

15 mg - 750 cc round wide mouth, white HDPE bottle, 53-400 finish, White Ribbed C/T cap with (b) (4) Liner, 53-400 finish, and 1 gram dual desiccant/charcoal canister (3 per bottle)

9. 5 mg – Round, biconvex, white coated tablets, imprinted in black with “KU” on one side and “270” on the other side
10 mg - Round, biconvex, white coated tablets, imprinted in black with “KU” on one side and “271” on the other side
15 mg - Round, biconvex, white coated tablets, imprinted in black with “KU” on one side and “272” on the other side

10. CONTACT INFORMATION
Osmotica Pharmaceutical Corp
Tel. 910-509-0114
Fax 910-509-0115
Mark Aikman, VP of Regulatory Affairs and Quality Assurance

Date of Review:	November 8, 2007	Date of Submission:	October 20, 2006
Primary Reviewer:	Postelle Birch-Smith		
Team Leader:	John Grace		

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cc: ANDA: 78-503
DUP/DIVISION FILE

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

/s/

Postelle Birch
11/11/2007 03:14:04 PM
LABELING REVIEWER

John Grace
11/14/2007 10:25:25 AM
LABELING REVIEWER

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-503 Date of Submission: December 11, 2007

Applicant's Name: Osmotica Pharmaceutical

Established Name: Oxybutinin Chloride Extended-release Tablets USP, 5 mg, 10 mg and 15 mg

---

BASIS OF APPROVAL:

APPROVAL SUMMARY
CONTAINER LABELS: (bottles of 30, 100, 500 and 1000 for all strengths)
Satisfactory in FPL as of December 11, 2007 e-submission.

PROFESSIONAL PACKAGE INSERT LABELING:
Satisfactory in FPL as of December 11, 2007 e-submission.

REFERENCE LISTED DRUG:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Ditropan XL
NDA Number: 18-211
NDA Drug Name: Oxybutinin Extended-release Tablets
NDA Firm: Alza
Date of Approval of NDA Insert and supplement #: June 30, 2004
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:

PATENT/ EXCLUSIVITIES

Patent Data – 18-211

No	Expiration	Use Code	Use	File
5674895	May 22, 2015			IV
5674895*PED	Nov 22, 2015			
5840754	May 22, 2015			IV
5840754*PED	Nov 22, 2015			
5912268	May 22, 2015			IV
5912268*PED	Nov 22, 2015			
6124355	May 22, 2015	U-378	Method for treating incontinence	IV
6124355*PED	Nov 22, 2015	U-378	Method for treating incontinence	
6262115	May 22, 2015	U-393	Management of incontinence, mgt of hormone replacement therapy, treatment of involuntary incontinence, mgt overactive bladder and increasing compliance in such pt	IV
6262115*PED	Nov 22, 2015	U-393	Management of incontinence, mgt of hormone replacement therapy, treatment of involuntary incontinence, mgt overactive bladder and increasing compliance in such pt	
6919092	May 22, 2015	U-667	Management of incontinence; method for treating incontinence	IV
6919092*PED	Nov 22, 2015			

Exclusivity Data -

There is no unexpired exclusivity.

FOR THE RECORD:

1. Review based on the labeling of Ditropan XL by Alza approved June 30, 2004 (NDA 20-897/S013).

2. PATENT/ EXCLUSIVITIES

See above table

3. MANUFACTURING FACILITY

The drug product is manufactured, packaged, labeled, and tested by
(b) (4)

4. STORAGE CONDITIONS:

NDA - Store at controlled room temperature 15 °to 25 °C (59 °to 77 °F).
ANDA - Store at 25 °(77 °C) excursions permitted to 15 °- 30 °C (59 °- 86 °F) [See USP for Controlled Room Temperature]. Protect from moisture and humidity.
USP- Preserve in tight, light-resistant containers.

5. DISPENSING RECOMMENDATIONS:

NDA - Dispense in a tight, light-resistant container as defined in the USP.
ANDA - Protect from moisture and humidity

6. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert IS consistent with the listing of inactive ingredients found in the statement of components and composition.

Lactose Anhydrous NF
Mannitol USP (b) (4)
Anhydrous Dextrose USP (b) (4)
Tartaric Acid NF, (b) (4)
Colloidal Silicon Dioxide NF (b) (4)
Magnesium Stearate NF (b) (4)
Cellulose Acetate NF (b) (4)
Polyethylene Glycol (b) (4)
(b) (4)

Non-Compendial
(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) (used only for ANDA batches)

(b) (4)

7. PACKAGING CONFIGURATIONS:

NDA- The 5 mg, 10 mg and 15 mg tablets are packaged in bottles of 100 tablets.

ANDA- The 5 mg, 10 mg and 15 mg tablets will be packaged in bottles of 30, 100, 500 and 1000 tablets.

8. CONTAINER/CLOSURE SYSTEM:

30 count for all three strengths: 50 cc round wide mouth, white opaque HDPE bottle, 33-400 finish, White CRC cap with (b) (4) Liner, 33-400 finish, and 1 gram dual desiccant/charcoal canister

100 count for 5 and 10 mg strengths: 50 cc round wide mouth, white opaque HDPE bottle, 33-400 finish, White Ribbed CT cap with (b) (4) Liner, 33-400 finish, and 1 gram dual desiccant/charcoal canister

100 count for 15 mg strength: 100 cc round white opaque HDPE bottle, 38-400 finish, White Ribbed CT cap with (b) (4) Liner, 38-400 finish, and 1 gram dual desiccant/charcoal canister

500 count

5 mg - 150 cc round wide mouth, white opaque HDPE bottle, 33-400 finish, White Ribbed C/T cap with (b) (4) Liner, 38-400 finish, and 1 gram dual desiccant/charcoal canister (2 per bottle)

10 mg - 225 cc white HDPE bottle, 45-400 finish, White CT cap with (b) (4) Liner, 45-400 finish, and 1 gram dual desiccant/charcoal canister (2 per bottle)

15 mg - 300 cc Round white HDPE bottle, 45-400 finish, White CT cap with (b) (4) Liner, 45-400 finish, and 1 gram dual desiccant/charcoal canister (2 per bottle)

1000 count

5mg - 300 cc white HDPE bottle, 45-400 finish, White CT cap with (b) (4) Liner, 45-400 finish, and 1 gram dual desiccant/charcoal canister (3 per bottle)

10 mg - 500 cc round, wide mouth white HDPE bottle, 53-400 finish, White Ribbed C/T cap with (b) (4) Liner, 53-400 finish, and 1 gram dual desiccant/charcoal canister (3 per bottle)

15 mg - 750 cc round wide mouth, white HDPE bottle, 53-400 finish, White Ribbed C/T cap with (b) (4) Liner, 53-400 finish, and 1 gram dual desiccant/charcoal canister (3 per bottle)

9. 5 mg – Round, biconvex, white coated tablets, imprinted in black with "KU" on one side and "270" on the other side
10 mg - Round, biconvex, white coated tablets, imprinted in black with "KU" on one side and "271" on the other side
15 mg - Round, biconvex, white coated tablets, imprinted in black with "KU" on one side and "272" on the other side

10. CONTACT INFORMATION
Osmotica Pharmaceutical Corp
Tel. 910-509-0114
Fax 910-509-0115
Mark Aikman, VP of Regulatory Affairs and Quality Assurance

Primary Reviewer: Postelle Birch-Smith

Team Leader: John Grace

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cc: ANDA: 78-503
DUP/DIVISION FILE

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

/s/

Postelle Birch
1/15/2008 04:52:06 PM
LABELING REVIEWER

John Grace
1/16/2008 11:43:19 AM
LABELING REVIEWER

This labeling approval summary supersedes the labeling approval summary dated 12/11/2007.

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-503 Date of Submission: January 13, 2009

Applicant's Name: Osmotica Pharmaceutical

Established Name: Oxybutinin Chloride Extended-release Tablets USP, 5 mg, 10 mg and 15 mg

---

BASIS OF APPROVAL:

APPROVAL SUMMARY
CONTAINER LABELS: (bottles of 30, 100, 500 and 1000 for all strengths)
Satisfactory in FPL as of December 11, 2007 e-submission.

PROFESSIONAL PACKAGE INSERT LABELING:
Satisfactory in FPL as of January 13, 2009 e-submission.

REFERENCE LISTED DRUG:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Ditropan XL
NDA Number: 20-897
NDA Drug Name: Oxybutinin Extended-release Tablets
NDA Firm: Ortho McNeil Janssen
Date of Approval of NDA Insert and supplement #: February 6, 2008
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:

PATENT/ EXCLUSIVITIES

Patent Data – 18-211

No	Expiration	Use Code	Use	File
5674895	May 22, 2015			IV
5674895*PED	Nov 22, 2015			
5840754	May 22, 2015			IV
5840754*PED	Nov 22, 2015			
5912268	May 22, 2015			IV
5912268*PED	Nov 22, 2015			
6124355	May 22, 2015	U-378	Method for treating incontinence	IV
6124355*PED	Nov 22, 2015	U-378	Method for treating incontinence	
6262115	May 22, 2015	U-393	Management of incontinence, mgt of hormone replacement therapy, treatment of involuntary incontinence, mgt overactive bladder and increasing compliance in such pt	IV
6262115*PED	Nov 22, 2015	U-393	Management of incontinence, mgt of hormone replacement therapy, treatment of involuntary incontinence, mgt overactive bladder and increasing compliance in such pt	
6919092	May 22, 2015	U-667	Management of incontinence; method for treating incontinence	IV
6919092*PED	Nov 22, 2015			

Exclusivity Data -

There is no unexpired exclusivity.

FOR THE RECORD:

1. Review based on the labeling of Ditropan XL by Ortho McNeil Janssen approved February 6, 2008 (NDA 20-897/S018).

2. PATENT/ EXCLUSIVITIES

   See above table

3. MANUFACTURING FACILITY

   The drug product is manufactured, packaged, labeled, and tested by
   (b) (4)

4. STORAGE CONDITIONS:

   NDA - Store at controlled room temperature 15˚to 25˚C (59˚to 77˚F).
   ANDA - Store at 25˚(77˚C) excursions permitted to 15˚- 30˚C (59˚- 86˚F) [See USP for Controlled Room Temperature]. Protect from moisture and humidity.
   USP- Preserve in tight, light-resistant containers.

5. DISPENSING RECOMMENDATIONS:

   NDA - Dispense in a tight, light-resistant container as defined in the USP.
   ANDA - Protect from moisture and humidity

6. INACTIVE INGREDIENTS:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert IS consistent with the listing of inactive ingredients found in the statement of components and composition.

   Lactose Anhydrous NF
   Mannitol USP (b) (4)
   Anhydrous Dextrose USP (b) (4)
   Tartaric Acid NF, (b) (4)
   Colloidal Silicon Dioxide NF (b) (4)
   Magnesium Stearate NF (b) (4)
   Cellulose Acetate NF (b) (4)
   Polyethylene Glycol (b) (4)
   (b) (4)

   Non-Compendial
   (b) (4)

   (b) (4)

   (b) (4)

(b) (4)

(b) (4) (used only for ANDA batches)

(b) (4)

7. PACKAGING CONFIGURATIONS:

NDA- The 5 mg, 10 mg and 15 mg tablets are packaged in bottles of 100 tablets.

ANDA- The 5 mg, 10 mg and 15 mg tablets will be packaged in bottles of 30, 100, 500 and 1000 tablets.

8. CONTAINER/CLOSURE SYSTEM:

30 count for all three strengths: 50 cc round wide mouth, white opaque HDPE bottle, 33-400 finish, White CRC cap with (b) (4) Liner, 33-400 finish, and 1 gram dual desiccant/charcoal canister

100 count for 5 and 10 mg strengths: 50 cc round wide mouth, white opaque HDPE bottle, 33-400 finish, White Ribbed CT cap with (b) (4) Liner, 33-400 finish, and 1 gram dual desiccant/charcoal canister

100 count for 15 mg strength: 100 cc round white opaque HDPE bottle, 38-400 finish, White Ribbed CT cap with (b) (4) Liner, 38-400 finish, and 1 gram dual desiccant/charcoal canister

500 count
5 mg - 150 cc round wide mouth, white opaque HDPE bottle, 33-400 finish, White Ribbed C/T cap with (b) (4) Liner, 38-400 finish, and 1 gram dual desiccant/charcoal canister (2 per bottle)

10 mg - 225 cc white HDPE bottle, 45-400 finish, White CT cap with (b) (4) Liner, 45-400 finish, and 1 gram dual desiccant/charcoal canister (2 per bottle)

15 mg - 300 cc Round white HDPE bottle, 45-400 finish, White CT cap with (b) (4) Liner, 45-400 finish, and 1 gram dual desiccant/charcoal canister (2 per bottle)

1000 count
5mg - 300 cc white HDPE bottle, 45-400 finish, White CT cap with (b) (4) Liner, 45-400 finish, and 1 gram dual desiccant/charcoal canister (3 per bottle)

10 mg - 500 cc round, wide mouth white HDPE bottle, 53-400 finish, White Ribbed C/T cap with (b) (4) Liner, 53-400 finish, and 1 gram dual desiccant/charcoal canister (3 per bottle)

15 mg - 750 cc round wide mouth, white HDPE bottle, 53-400 finish, White Ribbed C/T cap with (b) (4) Liner, 53-400 finish, and 1 gram dual desiccant/charcoal canister (3 per bottle)

9. 5 mg – Round, biconvex, white coated tablets, imprinted in black with “KU” on one side and “270” on the other side
10 mg - Round, biconvex, white coated tablets, imprinted in black with “KU” on one side and “271” on the other side
15 mg - Round, biconvex, white coated tablets, imprinted in black with “KU” on one side and “272” on the other side

10. CONTACT INFORMATION
Osmotica Pharmaceutical Corp
Tel. 910-509-0114
Fax 910-509-0115
Mark Aikman, VP of Regulatory Affairs and Quality Assurance

11. The font size of the text in the package insert submitted was only 3.55 pt. I emailed the firm to find out if the submitted package insert was true size. Another copy of the package insert was emailed to me that was true

text size and measured >4 pt. text size. A copy of the true size package insert has be attached to this approval summary.

Date of Review:	January 16, 2009	Date of Submission:	January 13, 2009
Primary Reviewer:	Postelle Birch-Smith		
Team Leader:	John Grace		

---

cc: ANDA: 78-503
DUP/DIVISION FILE

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

/s/

Postelle Birch-Smith
1/22/2009 10:05:33 AM
LABELING REVIEWER

John Grace
1/23/2009 01:24:36 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-503

CHEMISTRY REVIEWS

ANDA 78-503

Oxybutynin Chloride Extended Release Tablets, 5 mg , 10 mg , and 15 mg

Osmotica Pharmaceutical Corp.

Robert L. Iser
Office of Generic Drugs
Division of Chemistry III
Team 4

Table of Contents

Executive Summary Section

Chemistry Review Data Sheet

1. ANDA: 78-503

2. REVIEW #: 1

3. REVIEW DATE: 30-Mar-2007; revised 4-11-07

4. REVIEWER: Robert L. Iser

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	20-Oct-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Osmotica Pharmaceutical Corp.
Address:	1205 Culberth Drive Suite 200 Wilmington, NC 28405
Representative:	Mark Aikman
Telephone:	910-509-0114
Fax:	910-509-0115

8. DRUG PRODUCT NAME:

a) Proprietary Name:	N/A
b) Non-Proprietary Name (USAN):	Oxybutynin Chloride Extended Release Tablets

9. LEGAL BASIS FOR SUBMISSION: 505j, RLD is Ditropan XL® from Alza, NDA # 20897

10. PHARMACOL. CATEGORY:	Muscle Relaxant
11. DOSAGE FORM:	Extended Release Tablet
12. STRENGTH/POTENCY:	5, 10 & 15 mg (MDD = 30 mg/day)
13. ROUTE OF ADMINISTRATION:	Oral
14. Rx/OTC DISPENSED:	_X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

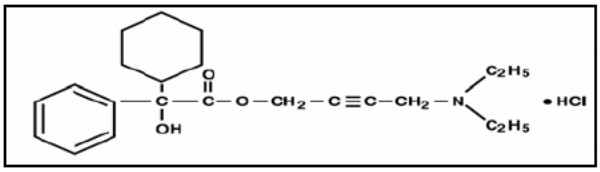
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Benzene acetic acid, α-cyclohexyl- α-hydroxy-4-(diethylamino)-2-butynyl ester Hydrochloride

Formula: $C_{22}H_{32}ClNO_3$
MW: 393.96
CAS: 1508-65-2



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	9-21-06	Reviewed by R. Iser
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: **None**

Executive Summary Section

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	1/29/07	
Methods Validation	N/A		
Labeling	Pending		P. Birch
Bioequivalence	Dissolution – Not Acceptable Bio-Review – Pending	10/20/06	S. Lu
EA	Acceptable	3/30/07	R. Iser
Radiopharmaceutical	N/A		
Pharm/Tox	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.

__X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-503

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC Not Approvable (Minor Amendment, review #1)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

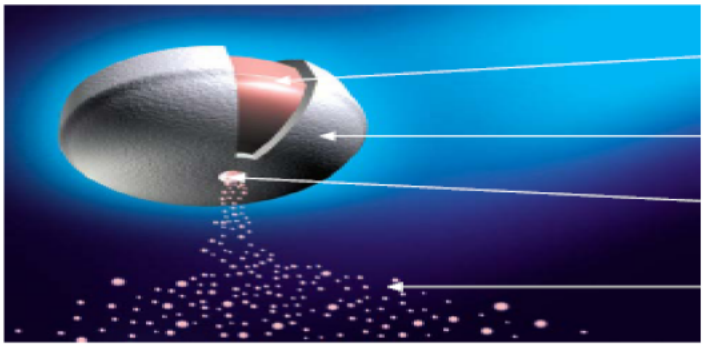
A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
The Oxybutynin Chloride drug substance is compendial (USP/EP). It is a white or off-white crystalline powder, which is a racemic mixture of the (R) and (S) isomers. The substance melts at 124 - 129°C and is freely soluble in water, is very soluble in methanol and in chloroform, is slightly soluble in ether, and is very slightly soluble in hexane. The substance is supplied by (b) (4) (DMF (b) (4), and specifications are based on manufacturer and USP.

Drug Product:
The Oxybutynin Chloride Extended-release Tablets 5, 10, and 15 mg are round, biconvex, white coated tablets, imprinted in black which are currently non-compendial (USP 30 monograph will be official May 1, 2007). The proposed generic drug product is an osmotic tablet in which a tablet core is produced by (b) (4) .

As the tablet passes through the gastrointestinal tract, water from intestinal fluid passes through the semi-permeable membrane coating. This water causes pressure to build up in the monolayer tablet core and the tablet core content is pumped out of the tablet through the laser drilled orifice.

The product is manufactured by a third-party ((b) (4), (b) (4) using a formulation and process developed by Osmotica. The size of the exhibit batches was based on the (b) (4). A (b) (4) (b) (4) is used for the 5 mg, 10 mg, and 15 mg strengths. The hole in the tablet is produced by a piece of equipment designed and built by Osmotica. It is referred to as a Tablet Laser Drilling Machine, Model (b) (4) TLDM (b) (4). The ability of the TLDM (b) (4) to produce holes in tablets on a consistent basis has been demonstrated during the IQ/OQ/PQ. This data is available on-site at the (b) (4) facility.



The excipients used are: Mannitol, Anhydrous Dextrose, Lactose Anhydrous (b) (4), Tartaric acid, Colloidal Silicon Dioxide, Magnesium Stearate, Cellulose acetate (b) (4) NF, Polyethylene glycol (b) (4) .

The tablets are packaged in the 50 cc, 100 cc, 150 cc, 225 cc, 300 cc, 500 cc, and 750 cc HDPE bottles depending on dose and tablet count. Also, a dual desiccant/charcoal canister is packaged inside the bottle.

B. Description of How the Drug Product is Intended to be Used

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

The label recommended storage condition is: Store at Controlled Room Temperature 25°C, excursions permitted to 15-30 °C (59° to 86°F). RLD has labeled storage at 25°C (77°F), excursions permitted to 15-30 °C (59° to 86°F) [See USP Controlled Room Temperature]. Both labels state protect from moisture and humidity.

C. Basis for Approvability or Not-Approval Recommendation

CMC portion is not approvable based on deficiencies listed in section III. The firm will be informed of the deficiencies as a minor amendment.

The EES, the Labeling review, and the bio-data review are currently pending. The bio-dissolution review is not acceptable.

Following this page, 50 pages withheld in full - (b)(4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all current stability data; and ensure that the stability data sheets include all current specifications.

2. The review of the labeling portions of your application is pending. Deficiencies, if any, will be conveyed to you under a separate cover.

3. Please be informed that when reporting the acceptable levels of excipients in a drug product formulation based on the Inactive Ingredients Guide (IIG), the Total Daily Intake (TDI) of the ingredients should be taken into account.

4. Please clearly describe the drug release mechanism, specifically how the proposed design promotes constant release of the drug.

5. With respect to the dissolution specifications, please provide the revised specifications and method based on any recommendations made by the Division of Bioequivalence (DBE). Also, stability data should be provided using the recommended method and criteria to justify the proposed expiry date.

6. To help facilitate the review process, when future applications are submitted in the Question-based Review format, please include the standard questions in the Quality Overall Summary (QOS) and please submit a MS-Word version of the QOS.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Appears this way on original.

cc: ANDA 77-503
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):
HFD-630/R. Iser-Review Chemist/3/30/2007; revised 4-11-07/
HFD-630/D. Gill-Team Leader/4/12/07
HFD-617/L. Matheny-PM/4/16/07

F/T by: LM 4/16/07

V:\FIRMSNZ\Osmotica\LTRS&REV\78503.R01.doc

TYPE OF LETTER: Not APPROVABLE - Minor Amendment

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

/s/

Robert Iser
4/17/2007 07:33:37 AM
CHEMIST
minor

Leigh Matheny
4/17/2007 10:02:29 AM
CSO

Devinder Gill
4/18/2007 11:28:53 AM
CHEMIST

ANDA 78-503

Oxybutynin Chloride Extended Release Tablets, 5 mg , 10 mg , and 15 mg

Osmotica Pharmaceutical Corp.

Gil-Jong Kang
Office of Generic Drugs
Division of Chemistry III
Team 4

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 78-503

2. REVIEW #: 2

3. REVIEW DATE: 05-JAN-2009

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	20-OCT-2006
Misc. correspondence	11-JAN-2007
Deficiency letter based on review #1	18-APR-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	19-OCT-2007
Amendment regarding USP <467>	24-JUL-2008
Telephone amendment	24-NOV-2008
Telephone amendment	15-DEC-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Osmotica Pharmaceutical Corp.
Address:	1205 Culberth Drive Suite 200 Wilmington, NC 28405
Representative:	Mark Aikman
Telephone:	910-509-0114
Fax:	910-509-0115

8. DRUG PRODUCT NAME:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Oxybutynin Chloride Extended Release Tablets

9. LEGAL BASIS FOR SUBMISSION: 505j, RLD is Ditropan XL® from Alza, NDA # 20897

10. PHARMACOL. CATEGORY: Muscle Relaxant

Chemistry Review Data Sheet

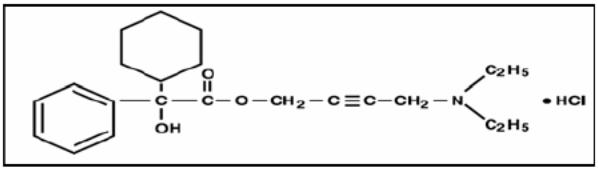
11. DOSAGE FORM: Extended Release Tablet
12. STRENGTH/POTENCY: 5, 10 & 15 mg (MDD = 30 mg/day)
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Benzene acetic acid, α-cyclohexyl- α-hydroxy-4-(diethylamino)-2-butynyl ester Hydrochloride

Formula: $C_{22}H_{32}ClNO_3$
MW: 393.96
CAS: 1508-65-2



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A. DMFs:

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(b) (4)	II	(b) (4)		1	Adequate (IR)	13-NOV-2008	Reviewed by G. Kang.
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

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5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: **None**

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	1/29/07	
Methods Validation	N/A		
Labeling	Acceptable	1/16/08	P. Birch
Bioequivalence	Dissolution – Acceptable Bio-Review – Acceptable	9/13/07 9/13/07	S. Lu X. Jiang
EA	Acceptable	3/30/07	R. Iser
Radiopharmaceutical	N/A		
Pharm/Tox	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
___ Yes __X__ No If no, explain reason(s) below:

MINOR Amendment

The Chemistry Review for ANDA 78-503

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA 78-503 is approvable. CMC deficiencies have been resolved with the firm via telephone amendment.
Bio and labeling sections are acceptable.
EES is acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
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Drug Product:
The Oxybutynin Chloride Extended-release Tablets 5, 10, and 15 mg are round, biconvex, white coated tablets, imprinted in black which are currently non-compendial (USP 30 monograph will be official May 1, 2007). The proposed generic drug product is an osmotic tablet in which a tablet core is produced by (b) (4)

As the tablet passes through the gastrointestinal tract, water from intestinal fluid passes through the semi-permeable membrane coating. This water causes pressure to build up in the monolayer tablet core and the tablet core content is pumped out of the tablet through the laser drilled orifice.

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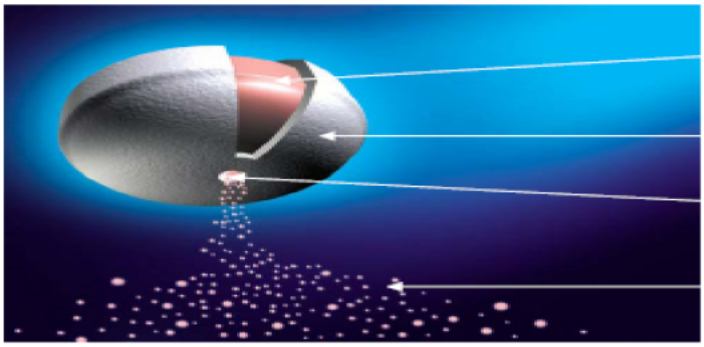

The excipients used are: Mannitol, Anhydrous Dextrose, Lactose Anhydrous (b) (4) Tartaric acid, Colloidal Silicon Dioxide, Magnesium Stearate, Cellulose acetate (b) (4) NF, Polyethylene glycol (b) (4) .

The tablets are packaged in the 50 cc, 100 cc, 150 cc, 225 cc, 300 cc, 500 cc, and 750 cc HDPE bottles depending on dose and tablet count. Also, a dual desiccant/charcoal canister is packaged inside the bottle.

B. Description of How the Drug Product is Intended to be Used

Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

The label recommended storage condition is: Store at Controlled Room Temperature 25°C, excursions permitted to 15-30 °C (59° to 86°F). RLD has labeled storage at 25°C (77°F), excursions permitted to 15-30 °C (59° to 86°F) [See USP Controlled Room Temperature]. Both labels state protect from moisture and humidity.

C. Basis for Approvability or Not-Approval Recommendation

CMC deficiencies were resolved with the firm by Telephone amendment.
Bio and labeling sections are acceptable.
EES is acceptable.

Amendment dated 24-JUL-2008: The firm submitted the information regarding USP change in OVI and Residual Solvents, USP <467>. The provided information included updated specifications and certificate of analysis for all excipients. The firm also committed to re-assess compliance with USP <467> if ingredient suppliers change or if current supplier change their process. --- However, the information submitted was not completely complied with USP <467> requirement for the approval of ANDA. Related issues were communicated with the firm by a telephone conference.

Telephone amendment dated 24-NOV-2008: the firm has provided the following additional information and they are satisfactory.
-The firm committed to provide within 6 months post-approval of this ANDA the verification data for (b) (4) in a special report.
-The firm revised the finished product release specifications to include the statement "meets the requirement of USP<467> (b) (4)".
-The firm provided 24 months controlled room temperature stability data. Full term stability data are required for the approval of this ANDA due to the change in the dissolution specification.

Following this page, 27 pages withheld in full - (b)(4)

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

1.3 Administrative Information

1.3.2	Field Copy Certification:	Provided and adequate
1.3.3	Debarment Certification:	Provided and adequate
1.3.5	Patent and Exclusivity:	Paragraph IV and current exclusivity

1.4 References

1.4.1 Letters of Authorization

Letter of Authorizations regarding Drug Master are provided (see section 17 above).

1.12 Other Correspondence

1.12.11 Basis for Submission — Provided

1.12.12 Comparison between Generic Drug and RLD — (see 3.2.P.1)

The conditions of use; active ingredient, Route of Administration, dosage form, and strength are the same as RLD. The firm notes that as per §314.94(a)(9), it is not necessary for the inactive ingredients of the proposed oral generic drug product to be identical to those of the reference listed drug product. As required in §314.94(a)(9)(ii), the different inactive ingredients do not affect the safety of the proposed generic drug product. This information is found in Section 3.2.P.1 of this application.

1.12.14 Environmental Impact Analysis — Satisfactory as per review #1

cc: ANDA 78-503
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/G. Kang, Ph.D./1/05/09
HFD-630/S. H. Liu, Ph.D., Team Leader/1/06/09
HFD-617/L. Bradford, PM/1/06/09

F/T by: LB 1/07/09

V:\FIRMSNZ\OSMOTICA\LTRS&REV\78503.R02tel.doc

TYPE OF LETTER: **APPROVABLE**

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

/s/

Gil Jong Kang
2/4/2009 03:25:36 PM
CHEMIST

Shing Hou Liu
2/5/2009 08:51:52 AM
CHEMIST

Leigh Ann Bradford
2/5/2009 10:53:13 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-503

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION CHECKLIST

ANDA No.	78-503
Drug Product Name	Oxybutynin Chloride Extended Release Tablets
Strength	5 mg, 10 mg, and 15 mg
Applicant Name	Osmotica Pharmaceutical 1205 Culbreth Dr. Suite 200 Wilmington, NC 28405
Submission Date(s)	October 20, 2006
First Generic	No
Reviewer	Shirley K. Lu, Ph.D.
Clinical Site	AAIPharma 200 Perimeter Park Dr. Morrisville, NC 27560
Analytical Site	(b) (4)
Contact	Mark S. Aikman
Phone #/Fax #	(910) 509-0114 / (910) 509-0115

Table 1. Submission Content Checklist

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method*			☐	☒	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☐	☒	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are all eight electronic summary biotables present			☒	☐	☐
Are electronic summary biotables in pdf format			☒	☐	☐

*The firm did not complete all the ER product FDA-recommended methods.

Comments

The firm has submitted dissolution testing for the test and reference products using the methods in the following table. For the tests using apparatus VII, the medium did not include enzymes, the volume used was 50 mL, and the dip time intervals were:

Row 1: 1 hour
Row 2: 3 hours
Row 3: 6 hours
Row 4: 5 hours
Row 5: 9 hours

Test	Product	Lot	Apparatus	Agitation Speed	Media
1	270 Oxybutynin Chloride ER Tablets, 5mg	P63970	II	50 rpm	pH 1.2 buffer
2	270 Oxybutynin Chloride ER Tablets, 5mg	P63970	II	50 rpm	pH 4.5 buffer
3	270 Oxybutynin Chloride ER Tablets, 5mg	P63970	II	50 rpm	pH 6.8 buffer
4	270 Oxybutynin Chloride ER Tablets, 5mg	P63970	II	50 rpm	water
5	271 Oxybutynin Chloride ER Tablets, 10mg	P63990	II	50 rpm	water
6	272 Oxybutynin Chloride ER Tablets, 15mg	P64010	II	50 rpm	pH 1.2 buffer
7	272 Oxybutynin Chloride ER Tablets, 15mg	P64010	II	50 rpm	pH 4.5 buffer
8	272 Oxybutynin Chloride ER Tablets, 15mg	P64010	II	50 rpm	pH 6.8 buffer
9	272 Oxybutynin Chloride ER Tablets, 15mg	P64010	II	50 rpm	water
10	272 Oxybutynin Chloride ER Tablets, 15mg	P64010	II	75 rpm	water
11	272 Oxybutynin Chloride ER Tablets, 15mg	P64010	II	100 rpm	water
12	270 Oxybutynin Chloride ER Tablets, 5mg	P63970	VII	30 dpm	simulated gastric fluid
13	271 Oxybutynin Chloride ER Tablets, 10mg	P63990	VII	30 dpm	simulated gastric fluid
14	272 Oxybutynin Chloride ER Tablets, 15mg	P64010	VII	30 dpm	simulated gastric fluid
15	Ditropan XL® ER Tablets, 5mg (ALZA lot)	0533889	II	50 rpm	water
16	Ditropan XL® ER Tablets, 10mg (ALZA lot)	0531570	II	50 rpm	water
17	Ditropan XL® ER Tablets, 15mg (ALZA lot)	0541690	II	50 rpm	water
18	Ditropan XL® ER Tablets, 5mg (ALZA lot)	0533889	VII	30 dpm	simulated gastric fluid
19	Ditropan XL® ER Tablets, 10mg (ALZA lot)	0531570	VII	30 dpm	simulated gastric fluid
20	Ditropan XL® ER Tablets, 15mg (ALZA lot)	0541690	VII	30 dpm	simulated gastric fluid

This product is not a USP product and the DBE does not have a method on the public database, however, the latest control document (#06-0822, (b) (4), 11/13/06) recommends:

Please conduct comparative in-vitro dissolution testing on 12 dosage units of each strength of the test and reference products in water and in at least three different media at pH 1.2, 4.5, and 6.8 using USP Apparatus 1 (Basket) at 100 rpm and Apparatus 2 (Paddle) at 50, 75 and 100 rpm. The recommended sampling times are 1, 2, 4, and every 2 hours thereafter for 24 hours, until 80% of the drug is released.

In addition, please conduct dissolution testing using the following suggested method:

Apparatus: *USP Apparatus VII*
Media: *Simulated Gastric Fluid without enzyme at 37^0C*

Volume: *50 ml*
Frequency/Amplitude: 30 cycles/minutes; 2-3 cm
Sampling times: *4, 10 and 24 hours.*

Tolerances are expressed as cumulative amount release per tablet over time interval (0-4, 0-10, and 0-24).

The firm's data on the 15-mg strength of the test product in water indicate that the dissolution rate of the tablet is not dependent on paddle speed:

F2 between 50 rpm and 75 rpm = **83.5**
F2 between 50 rpm and 100 rpm = **65.6**

Thus, dissolution testing using additional paddle speeds in all three different pH media will not be requested from the firm. However, the firm should still submit data for the *reference products* using the paddle method at 50 rpm (for comparative purposes) and dissolution testing data for both test and reference products using basket at 100 rpm.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-503 APPLICANT: Osmotica Pharmaceuticals

DRUG PRODUCT: Oxybutynin Chloride Extended Release Tablets, 5 mg, 10 mg, and 15 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. We acknowledge that you have conducted dissolution testing in simulated gastric fluid using apparatus VII and water using paddle at 50 rpm for the test and reference products. In addition, please conduct comparative dissolution testing on each strength of the test and reference products in water and in at least three different media at pH 1.2, 4.5, and 6.8 using USP Apparatus 1 (Basket) at 100 rpm. Please also submit dissolution data for the reference products using paddle at 50 rpm in the three different pH media.

2. In order to improve the review process, the Division of Bioequivalence requests that you provide electronic summary tables that can be found under the sub-heading "Model Bioequivalence Data Summary Tables" at the following web address: http://www.fda.gov/cder/ogd/index.htm. Please provide this information for any other applications pending in the Division and in applications to be submitted in the future.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA #: 78-503

Submission date: 10/20/06

[NOTE: The in vitro testing is incomplete. The fasting and fed BE studies and waiver requests are pending review]

1. **BDI**-DISSOLUTION (Dissolution Data)	Strengths: 5 mg, 10 mg, 15 mg

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/s/

Shirley Lu
2/27/2007 12:41:33 PM
BIOPHARMACEUTICS

Yih Chain Huang
2/27/2007 12:52:22 PM
BIOPHARMACEUTICS

Dale Conner
2/27/2007 01:58:07 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-503
Drug Product Name	Oxybutynin Chloride Extended Release Tablets
Strength	5 mg, 10 mg, and 15 mg
Applicant Name	Osmotica Pharmaceutical 1205 Culbreth Dr. Suite 200 Wilmington, NC 28405
Submission Date(s)	October 20, 2006
Amendment Date(s)	April 24, 2007
First Generic	No
Reviewer	Shirley K. Lu, Ph.D.
Clinical Site	AAIPharma 200 Perimeter Park Dr. Morrisville, NC 27560
Analytical Site	(b) (4)
Contact	Mark S. Aikman
Phone #/Fax #	(910) 509-0114 / (910) 509-0115

Review of a Dissolution Amendment

I. Executive Summary

This dissolution amendment was submitted in response to a request from the Division of Bioequivalence (DBE) requesting additional dissolution testing data for the reference product using 3 different pH aqueous media and the new electronic summary tables found on the FDA website. The firm's response is not acceptable. The firm did not include individual tablet data, test product data for the 10-mg strength for the 3 different pH media, and clarification on the dissolution summary table concerning the use of enzymes.

The DBE will review the fasting and fed studies and waiver requests at a later date.

II. Review of Submission

Deficiency #1: *We acknowledge that you have conducted dissolution testing in simulated gastric fluid using apparatus VII and water using paddle at 50 rpm for the test and reference products. In addition, please conduct comparative dissolution testing on each strength of the test and reference products in water and in at least three different media at pH 1.2, 4.5, and 6.8 using USP Apparatus 1 (Basket) at 100 rpm. Please also submit dissolution data for the reference products using paddle at 50 rpm in the three different pH media.*

Firm's Response: The firm has submitted dissolution data for the test and reference products using paddle at 50 rpm in water and apparatus 7 at 30 dpm in SGF. The firm has submitted data for only the 5-mg and 15-mg strengths of the test product in 3 different pH media.

Reviewer's Comment: The firm had previously called to clarify if they needed to conduct testing using basket at 100 rpm. It was agreed by the DBE that this additional testing was not necessary. However, the firm should submit their test product data for the 10-mg strength in the 3 different pH media (as it was not contained in their original submission). The firm should also provide individual tablet data for all media and strengths and clarify on the summary table if enzyme was used or not. The firm's response is not acceptable.

Deficiency #2: *In order to improve the review process, the Division of Bioequivalence requests that you provide electronic summary tables that can be found under the sub-heading "Model Bioequivalence Data Summary Tables" at the following web address: http://www.fda.gov/cder/ogd/index.htm. Please provide this information for any other applications pending in the Division and in applications to be submitted in the future.*

Firm's Response: The firm has submitted the summary tables in electronic format (located in the EDR).

Reviewer's Comment: The firm's response is acceptable.

III. Recommendations

The *in vitro* dissolution testing conducted by Osmotica, Pharmaceuticals on its test products, Oxybutynin Chloride ER Tablets, 5 mg (lot #P63970), 10 mg (lot # P63990), and 15 mg (lot # P64010) comparing them to Alza's Ditropan® XL Tablets, 5 mg (lot#0533889), 10 mg (lot # 0531570), and 15 mg (lot #0541690) is incomplete.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-503

APPLICANT: Osmotica Pharmaceuticals

DRUG PRODUCT: Oxybutynin Chloride Extended Release Tablets, 5 mg, 10 mg, and 15 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. We acknowledge that you have submitted dissolution testing data for the 5-mg and 15-mg strengths of the test product in 3 different pH media. Please submit the dissolution data for the 10-mg strength of the test product in the 3 different pH media as well.

2. Please submit all individual tablet data for the data already submitted and for the data requested in the deficiency comment above.

3. In all your dissolution summary tables that include testing with simulated gastric fluid, please indicate whether the testing was done with or without enzyme.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA #: 78-503 Submission date: 4/24/07

[NOTE: The in vitro testing is incomplete. The fasting and fed BE studies and waiver requests are pending review]

1. **BDI**-DISSOLUTION (Dissolution Data)	Strengths: 5 mg, 10 mg, 15 mg

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/s/

Shirley Lu
5/29/2007 09:44:44 AM
BIOPHARMACEUTICS

Yih Chain Huang
5/29/2007 09:48:51 AM
BIOPHARMACEUTICS

Barbara Davit
5/29/2007 02:42:12 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-503	
Drug Product Name	Oxybutynin Chloride Extended-Release Tablets, USP	
Strength(s)	5 mg, 10 mg and 15 mg	
Applicant Name	Osmotica Pharmaceutical Corp.	
Address	1205 Culbreth Drive Suite 200 Wilmington, NC 28405	
Applicant's Point of Contact **Contact's Telephone Number** **Contact's Fax Number**	Mark S. Aikman 1205 Culbreth Drive Suite 200 Wilmington, NC 28405 910.509.0114 910.509.0115	
Original Submission Date(s)	**Oct, 20, 2006**	
Submission Date(s) of Amendment(s) Under Review	**Apr. 24, 2007 (dissolution amendment), July. 05, 2007 (dissolution amendment, not previously reviewed)**	
Reviewer	Xiaojian Jiang, Ph.D.	
Study Number (s)	AAI-US-425	AAI-US-424
Study Type (s)	Fasting study	Fed Study
Strength (s)	15 mg	15 mg
Clinical Site and Address	AAI Pharma, Inc. 200 Perimeter Park Dr. Morrisville, North Carolina 27560 919-481-5700	Same as the fasting study
Analytical site and address	(b) (4)	Same as the fasting study
First Generic	No	
DSI Inspection	**This ANDA is not scheduled for DSI inspections.**	
Location	DFS	

1 EXECUTIVE SUMMARY

The firm submitted single-dose fasting and non-fasting bioequivalence (BE) studies comparing its test product, Oxybutynin Chloride Extended-Release Tablets, 15 mg to the reference listed drug (RLD), Ditropan XL ® (Oxybutynin Chloride) Tablets, 15 mg (ALZA). The firm also submitted waiver requests for the 5 mg and 10 mg tablets.

The design for the fasting BE study is a two-way, crossover study in healthy male and female subjects (n=64). The non-fasting BE study is also a two-way, crossover design in healthy male and female subjects (n=58). The firm measured plasma levels of both oxybutynin and the active metabolite, desethyloxybutynin. For the fasting BE study, Oxybutynin results (point estimate, 90% CI) are:

$lnAUC_{0-t}$ of 0.98, 88.36-108.79%; lnAUCinf of 1.00, 90.31-111.79 %; and lnCmax of 0.98, 90.15-106.15%. For the non-fasting BE study, Oxybutynin results (point estimate, 90% CI) are: $lnAUC_{0-t}$ of 0.99, 94.04-104.91%; lnAUCinf of 1.02, 96.45-107.53%; and lnCmax of 0.96, 90.74-101.61%. Plasma concentrations of the metabolite are comparable between the test and reference product in both studies. Both studies are **acceptable**.

The dissolution testing submitted in the original and the amendments dated 4/24/07 and 07/05/07 were acceptable. The firm's proposed method (USP method; 50 ml of simulated gastric fluid without enzymes at 37°C, using USP apparatus 7, 30 cycles per minutes; 2- to 3-cm amplitude) is acceptable. However, the firm's proposed dissolution specification is **not acceptable**. The firm should acknowledge the FDA-recommend specification (4 hr: NMT 25%, 10 hr: 40-65%, 24 hr: NLT 75%). It is slightly different from the USP specification.

The formulation of the 5 mg and 10 mg strength test product are proportionally similar to that of the 15 mg strength of the test product which underwent bioequivalence testing. The dissolution is comparable between the 5 mg, 10 mg and 15 mg. The DBE may deem lower strengths of the test product bioequivalent to the RLD based on CFR 320.24(b)(6), upon the firm's acknowledgement of its acceptance of the above specifications.

There is no DSI inspection scheduled for this application. This application is **incomplete.**

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Oxybutynin Chloride Extended-Release Tablets, 5 mg, 10 mg and 15 mg
Reference Product	Ditropan XL ® Tablets, 15 mg (also available as 5 mg and 10 mg)
RLD Manufacturer	ALZA Corporation
NDA No.	20-897
RLD Approval Date	Dec. 16, 1998 for the 5 mg and 10 mg strengths and Jun 22, 1999 for the 15 mg strength.
RLD product formulation	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.
Test product formulation	A similar technique was employed in the test product design.
Indication	Treatment of Overactive Bladder

3.2 PK/PD Information

Bioavailability	6%
Food Effect	The rate and extent of absorption and metabolism of oxybutynin are similar under fed and fasted conditions.
Tmax	4 – 6 hours
Metabolism	Extensively metabolized via enteric and hepatic CYP450 3A4

	enzymes. Desethyloxybutynin is an active metabolite.
Excretion	< 0.1% of oxybutynin or N-desethyloxybutynin appears in the urine unchanged
Half-life	12 hours (post-prandial) and 16 hours (fasting) (extended-release formulation)
Drug Specific Issues (if any)	1. The Division of Bioequivalence (DBE) recommends measurement of both oxybutynin and its active metabolite, desethyloxybutynin, using an achiral assay (without measurement of the individual enantiomers). The DBE recommends measurement of desethyloxybutynin because it is formed as a result of presystemic metabolism and contributes meaningfully to efficacy. However, only the parent compound, oxybutynin, should be analyzed using the confidence interval approach to establish bioequivalence. 2. Oxybutynin exhibits dose-dependent, linear pharmacokinetics. The R- and S-isomers of oxybutynin exhibit different pharmacokinetic and pharmacodynamic characteristics. However, there is insufficient evidence to support that R-oxybutynin, the minor enantiomer, is primarily responsible for efficacy. Therefore, measurement of individual enantiomer is unnecessary. See Memo written by Regulatory Policy Advisor to the Director, Cecelia M. Parise, for more details (DFS N076644 N000 21-Jan-2003)

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	15 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	NA

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	15 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	NA

Analytes to measure (in appropriate biological fluid):	Oxybutynin and Desethyloxybutynin in Plasma
Bioequivalence based on (90% CI):	Oxybutynin

Waiver request of in-vivo testing (appropriate strengths):	5 mg and 10 mg
Source of most recent recommendations:	06-0822 (b) (4) ANDA 78-293 (Mylan): (DFS)
Summary of OGD or DBE History (for details, see Appendix 4.4):	**see Appendix 4.4**
Application Specific Issue	_

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	0
In vitro dissolution	Yes	3
Waiver requests	Yes	2
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	Yes	2 (dissolution amendment)

Appears this way on original.

3.5 Pre-Study Bioanalytical Method Validation

Table 4 Bioanalytical Method Validation

Information Requested	DATA
Bioanalytical Method Validation Report location	(b) (4) V2306P2
Analyte	Oxybutynin
Internal standard (IS)	(b) (4)
Method description	LC/MS/MS – liquid-liquid extraction
Limit of Quantitation (ng/mL)	0.0500-6.40ng/mL for oxybutynin
Average recovery of drug (%)	30% for oxybutynin
Average recovery of IS (%)	(b) (4)
Standard curve concentrations (ng/mL)	0.0500, 0.100, 0.400, 0.800, 1.60, 3.20, 5.60, 6.40
QC concentrations (ng/mL)	0.0500, 0.150, 2.80, 4.80
QC intraday precision range (%)	10.47 to 15.84% (LLOQ); 0.94 to 10.79% (above LLOQ)
QC intraday accuracy range (%)	-5.29 to -4.70% (LLOQ); 0.70 to 3.59% (above LLOQ)
QC interday precision range (%)	12.82% (LLOQ); 6.29 to 7.31% (above LLOQ)
QC interday accuracy range (%)	-5.00% (LLOQ); 1.26 to 2.91% (above LLOQ)
Bench-top stability	22.83 hours
Stock stability	17 hours (room temperature) and 24 days (4 °C)
Processed stability	25.05 hours (room temp.) and 25.05 hours (4 °C)
Freeze-thaw stability (cycles)	5 cycles (-70 °C / room temperature), 5 cycles (-70 °C / 37 °C)
Long-term storage stability	51 days (-70 °C)
Dilution integrity	x2 and x5
Selectivity	8 lots of plasma were tested with no observed interference.

SOPs submitted	Yes
Bioanalytical method is acceptable	complete

Comments on the Pre-Study Method Validation:

1. The percentage recovery of the drug appears low; however, the precision of the extraction was fairly tight.

3.6 In Vivo Studies

Appears this way on original.

Table 1. Summary of all in vivo Bioequivalence Studies

Table 2 Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Oxybutynin Mean Parameters (%CV) Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng-hr/mL)	AUC (ng-hr/mL)	T½ (hr)	Kel (hr-1)	Study Report Location
AAI-US-425	Single Dose Two-Way Crossover Fasted Bioequivalence Study of Oxybutynin Chloride 15 mg Extended-Release Tablets in Healthy Subjects	Randomized, Single-Dose, Crossover	Oxybutynin Chloride 15 mg Extended-Release Tablet p.o. [P640102] Ditropan® XL 15 mg Extended-Release Tablet p.o. [0541690]	64(39M/25F) Healthy, normal subjects 29.4 years old (18-59)	4.30 (46.3%) 4.47 (51.5%)	7.00 (5.00 – 12.0) 11.0 (5.00 – 28.0)	80.0 (53.2%) 85.2 (61.0%)	91.8 (58.7%) 94.9 (65.1%)	16.5 (44.2%) 15.1 (38.9%)	0.0493 (37.8%) 0.0513 (31.0%)	AAI-US-425
AAI-US-424	Single Dose Two-Way Crossover Fed Bioequivalence Study of Oxybutynin Chloride 15 mg Extended-Release Tablets in Healthy Subjects	Randomized, Single-Dose, Crossover	Oxybutynin Chloride 15 mg Extended-Release Tablet p.o. [P640102] Ditropan® XL 15 mg Extended-Release Tablet p.o. [0541690]	58(36M/22F) Healthy, normal subjects 28.7 years old (19-65)	3.89 (61.8%) 4.06 (62.1%)	8.04 (5.00 – 13.0) 11.0 (5.00 – 15.0)	71.6 (68.6%) 70.1 (61.5%)	78.9 (68.1%) 75.7 (62.4%)	15.9 (45.9%) 14.7 (30.9%)	0.0511 (39.3%) 0.0523 (34.2%)	AAI-US-424

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Desmethyloxybutynin Mean Parameters (%CV) Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng-hr/mL)	AUC (ng-hr/mL)	T½ (hr)	Kel (hr-1)	Study Report Location
AAI-US-425	Single Dose Two-Way Crossover Fasted Bioequivalence Study of Oxybutynin Chloride 15 mg Extended-Release Tablets in Healthy Subjects	Randomized, Single-Dose, Crossover	Oxybutynin Chloride 15 mg Extended-Release Tablet p.o. [P640102] Ditropan® XL 15 mg Extended-Release Tablet p.o. [0541690]	64(39M/25F) Healthy, normal subjects 29.4 years old (18-59)	25.1 (38.5%) 23.9 (42.5%)	8.00 (4.00 – 13.0) 8.00 (5.00 – 15.0)	441 (50.1%) 445 (52.8%)	470 (53.6%) 468 (57.2%)	11.5 (54.6%) 9.85 (47.5%)	0.0796 (57.1%) 0.0895 (57.2%)	AAI-US-425
AAI-US-424	Single Dose Two-Way Crossover Fed Bioequivalence Study of Oxybutynin Chloride 15 mg Extended-Release Tablets in Healthy Subjects	Randomized, Single-Dose, Crossover	Oxybutynin Chloride 15 mg Extended-Release Tablet p.o. [P640102] Ditropan® XL 15 mg Extended-Release Tablet p.o. [0541690]	58(36M/22F) Healthy, normal subjects 28.7 years old (19-65)	29.3 (38.4%) 30.0 (38.4%)	11.0 (5.00 – 13.0) 10.0 (5.00 – 18.0)	500 (51.7%) 470 (45.5%)	513 (52.0%) 481 (46.0%)	9.23 (43.0%) 8.97 (51.6%)	0.0882 (41.1%) 0.0963 (49.3%)	AAI-US-424

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study# AAI-US-425, N=64					
Oxybutynin					
Parameter	Test	Reference	Ratio	90% C.I.	
				LowCI	UppCI
AUC0-t (ng.h/ml)	69.86	71.25	0.98	88.36	108.79
AUC∞ (ng.h/ml)	78.22	77.85	1.00	90.31	111.79
Cmax (ng/ml)	3.90	3.99	0.98	90.15	106.15

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study# AAI-US-424, N=58					
Oxybutynin					
Parameter	Test	Reference	Ratio	90% C.I.	
				LowCI	UppCI
AUC0-t (ng.h/ml)	60.99	61.40	0.99	94.04	104.91
AUC∞ (ng.h/ml)	67.07	65.85	1.02	96.45	107.53
Cmax (ng/ml)	3.39	3.53	0.96	90.74	101.61

Appears this way on original.

Table 3. Reanalysis of Study Samples

Oxybutynin AAI-US-425 Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Concentration exceeded the upper limit of calibration range	25	40	0.930	1.49	25	40	0.930	1.49
Sample or standard destroyed during the extraction procedure or chromatography	3	0	0.112	0.00	3	0	0.112	0.00
Internal standard outside acceptance criteria	1	1	0.037	0.037	1	1	0.037	0.037
Total	29	41	1.08	1.53	29	41	1.08	1.53

Oxybutynin AAI-US-424 Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Concentration exceeded the upper limit of calibration range	21	22	0.863	0.904	21	22	0.863	0.904
Sample or standard destroyed during the extraction procedure or chromatography	1	0	0.041	0.00	1	0	0.041	0.00
Internal standard outside acceptance criteria	1	11	0.041	0.452	1	11	0.041	0.452
Total	23	23	0.945	0.945	23	23	0.945	0.945

Did use of recalculated plasma concentration data change study outcome? NO for both studies. There were no PK repeats.

3.7 Formulation

Location in appendix	Section , Page 32
If a tablet, is the RLD scored?	Not scored for all strengths
If a tablet, is the test product biobatch scored	**Not scored (same as the RLD)**
Is the formulation acceptable?	**Yes**
If not acceptable, why?	NA

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DFS N078503 N000 20-Oct-2006 and N000 AB 24-Apr-2007
Source of Method (USP, FDA or Firm)	USP test 1
Medium	Simulated gastric fluid without enzyme
Volume (mL)	50 mL
Temperature	37°C
USP Apparatus type	VII (Reciprocating holder)
Rotation (rpm)	30 dpm
USP method	Same as above
USP specification	For 5 mg and 10 mg: 4 hr: NMT 20%, 10 hr: 34.5-59.5%, 24 hr: NLT 80% For 15 mg: 4 hr: NMT 20%, 10 hr: 34.5-59.5%, 24 hr: NLT 75%
Firm Proposed specifications	4 hr: NMT 25%, 10 hr (b) (4) %,

	24 hr: NLT 75%
If a modified-release tablet, was testing done on ½ Tablets?	NA
F2 metric calculated?	Yes
If no, reason why F2 not calculated	NA
Is method acceptable?	Yes, However, the firm should acknowledge the FDA-recommended specifications
If not then why?	

F2 metric, higher strengths compared to lower strength

Higher strength	Lower strength	F2 metric for test					F2 metric for RLD				
		USP test 1	Water paddle 50 rpm	pH 1.2 paddle 50 rpm	pH 4.5 paddle 50 rpm	pH 6.8 paddle 50 rpm	**USP test 1**	Water paddle 50 rpm	pH 1.2 paddle 50 rpm	pH 4.5 paddle 50 rpm	pH 6.8 paddle 50 rpm
5 mg	15 mg	**73**	70	77	71	43	**80**	62	84	85	68
10 mg	15 mg	**61**	67	62	54	54	**83**	75	78	93	86

F2 metric, test compared to reference

Strength	F2 metric				
	USP	Water	pH 1.2	pH 4.5	pH6.8
5 mg	63	51	59	57	39
10 mg	54	55	61	50	60
15 mg	66	85	66	66	67

Oxybutynin Chloride ER Tablets became a USP product in USP 30. There is a USP Dissolution Test 1, which was used for the RLD. The dissolution method which was used for Mylan's product under ANDA 78-293, 76-702 and 76-644, is currently listed in USP Pharmacopeial Forum 33 (4) in-process revision as USP Dissolution Test 2. Please see the following table for the dissolution method history.

Firm	AlZA (Ditropan XI®)	Mylan	Impax
	INNOVATOR: NDA 20-897	78-293, 76-702 and 76-644	76-745
Method	**USP Test 1**, SGF w/o enzymes, 50 ml, apparatus VII, 30 cycles per minutes, 2 to 3 cm amplitude	**US PF 33 (4) Test 2** Row 1: pH 1.2 SGF w/o enzymes; Row 2-4: pH 6.8 SIF w/o Enzymes, 120 ml, apparatus III, 25 dpm	0.1 N HCl for the first 2 hrs), phosphate buffer (with 0.2%SLS), 900 ml, paddle 50 rpm
Specification	For 5 mg and 10 mg: 4 hrs: NMT 20%, 10 hrs: 34.5-59.5%, 24 hr: NLT 80% For 15 mg: 4 hrs: NMT 20%, 10 hrs: 34.5-59.5%, 24 hr: NLT 75%	2 hr: 0 – 10% 4 hr: 10 – 30% 8 hr: 40 – 65% 16 hr: NLT 80%	2 hr NMT (b) (4) 4 hr: 6 hr: 14 hr: NLT

The dissolution data submitted in the original review were previously reviewed by the DBE. The firm conducted dissolution testing using the RLD method; however, it did not complete the multimedia dissolution test as requested by the DBE for ER products. Therefore, *the firm was asked to conduct comparative dissolution testing on each strength of the test and reference products in water and in at least three different media at pH 1.2, 4.5, and 6.8 using USP Apparatus 1 (Basket) at 100 rpm and for the reference products using paddle at 50 rpm in the three different pH media (see dissolution review in DFS N078503 N000 20-Oct-2006)*. The firm had previously called to clarify if they needed to conduct testing using basket at 100 rpm. It was agreed by the DBE that this additional testing was not necessary. In the amendment dated Apr. 24, 2007, the firm submitted some of the requested dissolution data but the multimedia dissolution data for the 10 mg test product was not submitted. *The firm was asked to submit dissolution data for the 10-mg strength of the test and reference product in the 3 different pH media (see dissolution review in DFS N000 AB 24-Apr-2007)*. In the amendment dated July. 5, 2007, the firm submitted the multimedia data for the 10 mg strength.

From the firm submitted data, the dissolution of this product appears independent of pH (except at pH 6.8, the dissolution rate was reduced due to the reduced solubility), agitation speed and apparatus used (apparatus II and apparatus VII were compared). The USP test 1 method is acceptable as a regulatory method for the test product. The dissolution test is **acceptable**. However, the firm's proposed dissolution specification is not acceptable. Based on the submitted data and consult with DBE dissolution focal point, Dr. Seo, the DBE recommended the following specifications:

4 hr: NMT 25%,
10 hr: 40-65%,
24 hr: NLT 75%

Please note these specifications are different from USP specifications and the firm's proposed specifications. The firm should acknowledge the FDA-recommended dissolution specifications.

3.9 Waiver Request(s)

Strengths for which waivers are requested	5 mg and 10 mg
Proportional to strength tested in vivo?	**Yes (see comments below)**
Is dissolution acceptable?	No pending acknowledgement of the FDA-recommended specification
BE for lower strength under CFR 320.24(b)(6) ?	No
If not then why?	pending acknowledgement of the FDA-recommended specification

Comments on the formulation proportionality:

The technology used for the test product is an osmotic tablet in which core tablet is manufactured by (b) (4) .

The three strengths (5, 10 and 15 mg) were developed in a (b) (4) **concept**. All formulations were coated using the same semi-permeable membrane consisting of (b) (4) During the formulation development,, the firm conducted titration studies for each strength to evaluate the impact of different semi-permeable membrane coating weight gains (from (b) (4) . The firm had also confirmed that color coating and imprinting do not affect drug release.

The firm stated in the waiver request that "*The amount of semi-permeable membrane coating weight gain between strengths is* (b) (4) ." Therefore, in this reviewer's opinion, the lower strengths are considered proportionally to the highest strengths.

The dissolution data show that the test product dissolution profiles are comparable to that of the reference for all strength and the dissolution profiles are similar between the lower strengths and the highest strengths for both test and reference product using USP test 1 and water, pH 1.2 and pH 4.5, paddle at 50 rpm (please see previous page for the F2 comparison). The F2 comparison for media of pH 6.8 between the 5 mg and 15 mg strength is less than 50 is

due to the reduced solubility at higher dose and not due to the performance of the formulation of different strengths.

3.10 Deficiency Comments-none

3.11 Recommendations

1. The in vivo bioequivalence study conducted under fasting conditions by Osmotica, on its Oxybutynin Chloride Extended-Release Tablets, 15 mg, lot # P64102, comparing to Ditropan XL ® ER Tablets, 15 mg, lot # 0541690, manufactured by ALZA, has been found **acceptable**.

2. The in vivo bioequivalence study conducted under fed conditions by Osmotica, on its Oxybutynin Chloride Extended-Release Tablets, 15 mg, lot # P64102, comparing to Ditropan XL ® ER Tablets, 15 mg, lot # 0541690, manufactured by ALZA, has been found **acceptable**..

3. The dissolution testing is **acceptable.** The dissolution testing should be conducted as specified in USP 30: 50 ml of simulated gastric fluid without enzymes at 37°C, using USP apparatus 7, 30 cycles per minutes; 2- to 3-cm amplitude. The firm's proposed dissolution specification is **not acceptable**. The firm should acknowledge the following FDA recommended specifications:

   4 hr: NMT 25%,
   10 hr: 40-65%,
   24 hr: NLT 75%

4. The formulations of the 5 mg and 10 mg strengths are proportionally similar to that of the 15 mg strength of the test product which underwent bioequivalence testing. The DBE may deem lower strengths of the test product bioequivalent to the RLD based on CFR 320.24(b)(6), upon the firm's acknowledge of its acceptance of above FDA-recommended dissolution specifications..

3.12 Comments for Other OGD Disciplines

Discipline	Comment
	This ANDA is not scheduled for a DSI inspection.

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	BOSMO7000P1, AAI-US-425
Study Title	Single Dose Two-Way Crossover Fasted Bioequivalence Study of Oxybutynin Chloride 15 mg Extended-Release Tablets in Healthy Subjects
Clinical Site (Name, Address, Phone #)	AAI Pharma, Inc. 200 Perimeter Park Dr. Morrisville, North Carolina 27560 919-481-5700
Principal Investigator	Evin H. Sides, M.D.
Dosing Dates	Period 1: 07/07/06 Period 2: 07/14/06
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	07/19/06 to 08/03/06
Analytical Director	(b) (6) M.S., R.Ph.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	07/07/06 to 08/03/06 (28 days)

Appears this way on original.

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Oxybutynin Chloride Extended-release Tablets	Ditropan XL®, Oxybutynin Chloride Extended-release Tablets
Manufacturer	Osmotica Pharmaceutical (b) (4)	Alza Corp.
Batch/Lot No.	P640102	0541690
Manufacture Date	3/16/2006	N/A
Expiration Date	N/A	5/2007
Strength	15 mg	15 mg
Dosage Form	Extended-release tablets	Extended-release tablets
Bio-batch Size	(b) (4) tablets (theoretical)	N/A
Production Batch Size	(b) (4) tablets	N/A
Potency	99.8%	102.9%
Content Uniformity (mean, %CV)	99.9%, 1.4%	N/A
Dose Administered	1 tablet	1 tablet
Route of Administration	Oral	oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Number of Subjects enrolled: 64 Number of Subjects completed: 64 Number of Subjects analyzed statistically: 64 per protocol

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 1, 2, 4, 6, 7, 10, 12, 14, 17, 23, 28, 32, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 47, 48, 50, 54, 55, 56, 58, 60, 63. BA: 3, 5, 8, 9, 11, 13, 15, 16, 18, 19, 20, 21, 22, 24, 25, 26, 27, 29, 30, 31, 33, 36, 46, 49, 51, 52, 53, 57, 59, 61, 62, 64
Blood Sampling Times	0, 1.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 18, 24, 28, 32, 36, 48, 60 h
Blood Volume Collected/Sample	10 ml in tubes containing K2 EDTA
Blood Sample Processing/Storage	The blood samples were centrifuged as soon as possible under refrigerated conditions at 3000 rpm for 10 minutes. The resulting plasma was aliquotted into two pre-cooled labeled polypropylene tubes. The samples were stored frozen at -70°C until assayed.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	Subjects fasted overnight for approximately 10 hours before dosing and for 4 hours following dose administration.
Length of Confinement	12 h prior to and until 36 h post-dose blood draw
Safety Monitoring	Each subject was tested for normal vital signs (temperature, pulse and sitting blood pressure) prior to dosing each study period.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

AAI-US-425 Oxybutynin Chloride 15 mg Extended Release Tablets Fasted Study			
		Treatment Groups	
		Test Product N = 64	Reference Product N = 64
Age (years)	Mean ± SD	29.4 ± 9.9	29.4 ± 9.9
	Range	18-59	18-59
Age Groups	< 18	0(0%)	0(0%)
	18 – 40	56(88%)	56(88%)
	41 – 64	8(13%)	8(13%)
	65 – 75	0(0%)	0(0%)
	> 75	0(0%)	0(0%)
Sex	Male	39(61%)	39(61%)
	Female	25(39%)	25(39%)
Race	Asian	3(5%)	3(5%)
	Black	37(58%)	37(58%)
	Caucasian	23(36%)	23(36%)
	Hispanic	1(2%)	1(2%)
	Other	0(0%)	0(0%)
BMI	Mean ± SD	25.4 ± 2.7	25.4 ± 2.7
	Range	19.4-30.1	19.4-30.1
Other Factors			
Height (Inches)	Mean ± SD	67.4 ± 3.9	67.4 ± 3.9
	Range	60-77	60-77
Weight (pounds)	Mean ± SD	163.8 ± 23.9	163.8 ± 23.9
	Range	121-225	121-225

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. AAI-US-425 Oxybutynin Chloride 15 mg Extended Release Tablets Fasted Study				
Subject No	Reason for dropout/replacement*	Period	Replaced?	Replaced with
N/A	N/A	N/A	N/A	N/A
** N/A = Not Applicable				

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	AAI-US-425 Oxybutynin Chloride 15 mg Extended Release Tablets Fasted Bioequivalence Study	
	Test	Reference
Body as a Whole		
Headache	4 (44.4%)	4 (22.2%)
Lightheadedness		1 (5.6%)
Dizziness	1 (11.1%)	
Fatigue		1 (5.6%)
Sleepiness	1 (11.1%)	1 (5.6%)
Cardiovascular		
Chest Pain		1 (5.6%)
Gastrointestinal		
Vomiting		2 (11.1%)
Nausea	2 (22.2%)	5 (27.8%)
Other organ systems		
Dry Mouth	1 (11.1%)	2 (11.1%)
Right Leg Pain		1 (5.6%)
Total	9 (100%)	18 (100%)

Subject#22 vomited 2 times 16 hrs after administration of the reference product. Since it is within the labeled dosing interval (24 hrs), the subject should be excluded from the statistical analysis per General BA/BE guidance. The outcome did not change after exclusion of this subject from statistical analysis.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. AAI-US-425 Oxybutynin Chloride 15 mg Extended Release Tablets Fasted Study				
Type	Time Point (Hr.)	Period	Subject (Test)	Subject (Ref.)
Temperature Excursions	N/A	N/A	All	All
Late Phlebotomy	N/A	N/A	3, 23, 47, 59	3, 9, 16, 18, 42, 61

Comments on Dropouts/Adverse Events/Protocol Deviations:

- A total of 27 adverse events (9 in test product, 18 in reference product) were reported throughout the course of the study. The adverse events were mild or moderate in severity.
- The sampling time deviations were adjusted for PK analysis.
- The overall protocol deviations did not compromise the integrity of the study.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. BOSMO7000P1 Analyte Oxybutynin								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	0.0500	0.100	0.400	1.20	2.80	4.00	5.60	6.40
Inter day Precision (%CV)	5.99	5.80	5.39	4.04	4.52	4.72	5.01	5.92
Inter day Accuracy (%Actual)	-0.06	0.12	-0.05	0.51	0.00	-1.06	0.06	0.46
Linearity	(Range of r^2 values) 0.99172 to 0.99906							
Linearity Range (ng/mL)	0.0500 to 6.40 ng/mL							
Sensitivity/LOQ (ng/mL)	0.0500 ng/mL							

Bioequivalence Study No. BOSMO7000P1 Analyte Oxybutynin			
Parameter	Quality Control Samples		
Concentration (ng/mL)	0.150	1.60	4.80
Inter day Precision (%CV)	5.82	5.31	4.72
Inter day Accuracy (%Actual)	0.68	0.60	1.86

Comments on Study Assay Validation: ok

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	serially

Comments on Chromatograms: Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
62470-01	11-13-2006	Sample Re-Assays for Bioanalytical Projects

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	NA

Summary/Conclusions, Study Assays: acceptable

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Oxybutynin

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		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	80.02	53.19	23.62	211.98	85.17	61.02	6.07	284.73	0 94
AUCI	ng hr/mL	91.84	58.75	24.54	270.55	94.95	65.11	6.80	306.47	0 97
CMAX	ng/mL	4.30	46.26	1.47	10.90	4.47	51.50	1.49	14.40	0 96
TMAX	hr	7.00	.	5.00	12.00	11.00	.	5.00	28.00	0.64
KE	hr-1	0.05	37.76	0.02	0.10	0.05	30.96	0.02	0.09	0 96
THALF	hr	16.46	44.19	6.86	41.86	15.14	38.89	7.66	41.67	1.09

Desethyloxybutynin

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	441.32	50.10	107.56	1049.43	444.81	52.78	103.20	1162.48	0.99
AUCI	ng hr/mL	469.97	53.55	114.38	1224.22	468.45	57.18	105.12	1382.34	1.00
CMAX	ng/mL	25.05	38.52	9.95	53.00	23.92	42.50	11.10	62.70	1.05
TMAX	hr	8.00	.	4.00	13.00	8.00	.	5.00	15.00	1.00
KE	hr-1	0.08	57.13	0.02	0.22	0.09	57.20	0.03	0.28	0.89
THALF	hr	11.48	54.63	3.08	34.47	9.85	47.49	2.47	25.08	1.17

Metabolite plasma concentrations were comparable for the test and reference products
* Tmax values are presented as median.

Appears this way on original.

Table 15. Geometric Means and 90% Confidence Intervals Calculated by the Firm

Oxybutynin Chloride
15 mg Extended-Release Tablets
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals
Fasted Bioequivalence Study (AAI-US-425)

Oxybutynin				
Parameter	Test	Reference	Ratio	90% C.I.
AUC0-t	69.9	71.3	0.980	0.884 – 1.088
AUC	78.2	77.8	1.005	0.902 – 1.120
Cmax	3.90	3.99	0.978	0.902 – 1.061
Desmethyloxybutynin				
AUC0-t	393	392	1.001	0.921 – 1.088
AUC	414	407	1.015	0.933 – 1.105
Cmax	23.5	22.2	1.057	0.992 – 1.126

Table 16. Geometric Means and 90% Confidence Intervals Calculated by the Reviewer

Oxybutynin

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	69.86	71.25	0.98	88.36	108.79
LAUCI	78.22	77.85	1.00	90.31	111.79
LCMAX	3 90	3.99	0.98	90.15	106.15

Desethyloxybutynin

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	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	392.74	392.47	1.00	92.06	108.78
LAUCI	413.55	407.37	1.02	93.30	110.46
LCMAX	23.47	22.21	1.06	99.21	112.56

Table 17. Additional Study Information, for parent drug only

ROOT MEAN SQUARE ERROR

Parameter	RMSE
LAUCT	0.3523
LAUCI	0.3613
LCMAX	0.2767

STATISTICS ON AUCT/AUCI RATIOS

Treatment	n	Mean	Minimum	Maximum
TEST	62	0 91	0.70	0.99
REFERENCE	64	0 92	0.70	0.98

	Test	Test
Kel and AUC∞ determined for how many subjects?	All except for Subjects#16, 39	All
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	20 (<5% of the corresponding Cmax)	1 (<5% of the corresponding Cmax)
first measurable drug concentration as Cmax	none	none
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:

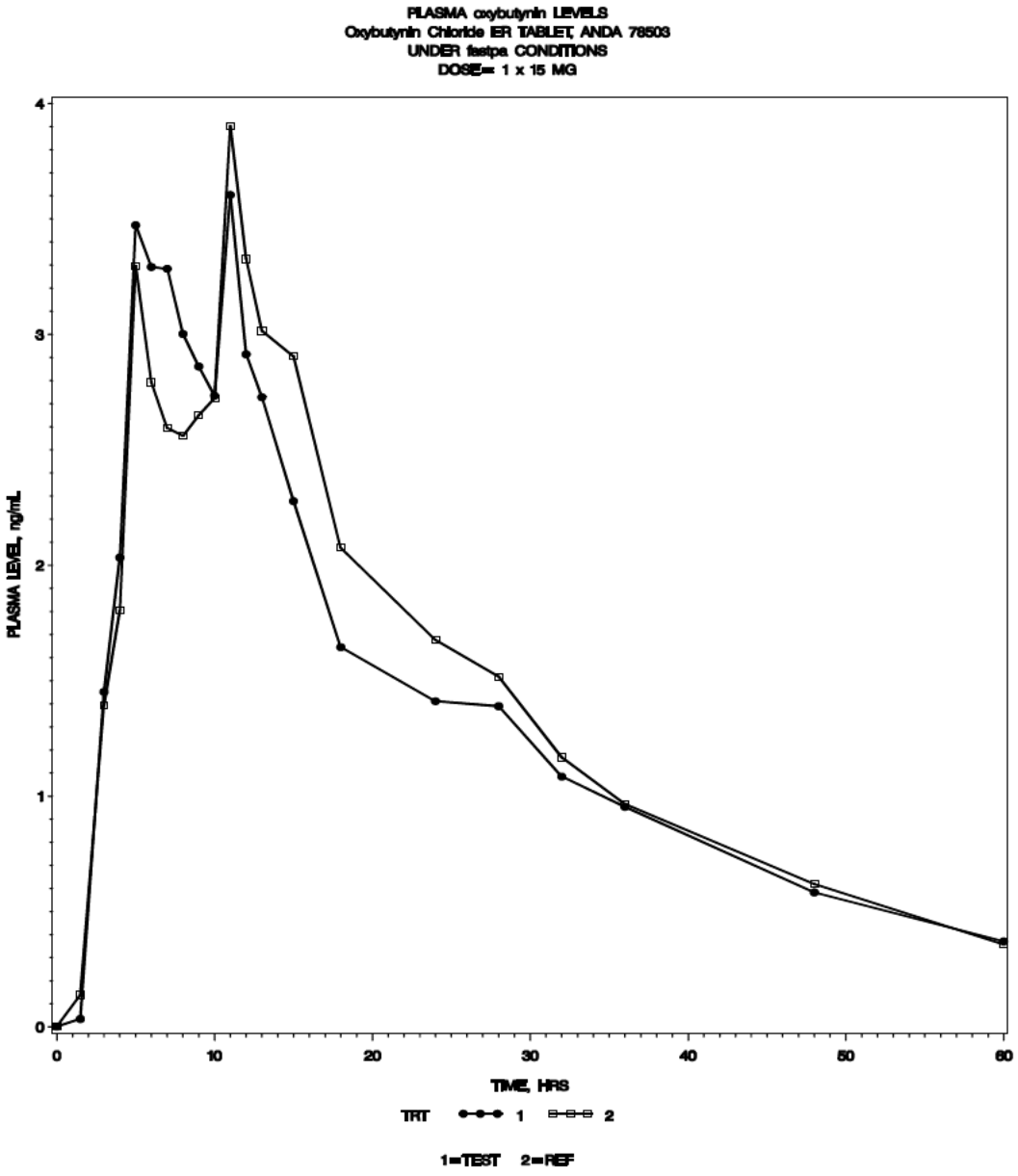
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The 90% confidence intervals for lnAUC0-t, lnAUC∞, and lnCmax are within the acceptable limits of 80-125%.
- Statistically significant sequence effect was observed for Cmax of parent drug. However, this study meets the criteria for acceptability of studies with sequence effects listed in Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (Jan. 2001). Therefore, the observed sequence effect should not compromise the assessment of bioequivalence.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: acceptable

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=64)		Reference (n=64)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	800.00	0.00	800.00	0.69
1.50	0.03	235.43	0.14	121.76	0.25
3.00	1.45	68.65	1.39	79.19	1.04
4.00	2.03	65.11	1.80	67.58	1.13
5.00	3.47	45.46	3.30	61.59	1.05
6.00	3.29	48.43	2.79	69.91	1.18
7.00	3.28	47.71	2.59	69.81	1.27
8.00	3.00	51.68	2.56	67.26	1.17
9.00	2.86	50.51	2.65	64.87	1.08
10.00	2.74	54.56	2.72	64.38	1.00
11.00	3.60	54.45	3.90	55.82	0.92
12.00	2.91	51.48	3.33	67.19	0.88
13.00	2.73	54.60	3.02	60.53	0.90
15.00	2.28	55.35	2.91	62.44	0.78
18.00	1.65	55.32	2.08	64.51	0.79
24.00	1.41	60.79	1.68	64.07	0.84
28.00	1.39	63.26	1.52	67.67	0.92
32.00	1.08	68.37	1.17	70.80	0.93
36.00	0.95	66.84	0.97	82.52	0.99
48.00	0.58	86.67	0.62	101.59	0.94
60.00	0.37	93.82	0.36	99.47	1.04

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study


PLASMA oxybutynin LEVELS
Oxybutynin Chloride ER TABLET, ANDA 78503
UNDER fastpa CONDITIONS
DOSE= 1 x 15 MG
PLASMA LEVEL, ng/mL
0
1
2
3
4
0
10
20
30
40
50
60
TIME, HRS
TRT 1 2
1=TEST 2=REF

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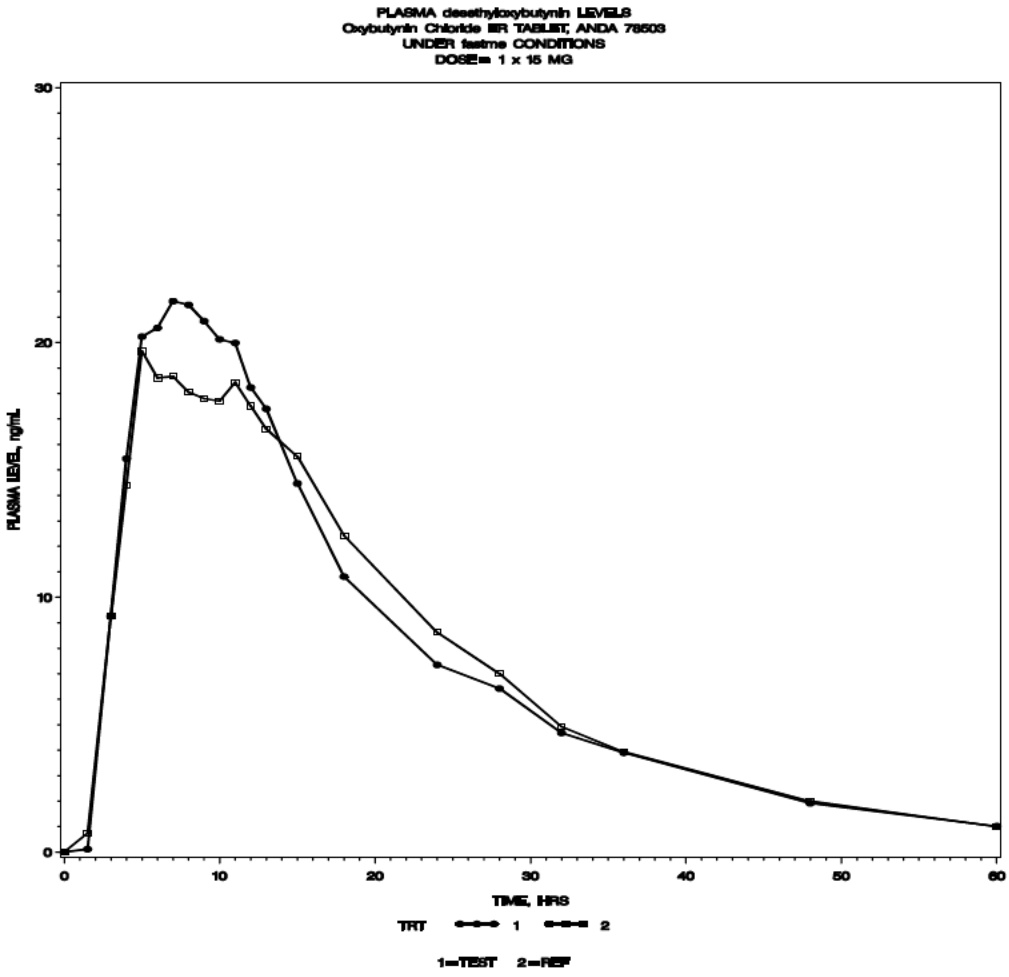

4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	BOSMO7001P1, AAI-US-424
Study Title	Single Dose Two-Way Crossover Fed Bioequivalence Study of Oxybutynin Chloride 15 mg Extended-Release Tablets in Healthy Subjects
Clinical Site (Name, Address, Phone #)	AAI Pharma, Inc. 200 Perimeter Park Dr. Morrisville, North Carolina 27560 919-481-5700
Principal Investigator	Evin H. Sides, M.D.
Dosing Dates	Period 1: 06/21/06 Period 2: 06/28/06
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	07/07/06 to 07/28/06
Analytical Director	(b) (6) M.S., R.Ph.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	06/21/06 to 07/28/06 (38 days)

Table 20. Product Information

Appears this way on original.

Product	Test	Reference
Treatment ID	A	B
Product Name	Oxybutynin Chloride Extended-release Tablets	Ditropan XL®, Oxybutynin Chloride Extended-release Tablets
Manufacturer	Osmotica Pharmaceutical/	Alza Corp.
Batch/Lot No.	P640102	0541690
Manufacture Date	3/16/2006	N/A
Expiration Date	N/A	5/2007
Strength	15 mg	15 mg
Dosage Form	Extended-release tablets	Extended-release tablets
Bio-batch Size	(b) (4) tablets (theoretical)	N/A
Production Batch Size	(b) (4) tablets	N/A
Potency	99.8%	102.9%
Content Uniformity (mean, %CV)	99.9%, 1.4%	N/A
Dose Administered	1 tablet	1 tablet
Route of Administration	Oral	oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	Number of Subjects planned in the protocol: 64 Number of Subjects enrolled: 59 Number of Subjects completed: 58 Number of Subjects analyzed statistically: 58
No. of Sequences	2
No. of Periods	2

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No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 4, 11, 15, 18, 19, 20, 21, 23, 24, 28, 29, 30, 31, **32**, 35, 36, 38, 41, 42, 45, 46, 47, 50, 52, 53, 56, **58**, 60, 61, 62, **63, 64** BA: 1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 14, 16, 17, 22, 25, 26, 27, 33, 34, 37, 39, 40, **43**, 44, 48, 49, **51,** 54, 55, 57, 59, Subject numbers in bold were not used in the study.
Blood Sampling Times	Same as in the fasting study
Blood Volume Collected/Sample	Same as in the fasting study
Blood Sample Processing/Storage	Same as in the fasting study
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	Following an overnight fast, subjects were given a standardized, high fat breakfast 30 minutes prior to dosing. Subjects fasted for at least 4 hrs after dosing.
Length of Confinement	Same as in the fasting study
Safety Monitoring	Same as in the fasting study
Standard FDA Meal Used?	Yes
If No, then meal composition is listed in the table below	NA

Composition of Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics of Subjects Completing the Bioequivalence Study

AAI-US-424 Oxybutynin Chloride 15 mg Extended Release Tablets Fed Study			
		Treatment Groups	
		Test Product N = 58	Reference Product N = 58
Age (years)	Mean ± SD	28.7 ± 9.5	28.7 ± 9.5
	Range	19-65	19-65
Age Groups	< 18	0(0%)	0(0%)
	18 – 40	52(90%)	52(90%)
	41 – 64	5(9%)	5(9%)
	65 – 75	1(2%)	1(2%)
	> 75	0(0%)	0(0%)
Sex	Male	36(62%)	36(62%)
	Female	22(38%)	22(38%)
Race	Asian	0(0%)	0(0%)
	Black	35(60%)	35(60%)
	Caucasian	21(36%)	21(36%)
	Hispanic	1(2%)	1(2%)
	Other	1(2%)	1(2%)
BMI	Mean ± SD	25.8 ± 3.0	25.8 ± 3.0
	Range	19.1-30.3	19.1-30.3
Other Factors			
Height (Inches)	Mean ± SD	67.5 ± 3.0	67.5 ± 3.0
	Range	59-72	59-72
Weight (pounds)	Mean ± SD	167.7 ± 24.5	167.7 ± 24.5
	Range	115-208	115-208

Table 23. Dropout Information, Fed Bioequivalence Study

Study No. AAI-US-424 Oxybutynin Chloride 15 mg Extended Release Tablets Fed Study				
Subject No	**Reason for dropout/replacement***	**Period**	**Replaced?**	**Replaced with**
51	Withdrew Consent	1	No	N/A
** N/A = Not Applicable				

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	**Reported Incidence by Treatment Groups**	
	AAI-US-424 Oxybutynin Chloride 15 mg Extended Release Tablets Fed Bioequivalence Study	
	Test	**Reference**
Body as a Whole		
Headache	5 (41.7%)	5 (38.5%)
Sleepiness	1 (8.3%)	
Vasovagal	1 (8.3%)	
Nausea		1 (7.7%)
Cardiovascular		
Chest Pain	2 (16.7%)	
Gastrointestinal		
Increased urination		1 (7.7%)
Other organ systems		
Dry Mouth	3 (25.0%)	4 (30.8%)
Bilateral Flank Pain		1 (7.7%)
Dry Eyes		1 (7.7%)
Total	12 (100%)	13 (100%)

Table 25. Protocol Deviations, Fed Bioequivalence Study

Study No. AAI-US-424 Oxybutynin Chloride 15 mg Extended Release Tablet Fed Study				
Type	**Time Point (Hr.)**	**Period**	**Subject (Test)**	**Subject (Ref.)**
Late Phlebotomy	N/A	N/A	8, 15, 24, 36, 47, 50, 56, 60, 62	4, 8, 40, 50
No Exclusion of Emesis	N/A	N/A	22	22
Temperature Excursions	N/A	N/A	All	All
Out of Range BMI	Screening	Screening	51**	51**
** Subject has < 10% body fat and is an athlete in football.				

* The deviation of "no exclusion of emesis" should be in the fasting study. The firm mistakenly reported in the fed study.

Comments on Adverse Events/Protocol Deviations:

- A total of 25 adverse events (12 in test product, 13 in reference product) were reported throughout the course of the study. The adverse events were mild or moderate in severity.
- The sampling time deviations were adjusted for PK analysis.
- The overall protocol deviations did not compromise the integrity of the study.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. BOSMO7001P1 Analyte Oxybutynin								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.0500	0.100	0.400	1.20	2.80	4.00	5.60	6.40
Inter day Precision (%CV)	6.79	6.25	6.09	5.38	5.90	5.07	5.21	6.43
Inter day Accuracy (%Actual)	0.13	-0.66	1.47	0.63	-0.19	-1.46	-0.43	0.50
Linearity	(Range of r^2 values) 0.98903 to 0.99906							
Linearity Range (ng/mL)	0.0500 to 6.40 ng/mL							
Sensitivity/LOQ (ng/mL)	0.0500 ng/mL							

Bioequivalence Study No. BOSMO7001P1 Analyte Oxybutynin			
Parameter	**Quality Control Samples**		
Concentration (ng/mL)	0.150	1.60	4.80
Inter day Precision (%CV)	7.34	6.56	7.17
Inter day Accuracy (%Actual)	1.33	1.59	-0.59

Comments on Study Assay Validation: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

Same as in the fasting study

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	NA

Summary/Conclusions, Study Assays: acceptable

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

Oxybutynin

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		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	71.65	68.58	23.54	326.36	70.07	61.49	23.26	296.25	1.02
AUCI	ng hr/mL	79.00	68.70	24.32	345.76	75.72	62.44	24.41	317.79	1.04
CMAX	ng/mL	3.89	61.81	1.43	15.40	4.06	62.14	1.47	15.40	0.96
TMAX	hr	8.04	.	5.00	13.00	11.00	.	5.00	15.00	0.73
KE	hr-1	0.05	37.94	0.02	0.11	0.05	34.21	0.03	0.10	0.99
THALF	hr	15.37	38.49	6.40	36.65	14.69	30.92	7.08	26.36	1.05

Desethyloxybutynin

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	500.30	51.73	192.33	1399.58	469.92	45.45	181.45	1229.67	1.06
AUCI	ng hr/mL	512.60	52.00	194.02	1417.61	481.11	46.03	183.02	1244.71	1.07
CMAX	ng/mL	29.30	38.37	12.80	68.60	29.98	38.37	11.60	66.40	0.98
TMAX	hr	11.00	.	5.00	13.00	10.00	.	5.00	18.00	1.10
KE	hr-1	0.09	41.08	0.03	0.23	0.10	49.32	0.02	0.24	0.92
THALF	hr	9.23	43.05	3.06	23.09	8.97	51.63	2.93	31.05	1.03

* Tmax values are presented as median, range.

Table 30. Geometric Means and 90% Confidence Intervals Calculated by the Firm

Fed Bioequivalence Study (AAI-US-424)				
Oxybutynin				
Parameter	Test	Reference	Ratio	90% C.I.
AUC0-t	61.0	61.4	0.993	0.940 – 1.049
AUC	66.9	65.9	1.016	0.962 – 1.073
Cmax	3.39	3.53	0.960	0.907 – 1.016
Desmethyloxybutynin				
AUC0-t	448	431	1.040	0.988 – 1.094
AUC	459	440	1.042	0.991 – 1.097
Cmax	27.4	28.0	0.980	0.919 – 1.045

Table 31. Geometric Means and 90% Confidence Intervals Calculated by the Reviewer

Oxybutynin

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	60.99	61.40	0.99	94.04	104.91
LAUCI	67.07	65.85	1.02	96.45	107.53
LCMAX	3 39	3.53	0.96	90.74	101.61

Desethyloxybutynin

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	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	447.67	430.60	1.04	98.81	109.38
LAUCI	458.80	440.13	1.04	99.07	109.68
LCMAX	27.40	27.95	0.98	91.94	104.53

Table 32. Additional Study Information for Parent drug only

ROOT MEAN SQUARE ERROR

Parameter	RMSE
LAUCT	0.1759
LAUCI	0.1749
LCMAX	0.1821

STATISTICS ON AUCT/AUCI RATIOS

Treatment	n	Mean	Minimum	Maximum
TEST	56	0 92	0.73	0.99
REFERENCE	58	0 93	0.77	0.99

	Test	Reference
Kel and AUC∞ determined for how many subjects?	All except 61, 56	All
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	None	None
first measurable drug concentration as Cmax	None	none
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:

- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The 90% confidence intervals for lnAUC0-t, lnAUC∞, and lnCmax are within the acceptable limits of 80-125%.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study: acceptable

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	Test (n=58)		Reference (n=58)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.50	0.01	276.25	0.09	93.08	0.09
3.00	1.23	88.29	1.40	97.46	0.88
4.00	2.04	76.98	2.08	78.75	0.98
5.00	3.02	54.83	2.63	54.59	1.15

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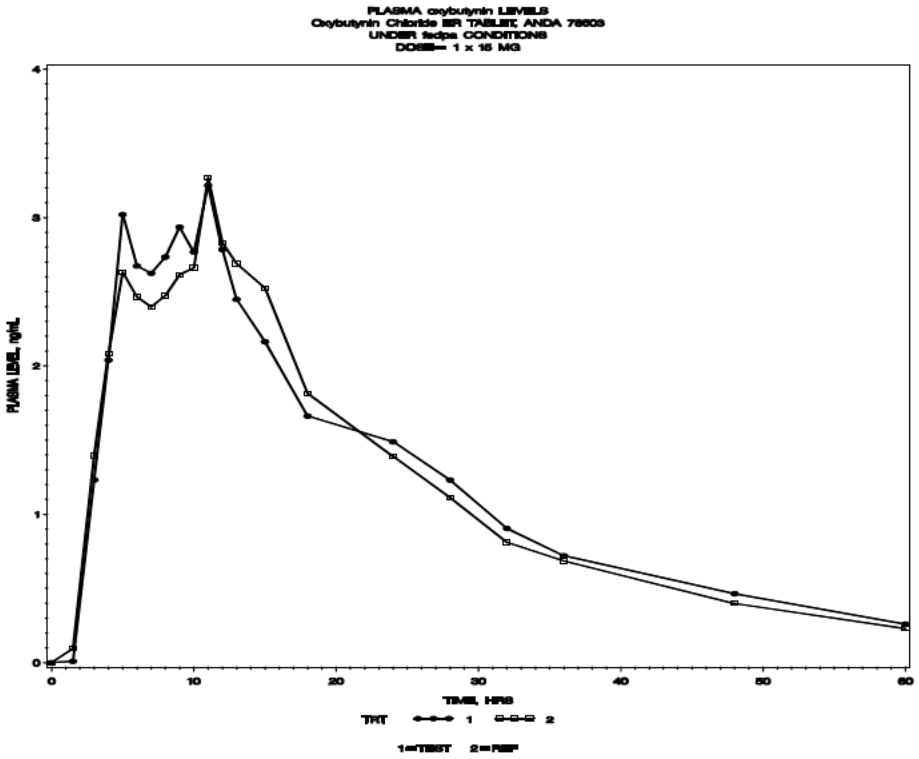
	Test (n=58)		Reference (n=58)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
6.00	2.67	53.12	2.46	54.91	1.08
7.00	2.63	54.27	2.40	62.08	1.09
8.00	2.73	62.89	2.47	61.11	1.11
9.00	2.94	76.35	2.61	63.66	1.12
10.00	2.77	74.35	2.66	57.81	1.04
11.00	3.22	63.54	3.27	65.89	0.98
12.00	2.78	61.30	2.83	62.37	0.98
13.00	2.45	59.84	2.69	65.39	0.91
15.00	2.16	76.92	2.53	79.09	0.86
18.00	1.66	80.69	1.81	84.66	0.92
24.00	1.49	92.92	1.39	78.16	1.07
28.00	1.23	95.53	1.11	74.63	1.11
32.00	0.90	76.03	0.81	75.83	1.12
36.00	0.72	75.72	0.69	75.54	1.05
48.00	0.46	84.59	0.40	84.00	1.17
60.00	0.26	84.47	0.23	88.47	1.13

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



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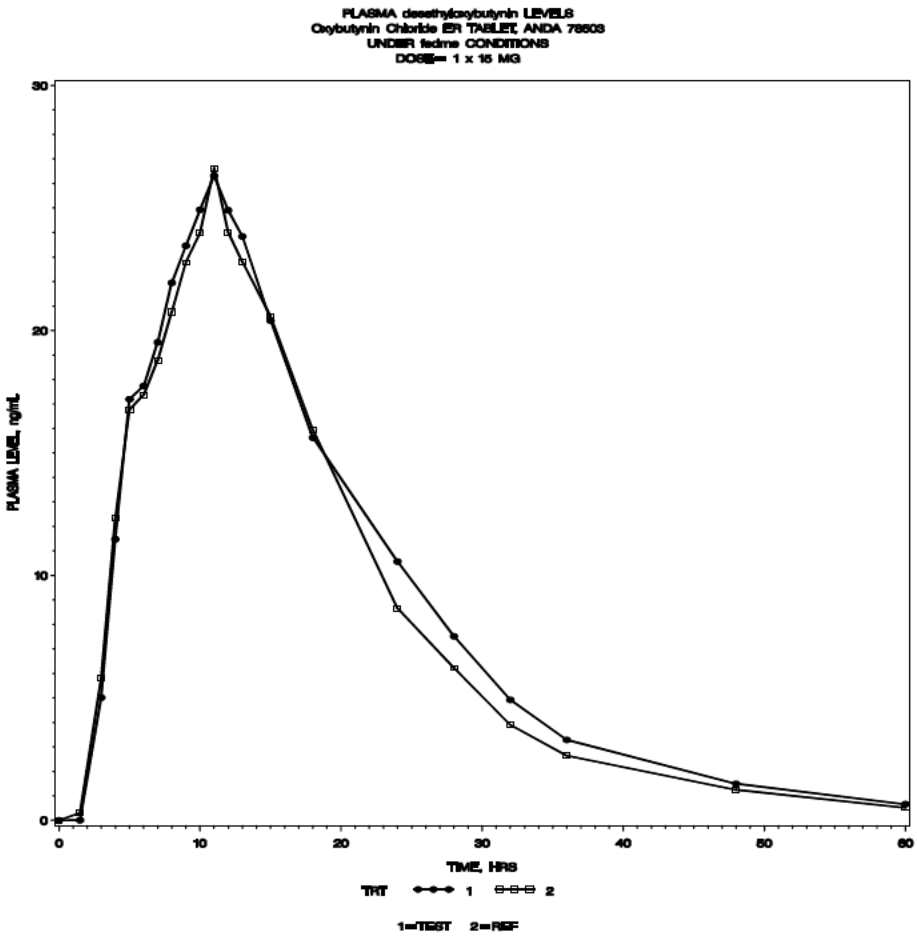


4.2 Formulation Data

Formulation of the reference product:

Following this page, 1 page withheld in full - (b)(4)

4.3 Dissolution Data

Dissolution data submitted in the original review and the two amendments were presented below. Please note that the firm has used a different batch of the reference product in multimedia testing because the initial batches were expired.

Appears this way on original.

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	water
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4)% 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference-Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	7/24/06	Test Product P63970 3/15/2006	5 mg ER tablet	12	Mean	0	0	14	28	40	50	60	67	72	74	78	82	83	NA
					Range	(b) (4)													
					%CV	0	180.9	13.5	7.5	5.3	4.6	2.2	2.7	2.3	2.3	2.8	1.8	2.6	
NA	7/10/06	Reference Product 0533889 8/2007	5 mg ER tablet	12	Mean	0	1	12	25	39	53	67	78	86	90	93	94	96	NA
					Range	(b) (4)													
					%CV	0	114.6	20.4	10.3	10.4	7.6	8.0	7.0	6.2	5.6	5.9	6.0	6.2	

NA - No study report

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	water
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4)% 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference-Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	6/26/06	Test Product P63990 3/15/2006	10 mg ER tablet	12	Mean	0	1	14	27	37	48	57	65	70	75	78	81	84	NA
					Range	(b) (4)													
					%CV	0	82.2	13.1	12.3	6.3	6.2	5.0	4.3	3.6	3.1	3.3	2.9	2.7	
NA	7/10/06	Reference Product 0531570 1/2007	10 mg ER tablet	12	Mean	0	1	12	25	39	54	68	78	84	86	87	88	89	NA
					Range	(b) (4)													
					%CV	0	71.6	20.7	18.2	16.7	15.8	13.7	8.9	5.5	3.7	3.2	3.6	3.4	

NA - No study report.

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	water
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4)% 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference-Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	6/28/06	Test Product P64010 3/16/2006	15 mg ER tablet	12	Mean	0	3	14	26	39	53	62	72	77	81	84	86	86	NA
					Range	(b) (4)													
					%CV	0	40.0	20.9	17.4	13.5	8.4	5.7	5.4	3.9	3.7	3.1	3.0	1.8	
NA	7/12/06	Reference Product 0541690 5/2007	15 mg ER tablet	12	Mean	0	2	12	25	39	53	67	73	77	81	83	86	88	NA
					Range	(b) (4)													
					%CV	346.4	52.2	15.6	11.2	9.4	7.8	7.4	2.1	2.2	1.8	1.7	1.9	1.5	

NA - No study report.

Dissolution Conditions	Apparatus:	7
	Dips per minute:	30 dpm
	Medium:	Simulated gastric fluid without enzyme
	Volume:	50 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications associated with Apparatus 7 (simulated gastric fluid without enzyme)	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4)% 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference-Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	6/26/06	Test Product P63970 3/15/2006	5 mg ER tablet	12	Mean	0	0	12	27	39	51	60	68	73	77	80	82	84	NA
					Range	(b) (4)													
					%CV	0	346.4	15.9	7.3	5.2	4.6	3.7	3.2	2.2	1.9	1.8	1.9	1.7	
NA	6/27/06	Reference Product 0533889 8/2007	5 mg ER tablet	12	Mean	0	1	11	22	33	44	56	67	78	84	88	90	91	NA
					Range	(b) (4)													
					%CV	0	26.6	19.0	11.6	10.8	10.4	9.9	9.0	7.5	5.6	3.3	2.4	2.2	

NA - No study report.

Dissolution Conditions	Apparatus:	7
	Dips per minute:	30 dpm
	Medium:	Simulated gastric fluid without enzyme
	Volume:	50 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications associated with Apparatus 7 (simulated gastric fluid without enzyme)	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4)% 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference-Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours)													Study Report Location
						1	2	4	6	8	10	12	14	16	18	20	22	24	
NA	6/20/06	Test Product P63990 3/15/2006	10 mg ER tablet	12	Mean	0	1	12	24	35	46	55	63	70	75	78	81	83	NA
					Range	(b) (4)													
					%CV	0	69.3	12.3	6.2	5.0	4.5	4.0	3.5	2.9	2.6	2.3	2.0	2.0	
NA	6/21/06	Reference Product 0531570 1/2007	10 mg ER tablet	12	Mean	0	1	11	23	36	49	63	75	84	88	90	91	92	NA
					Range	(b) (4)													
					%CV	0	47.5	17.8	14.1	12.5	11.9	11.2	9.2	5.7	3.1	2.5	2.5	2.5	

Dissolution Conditions	Apparatus:	7
	Dips per minute:	30 dpm
	Medium:	Simulated gastric fluid without enzyme
	Volume:	50 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications associated with Apparatus 7 (simulated gastric fluid without enzyme)	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4)% 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference-Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours)													Study Report Location
						1	2	4	6	8	10	12	14	16	18	20	22	24	
NA	6/28/06	Test Product P64010 3/16/2006	15 mg ER tablet	12	Mean	0	3	14	27	40	53	64	72	77	81	84	87	89	NA
					Range	(b) (4)													
					%CV	0	36.2	7.7	4.2	3.2	2.1	2.0	1.8	1.5	1.6	1.6	1.6	1.3	
NA	6/29/06	Reference Product 0541690 5/2007	15 mg ER tablet	12	Mean	0	1	10	21	34	46	59	72	82	87	89	91	92	NA
					Range	(b) (4)													
					%CV	0	83.1	32.9	21.4	15.0	13.1	11.5	10.0	6.6	3.6	2.5	2.4	2.3	

NA - No study report.

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	pH 1.2 buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4)% 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference-Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	7/18/06	Test Product P63970 3/15/2006	5 mg ER tablet	12	Mean	0	0	13	27	38	49	58	66	71	75	77	80	83	NA
					Range	(b) (4)													
					%CV	0	0	11.0	6.7	5.0	3.8	3.7	3.0	2.5	2.1	2.2	2.0	2.2	
NA	3/28/07	Reference Product 0604348 1/2008	5 mg ER tablet	12	Mean	0	1	11	23	34	45	57	68	78	85	89	91	92	NA
					Range	(b) (4)													
					%CV	346.4	60.3	29.5	17.2	14.1	12.2	10.7	9.5	7.9	5.3	3.9	2.9	2.9	

NA - No study report.

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	pH 4.5 buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4)% 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference-Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	7/18/06	Test Product P63970 3/15/2006	5 mg ER tablet	12	Mean	0	0	14	28	40	51	59	69	73	77	80	83	85	NA
					Range	(b) (4)													
					%CV	0	346.4	11.7	6.9	5.4	4.5	4.0	3.4	3.4	2.8	2.7	2.4	2.7	
NA	3/27/07	Reference Product 0604348 1/2008	5 mg ER tablet	12	Mean	0	1	11	24	36	48	60	72	82	89	92	94	95	NA
					Range	(b) (4)													
					%CV	0	86.1	25.1	15.8	14.7	13.5	12.7	11.1	9.4	5.7	3.4	2.5	2.6	

NA - No study report.

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	pH 6.8 buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4), 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference- Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	7/24/06	Test Product P63970 3/15/2006	5 mg ER tablet	12	Mean	0	0	8	18	27	34	42	48	51	56	52	56	61	NA
					Range	(b) (4)													
					%CV	0	0	16.0	8.6	8.8	6.4	6.3	4.5	5.1	4.2	4.1	5.3	4.3	
NA	3/27/07	Reference Product 0604348 1/2008	5 mg ER tablet	12	Mean	0	1	11	22	32	42	53	63	73	78	82	83	84	NA
					Range	(b) (4)													
					%CV	0	73.9	26.3	16.7	14.0	13.1	11.3	10.2	9.4	7.7	5.6	3.4	2.7	

NA - No study report.

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	pH 1.2 buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications associated with Apparatus 7 (simulated gastric fluid without enzyme)	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4), 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference- Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	6/11/07	Test Product P63990 3/15/2006	10 mg ER tablet	12	Mean	0	0	9	21	32	43	53	61	68	73	77	79	82	NA
					Range	(b) (4)													
					%CV	0	346.4	16.0	8.7	7.4	6.5	5.3	4.7	4.4	3.3	2.8	2.3	2.4	
NA	3/28/07	Reference Product 6KA001 12/2007	10 mg ER tablet	12	Mean	0	1	11	21	32	43	55	67	77	83	86	88	90	NA
					Range	(b) (4)													
					%CV	0	56.2	23.9	16.5	15.3	13.1	11.5	9.9	8.1	5.8	4.1	3.8	3.8	

NA - No study report.

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	pH 4.5 buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications associated with Apparatus 7 (simulated gastric fluid without enzyme)	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4)% 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference- Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	6/11/07	Test Product P63990 3/15/2006	10 mg ER tablet	12	Mean	0	0	10	22	33	43	53	61	68	73	77	80	82	NA
					Range	(b) (4)													
					%CV	0	147.7	162.2	8.0	7.5	5.9	4.7	3.9	3.5	3.4	3.0	2.8	2.9	
NA	3/27/07	Reference Product 6KA001 12/2007	10 mg ER tablet	12	Mean	0	1	12	25	37	50	62	74	84	89	91	92	93	NA
					Range	(b) (4)													
					%CV	0	84.4	20.8	14.9	14.6	14.1	13.3	11.5	8.6	5.1	2.9	2.4	2.6	

NA - No study report.

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	pH 6.8 buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications associated with Apparatus 7 (simulated gastric fluid without enzyme)	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4)% 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference- Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	6/11/07	Test Product P63990 3/15/2006	10 mg ER tablet	12	Mean	0	0	9	18	29	38	46	53	57	61	66	68	69	NA
					Range	(b) (4)													
					%CV	0	346.4	9.5	6.9	5.9	5.8	5.1	3.5	4.0	3.7	2.6	2.7	2.1	
NA	3/27/07	Reference Product 6KA001 12/2007	10 mg ER tablet	12	Mean	0	1	9	19	29	38	48	58	67	72	75	78	78	NA
					Range	(b) (4)													
					%CV	0	82.9	28.1	19.5	17.2	14.0	14.3	13.0	10.8	7.7	6.5	4.5	3.4	

NA - No study report.

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	pH 1.2 buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4) 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference-Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	7/24/06	Test Product P64010 3/16/2006	15 mg ER tablet	12	Mean	0	2	14	26	39	51	61	69	74	79	81	84	86	NA
					Range	(b) (4)													
					%CV	0	47.7	11.0	6.7	6.1	5.0	3.6	2.6	2.9	2.5	2.1	2.3	1.9	
NA	3/28/07	Reference Product 6LA085 1/2008	15 mg ER tablet	12	Mean	0	1	11	22	34	46	58	72	82	86	88	89	90	NA
					Range	(b) (4)													
					%CV	0	61.5	16.4	9.2	6.7	6.0	5.1	4.3	2.9	3.1	3.4	3.6	3.5	

NA - No study report.

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	pH 4.5 buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4) 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

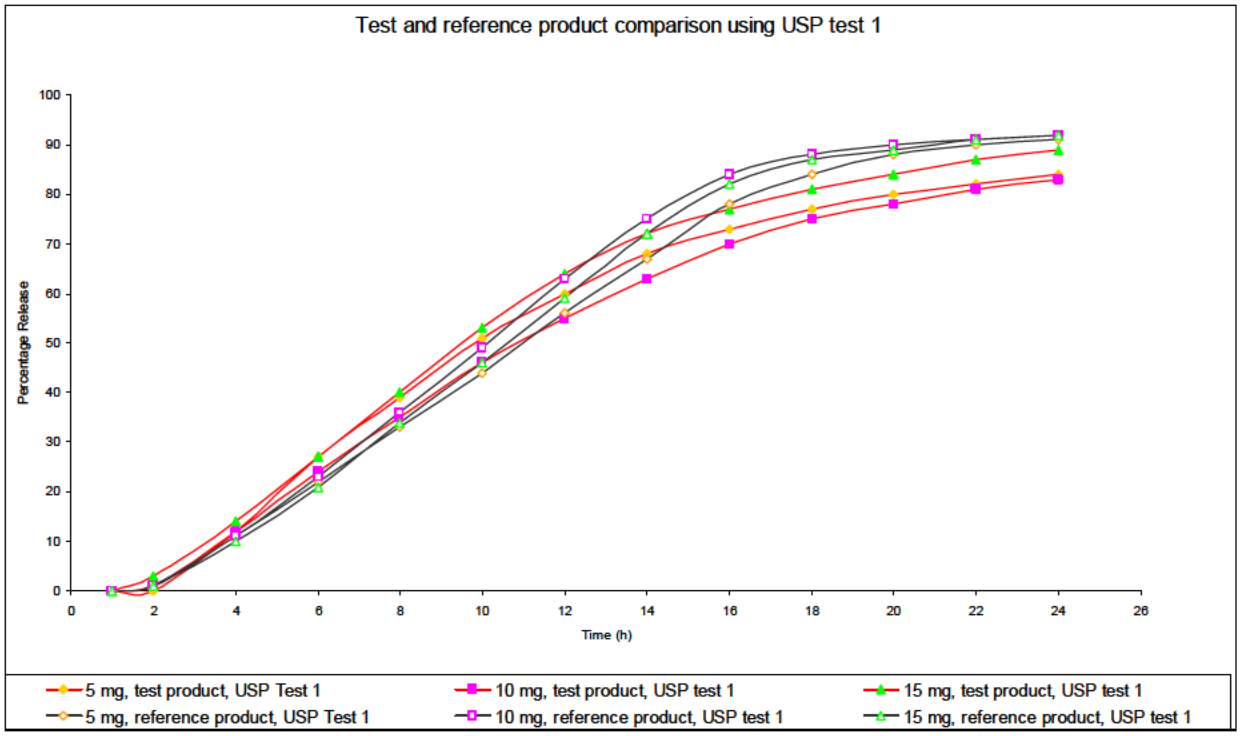
Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference-Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	7/18/06	Test Product P64010 3/16/2006	15 mg ER tablet	12	Mean	0	3	16	29	41	54	64	72	78	82	85	88	90	NA
					Range	(b) (4)													
					%CV	0	30.7	9.3	6.4	5.2	4.5	3.6	2.8	2.2	1.8	1.5	1.7	1.3	
NA	3/27/07	Reference Product 6LA085 1/2008	15 mg ER tablet	12	Mean	0	1	11	23	36	49	63	76	84	89	91	92	93	NA
					Range	(b) (4)													
					%CV	0	73.9	24.9	17.4	15.6	13.5	11.4	8.9	5.5	2.6	1.9	1.9	1.9	

NA - No study report.

Dissolution Conditions	Apparatus:	2
	Speed of Rotation:	50 rpm
	Medium:	pH 6.8 buffer
	Volume:	900 mL
	Temperature:	37±0.5°C
Firm's Proposed Specifications	4 hr: Each must be NMT 25% 10 hr: Each must be (b) (4)% 24 hr: Each must not be less than 75%	
Dissolution Testing Site	(b) (4)	

Study Ref. No.	Testing Date	Product ID/Batch No. (Test – Manufacture Date Reference- Expiration Date)	Dosage Strength and Form	No. of Dosage Units		Collection Times (Hours) 1	2	4	6	8	10	12	14	16	18	20	22	24	Study Report Location
NA	7/24/06	Test Product P64010 3/16/2006	15 mg ER tablet	12	Mean	0	2	13	24	35	45	57	64	69	73	68	74	82	NA
					Range	(b) (4)													
					%CV	0	60.8	9.3	8.8	8.2	6.9	6.8	7.5	7.4	6.6	4.0	5.4	5.2	
NA	3/27/07	Reference Product 6LA085 1/2008	15 mg ER tablet	12	Mean	0	1	9	19	29	39	51	62	69	73	75	77	76	NA
					Range	(b) (4)													
					%CV	0	82.9	17.5	13.9	10.9	9.0	9.2	7.4	5.4	3.3	3.8	4.4	4.0	

NA - No study report.



4.4 Detailed Regulatory History (If Applicable)

The DBE has reviewed the following submissions:

ANDAs: 76745 (Impax, 5 mg, 10 mg and 15 mg): fasting and fed studies on the 15 mg strength and biowaivers on the 5 mg and 10 mg strengths.
76-644 (Mylan, 10 mg): fasting study and fed studies on the 10 mg strength
76-702 (Mylan, 5 mg): fasting and fed studies on the 5 mg strength; 5 mg and 10 mg strengths are not proportionally similar in the formation.
78-293 (Mylan, 15 mg): fasting study on the 15 mg strength

The Division has responded to many control documents (99-276, (b) (4); 00-025, (b) (4); 00-496 (b) (4); 00-517, (b) (4); 01-297, (b) (4).; 02-059, (b) (4) 02-034, (b) (4); 02-390, (b) (4) 04-203, (b) (4) 04-603, (b) (4); 05-1194, (b) (4); 07-0351, Ortho Urology - Citizen Petition; 06-0282, (b) (4) 06-0822, (b) (4)).

Current DBE recommendations for demonstration of bioequivalence of Oxybutynin Chloride Extended-Release Tablets are as follows:

1. The following studies are recommended to establish bioequivalence of oxybutynin chloride extended-release tablets:

    a. A single-dose, two-way crossover fasting *in-vivo* bioequivalence study comparing Oxybutynin Chloride Extended-Release Tablets, 15 mg, to the reference listed drug (RLD), Ditropan XL® (Oxybutynin Chloride) Extended-Release Tablets, 15 mg.

    b. A single-dose, non-replicate fed *in-vivo* bioequivalence study comparing Oxybutynin Chloride Extended-Release Tablets, 15 mg, to the RLD.

2. Desethyloxybutynin is formed as a result of presystemic metabolism and contributes meaningfully to efficacy. Therefore, please measure both oxybutynin and desethyloxybutynin using an achiral assay. Measurement of the individual enantiomers is not necessary. Only the oxybutynin data should be analyzed using the confidence interval approach. For desethyloxybutynin, the following data should be submitted: Individual and mean plasma concentrations; Individual and mean pharmacokinetic parameters; and Geometric means and ratios of means for AUC and Cmax

3. Oxybutynin Chloride Extended-Release Tablets, 5 mg and 10 mg, may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) an acceptable bioequivalence study on the 15 mg strength, (2) acceptable dissolution testing of the 5 mg, 10 mg, and 15 mg strengths, and (3) proportional similarity in the formulations of the 5 mg, 10 mg, and 15 mg strengths.

4. Please conduct comparative *in-vitro* dissolution testing on 12 dosage units of each strength of the test and reference products in water and in at least three different media at pH 1.2, 4.5, and 6.8 using USP Apparatus 1 (Basket) at 100 rpm and Apparatus 2 (Paddle) at 50, 75 and 100 rpm. The recommended sampling times are 1, 2, 4, and every 2 hours thereafter for 24 hours, until 80% of the drug is released.

   In addition, please conduct dissolution testing using the following suggested method:

   Apparatus: USP Apparatus VII
   Media: Simulated Gastic Fluid without enzyme at 37^0C
   Volume: 50 ml
   Frequency/Amplitude: 30 cycles/minutes; 2-3 cm
   Sampling times: 4, 10 and 24 hours.

   Tolerances are expressed as cumulative amount release per tablet over time interval (0-4, 0-10, and 0-24).

4.5 Dissolution Consult

From: Seo, Paul
Sent: Thursday, July 19, 2007 5:45 PM
To: Jiang, Xiaojian
Cc: Seo, Paul
Subject: RE: Consult for dissolution of oxybutynin ER Tab

Hi Xiaojian,

After looking at the data, I have no problems with your specs. There seems to be adequate room on both the higher and lower ends of the proposed specs while at the same time providing discrimination for all strengths. Also, the extra media testing indicates no dose dumping of the product at various pHs. Nice job.

Thanks,
Paul

From: Jiang, Xiaojian
Sent: Thursday, July 19, 2007 2:49 PM
To: Seo, Paul
Subject: Consult for dissolution of oxybutynin ER Tab

Hi, Paul:
I am consulting you with ANDA 78503 oxybutynin ER Tab. You might have been consulted with this product previously from Shirley. Now the data is complete. Please see the attachment for the history of this product and data. This is a USP product now. The firm proposed to use USP test method which is apparatus 7, 30 cycles per minute, Simulated gastric fluid without enzyme. However the firm proposed specificaiton is not the same as the USP spec. I want to propose a different spec from USP and firm's as follows:

4 hrs: NMT 25%,
10 hrs: 40-65%,
24 hr: NLT 75%

<< File: 78503N1006_Oxybutynin ER Tab.doc >>

Please give me your suggestion.

BIOEQUIVALENCE DIFICIENCIES

ANDA: 78-503 APPLICANT: Osmotica Pharmaceutical Corp.

DRUG PRODUCT: Oxybutynin Chloride Extended-Release Tablets USP, 5 mg, 10 mg and 15 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Oxybutynin Chloride Extended-Release Tablets is currently a USP product. Your proposed dissolution method is the same as the USP method and it is acceptable. However, your proposed dissolution specifications are not acceptable. The dissolution testing should be conducted as specified in USP 30, in 50 ml of simulated gastric fluid without enzymes at 37°C, using USP apparatus 7, 30 cycles per minutes; 2- to 3-cm amplitude. The test product should meet the following specification:

4 hr: NMT 25%,
10 hr: 40-65%,
24 hr: NLT 75%

Your dissolution data meet the FDA-recommended specification listed above. Please acknowledge the acceptance of the FDA-recommended dissolution method and specification.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 78-503

1.	**Fasting Study**	Strength:	15 mg
	(STF)	Outcome:	**AC**
	Submission Date(s)	**10/20/06**	
	Clinical Site:	See Page 1 of this review	
	Analytical Site:	See Page 1 of this review	
2.	**Fed Study**	Strength:	15 mg
	(STP)	Outcome:	**AC**
	Submission Date(s)	**10/20/06**	
	Clinical Site:	See Page 1 of this review	
	Analytical Site:	See Page 1 of this review	
3.	**Dissolution Waiver**	Strength:	10 mg
	(DIW)	Outcome:	**IC**
	Submission Date(s)	**10/20/06**	
4.	**Dissolution Waiver**	Strength:	5 mg
	(DIW)	Outcome:	**IC**
	Submission Date(s)	**10/20/06**	
5.	**Study Amendment**	Strength:	All strengths **(dissolution amendment, not previously reviewed)**
	(STF)	Outcome:	**IC**
	Submission Date(s)	**7/05/07**	
6.	**Study Amendment**	Strength:	All strengths **(dissolution amendment)**
	(STF)	Outcome:	**WC**
	Submission Date(s)	**4/24/07**	

BIOEQUIVALENCE OUTCOME DECISIONS:	IC– incomplete

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

/s/

Xiaojian Jiang
8/3/2007 04:11:25 PM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
8/6/2007 07:48:12 AM
BIOPHARMACEUTICS

Barbara Davit
8/6/2007 02:05:20 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	78-503
Drug Product Name	Oxybutynin Chloride Extended Release Tablets
Strength	5 mg, 10 mg, 15 mg
Applicant Name	Osmotica Pharmaceutical
Submission Date	August 29, 2007
Reviewer	Keri Suh, Pharm.D.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

The firm has accepted the FDA-recommended dissolution method and specification.

The application is complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing and the application is approvable.

ANDA 78-503

BIOEQUIVALENCE - ACCEPTABLE

Submission date: August 29, 2007

1. Study Amendment (STA) Strengths: All
Outcome: AC

Outcome Decisions: **AC** - Acceptable

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

/s/

Keri Suh
9/13/2007 10:41:56 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-503

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Osmotica Pharmaceutical

October 20, 2006

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN 4, HFD-600
7519 Standish Place
Rockville, MD 20855

PRE-ASSIGNED ORIGINAL ANDA APPLICATION 078503
OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS
5 MG , 10 MG, AND 15 MG

Dear Mr. Buehler,

Osmotica Pharmaceutical Corp is submitting an abbreviated new drug application (ANDA) for Oxybutynin Extended-release Tablets 5 mg, 10 mg, and 15 mg. The reference listed drug (RLD) product for this ANDA is Ditropan XL® Tablets (Application 020897, ALZA) and this application contains 6 Paragraph IV patent certifications, one for each of the patents listed in Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

As required by 21 CFR § 314.94 (a)(12)(iii), also note that certain claims of US Patent 6,262,115 are method of use patents for Oxybutynin which are indications that Osmotica is not seeking for Oxybutynin Chloride Extended-release Tablets within this application. There are two exclusivities listed in the Orange that are applicable. However, one expired on April 15, 2006 and the other expired October 15, 2006.

This submission is in an electronic Common Technical Document (eCTD) format. Also, Module 2 follows the Question-based Review format. The data from the bioequivalence studies is also being submitted in electronic format in SAS Transport File format. There is no sterility assurance data contained within this application.

Bioequivalence to the reference listed drug was demonstrated under fasting and fed (non-fasting) conditions for the 15 mg strength. Because the three strengths are dose-proportional and demonstrated in-vitro equivalency, this ANDA contains a request for a waiver of in-vivo bioequivalence being demonstrated on the 5 mg and 10 mg strengths. The evidence of bioequivalence was generated following Agency recommendations.

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

It should be also noted that the bioequivalence confidence interval requirements were met for both the parent compound Oxybutynin as well as the active metabolite, Desethyloxybutynin in both the fed and fasted studies. Therefore, the concerns expressed by Ortho Urology in the August 29, 2005 Citizen Petition (2005-0352 CP1) do not apply to the Osmotica product in this application.

The technology used for this product is an osmotic tablet in which a tablet core is produced by (b) (4) .

This technology has previously been successfully used in Nifedipine Extended-release Tablets (ANDA 77-127) and Nifedipine Extended-release 90 mg (ANDA 77-410). The Osmotica Oxybutynin Chloride Extended-release Tablet has also been marketed in Argentina by Laboratorios Phoenix under the name Ditropan UD since 1998.

The product is manufactured and tested by a third-party ((b) (4) (b) (4)) using a formulation and process developed by Osmotica. The product is packaged into bottles at (b) (4).

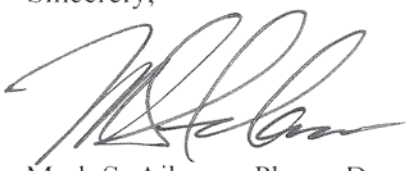
The size of the exhibit batches and the largest intended commercial batches are based upon the (b) (4). A (b) (4) is used for all three strengths of product. The scale up from the exhibit batches to the largest intended commercial batch is only a (b) (4) increase. Furthermore, the (b) (4) coating, and drilling operations used for the exhibit batches are identical in process and scale with those used for the largest intended commercial batches. Therefore, the exhibit batches are very representative of the commercial process.

This application contains stability data from six batches of finished product, two of each of the three strengths. One lot of active pharmaceutical ingredient was used to manufacture the different lots of product.

Although there is not a monograph in the current United States Pharmacopeia for Oxybutynin Chloride Extended-Release Tablets, there is a proposed monograph in the Pharmaceutical Forum and this product complies with the elements of the proposed monograph other than the drug release acceptance criteria. It is anticipated that once this ANDA has been approved and the monograph is finalized, the USP will be requested to include the drug release criteria for this product. Therefore, this is anticipated to be a USP product.

Osmotica commits to resolve any issues which are identified in the methods validation process. Because this application is being sent as an electronic submission, the additional bound copies of the analytical methods are not provided.

Sincerely,



Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 78-503 **FIRM NAME**: OSMOTICA PHARMACEUTICAL CORP.

PIV: YES **Electronic or Paper Submission:** ELECTRONIC (ECTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: OXYBUTYNIN CHLORIDE EXTENDED RELEASE

DOSAGE FORM: TABLETS, 5 MG, 10 MG, AND 15 MG

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☐ **Micro Review (No)**
☐ **BST**	☒ **BDI**	

Random Queue: 4
Chem Team Leader: Gill, Dave PM: Leign Ann Matheny Labeling Reviewer: Postelle Birch

Letter Date: OCTOBER 20, 2006 **Received Date**: OCTOBER 23, 2006

Comments: EC - 3 YES **On Cards:** YES
Therapeutic Code: 6050300 RELIEVE VOIDING SYMPTOMS/NEUROGENIC BLADDER

Archival copy: ELECTRONIC **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Saundra T. Middleton Date 1/16/07	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: ____ **Date:** ____

ADDITIONAL COMMENTS REGARDING THE ANDA:
1/11/07 – Called for batch reconciliation, cGMP statement from the ANDA holder and justification for submitting two batches for each strength.

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES YES	☒
1.2	**Cover Letter** Dated: OCTOBER 20, 2006 YES	☒
*	**Table of Contents (paper submission only)** YES (ELECTRONIC YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES (ELECTRONIC) YES 2. List of Convictions statement (original signature)	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES (ELECTRONIC)	☒

1.3.5

1.3.5.1

Patent Information

Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations

1.3.5.2

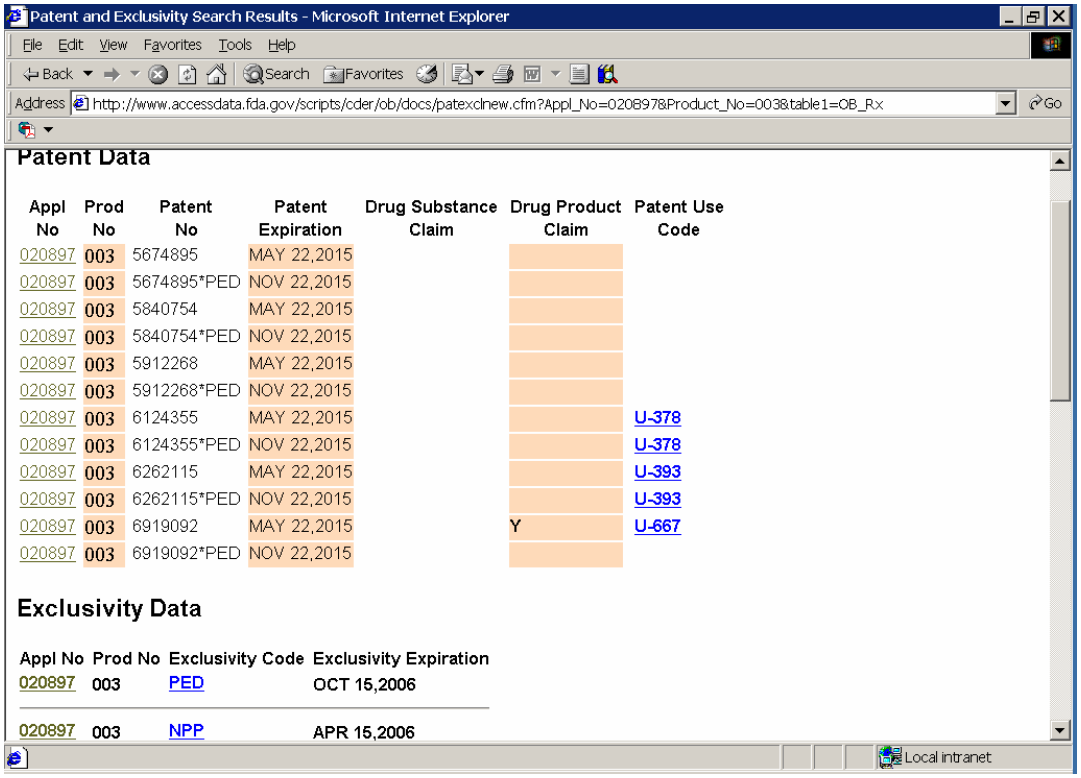
Patent Certification

1. Patent number(s)
2. Paragraph: (Check all certifications that apply)

MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ PIV to all patents - also MOU to '115 (for U-393 MGT of hormone replacement therapy)

No Relevant Patents ☐

3. Expiration of Patent(s): 11/22/2015
   a. Pediatric exclusivity submitted?
   b. Expiration of Pediatric Exclusivity?
4. Exclusivity Statement: YES (ELCTRONIC)



Patent Use Codes

This page defines the patent use codes.

Code	Definition
U-378	METHOD FOR TREATING INCONTINENCE
U-393	MANAGEMENT OF INCONTINENCE, MGT OF HORMONE REPLACEMENT THERAPY, TREATMENT OF INVOLUNTARY INCONTINENCE, MGT OVERACTIVE BLADDER AND INCREASING COMPLIANCE IN SUCH PT
U-667	MANAGEMENT OF INCONTINENCE; METHOD FOR TREATING INCONTINENCE

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES # (b) (4) b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])	☒
1.12.11	**Basis for Submission** NDA# : 20-897 Ref Listed Drug: DITROPAN XL Firm: ALZA ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use YES 2. Active ingredients YES 3. Inactive ingredients YES 4. Route of administration YES 5. Dosage Form YES 6. Strength YES	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): ELECCTRONIC, YES ON 5 MG AND 10 MG	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.) 30, 100, 100 and 1000 count	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

MODULE 2
SUMMARIES

ACCEPTABLE **2.3**	**Quality Overall Summary** **E-Submission: _YES____PDF (archive) ____ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) _____ YES _____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product YES** **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix**	☐

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature YES** **3.2.S.1.2** **Structure YES** **3.2.S.1.3** **General Properties YES**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers **YES** 2. Manufacturing Responsibilities **YES** 3. Type II DMF number for API **YES - #** (b) (4) 4. CFN or FEI numbers NO	☒
3.2.S.3	**Characterization**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) **YES** **3.2.S.4.2** **Analytical Procedures YES** **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples **YES** 2. Samples-Statement of Availability and Identification of: a. Drug Substance **YES** b. Same lot number(s) **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) **YES** 2. Applicant certificate of analysis **YES** **3.2.S.4.5** **Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition **YES** 2) Inactive ingredients are appropriate per IIG **YES – see below**	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report **YES**	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) **YES** 2. CGMP Certification: YES (ELECTRONIC) **NOT from ANDA holder – see 1/11/07 correspondence** 3. Function or Responsibility **YES** 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation **YES** **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process **YES** 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified **YES** 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement **YES** **3.2.P.3.4** **Controls of Critical Steps and Intermediates** **3.2.P.3.5** **Process Validation and/or Evaluation** 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients) YES** Source of inactive ingredients identified **YES** **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) **YES** 2. Suppliers' COA (specifications and test results) **YES** **3.2.P.4.2** **Analytical Procedures** **3.2.P.4.3** **Validation of Analytical Procedures** **3.2.P.4.4** **Justification of Specifications** Applicant COA **YES**	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s) YES** **3.2.P.5.2** **Analytical Procedures YES** **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form **YES** 2. Same lot numbers **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form **YES** **3.2.P.5.5** **Characterization of Impurities** **3.2.P.5.6** **Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) **YES** 2. Components Specification and Test Data **YES** 3. Packaging Configuration and Sizes **YES** 4. Container/Closure Testing **YES** 5. Source of supply and suppliers address **YES**	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted **YES** 2. Expiration Dating Period **YES – 24 MONTHS** **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments **YES** **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data **YES** 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available) YES** **3.2.R.2.S** **Comparability Protocols YES** **3.2.R.3.S** **Methods Validation Package YES** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES – SEE BELOW **3.2.R.1.P.2** **Information on Components** YES **3.2.R.2.P** **Comparability Protocols** YES **3.2.R.3.P** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

	P63960			P63970		
Step	**Actual**	**Theoretical**	**% Yield**	**Actual**	**Theoretical**	**% Yield**
(b) (4)						

	P63980			P63990		
Step	**Actual**	**Theoretical**	**% Yield**	**Actual**	**Theoretical**	**% Yield**
(b) (4)						

	P64000			P64010		
Step	**Actual**	**Theoretical**	**% Yield**	**Actual**	**Theoretical**	**% Yield**
	(b) (4)					

MODULE 5
CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) YES b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
	5.3.1.2 **Comparative BA/BE Study Reports** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study Table 7. Incidence of Adverse Events in Individual Studies Table 8. Reanalysis of Study Samples **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies Table 5. Formulation Data **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation **5.3.7** **Case Report Forms and Individual Patient Listing**	☐
5.4	**Literature References**	

	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 15 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Osmotica Pharmaceutical

Oxybutynin Chloride Extended-release Tablets
5 mg, 10 mg, and 15 mg
Module 2: Summaries
2.7 Clinical Summary

Table 2. Statistical Summary of the Comparative Bioavailability Data

Oxybutynin Chloride
15 mg Extended-Release Tablets
Geometric Means, Ratio of Means, and 90% Confidence Intervals

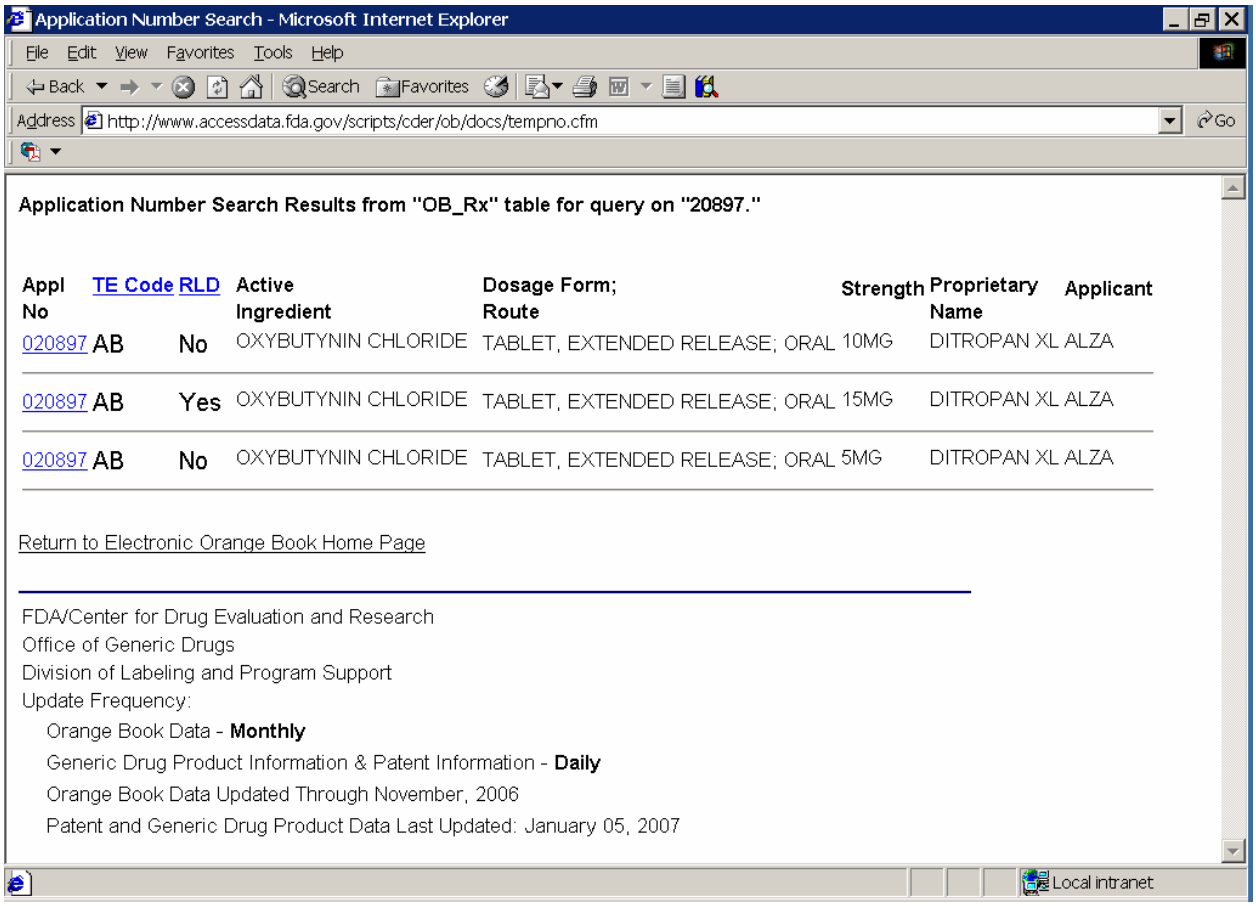
AAI-US-425 Fasted Bioequivalence Study

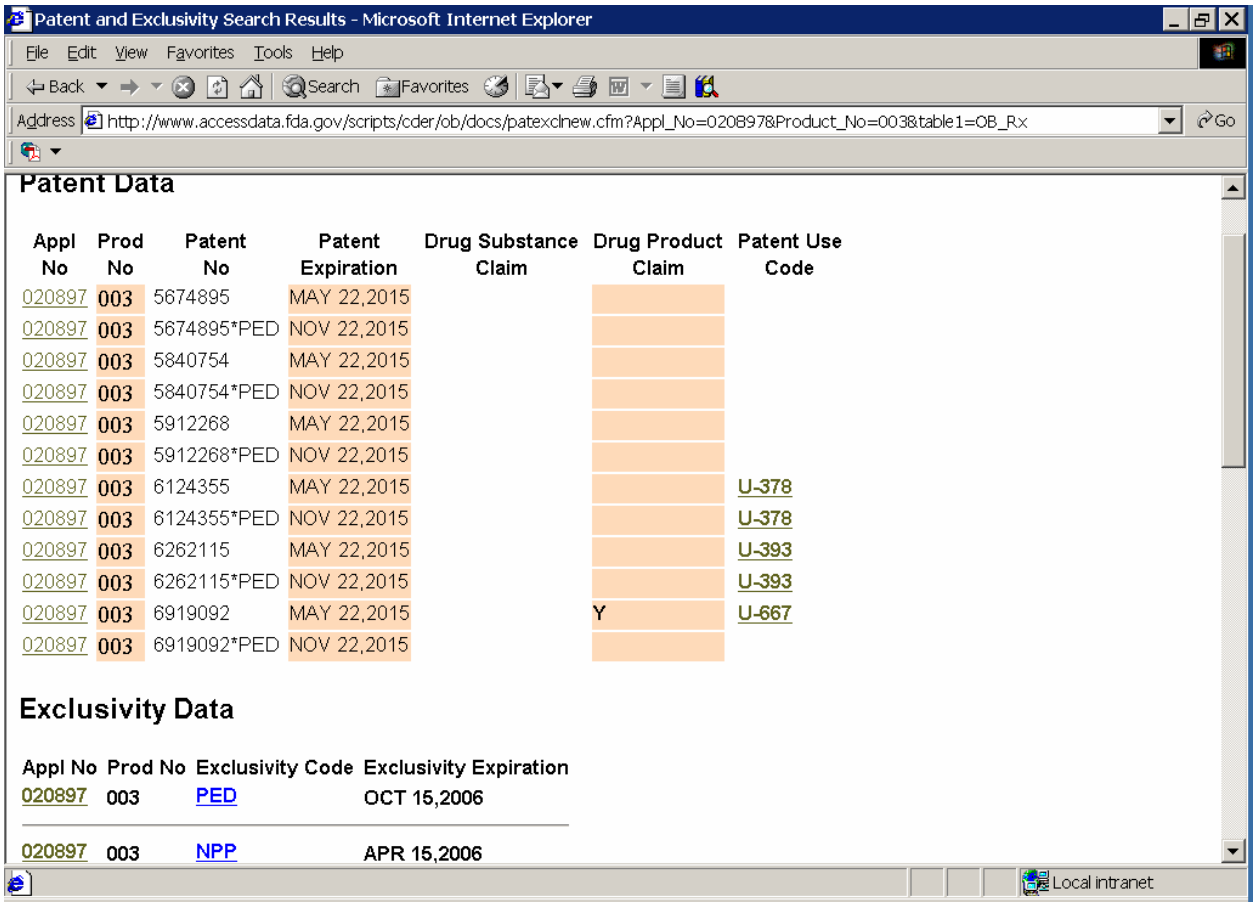
Parameter	Test	Reference	Ratio	90% C.I.
Oxybutynin				
AUCt	69.9	71.3	0.980	0.884 – 1.088
AUC∞	78.2	77.8	1.005	0.902 – 1.120
Cmax	3.90	3.99	0.978	0.902 – 1.061
Desethyloxybutynin				
AUCt	393	392	1.001	0.921 – 1.088
AUC∞	414	407	1.015	0.933 – 1.105
Cmax	23.5	22.2	1.057	0.992 – 1.126

AAI-US-424 Fed Bioequivalence Study

Parameter	Test	Reference	Ratio	90% C.I.
Oxybutynin				
AUCt	61.0	61.4	0.993	0.940 – 1.049
AUC∞	66.9	65.9	1.016	0.962 – 1.073
Cmax	3.39	3.53	0.960	0.907 – 1.016
Desethyloxybutynin				
AUCt	448	431	1.040	0.988 – 1.094
AUC∞	459	440	1.042	0.991 – 1.097
Cmax	27.4	28.0	0.980	0.919 – 1.045

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐


Application Number Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempno.cfm
Go
Application Number Search Results from "OB_Rx" table for query on "20897."
Appl No
TE Code
RLD
Active Ingredient
Dosage Form; Route
Strength
Proprietary Name
Applicant
020897 AB No OXYBUTYNIN CHLORIDE TABLET, EXTENDED RELEASE; ORAL 10MG DITROPAN XL ALZA
020897 AB Yes OXYBUTYNIN CHLORIDE TABLET, EXTENDED RELEASE; ORAL 15MG DITROPAN XL ALZA
020897 AB No OXYBUTYNIN CHLORIDE TABLET, EXTENDED RELEASE; ORAL 5MG DITROPAN XL ALZA
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through November, 2006
Patent and Generic Drug Product Data Last Updated: January 05, 2007
Local intranet



Patent Use Codes

This page defines the patent use codes.

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U-667	MANAGEMENT OF INCONTINENCE; METHOD FOR TREATING INCONTINENCE

Following this page, 5 pages withheld in full - (b)(4)

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

/s/

Martin Shimer

1/19/2007 11:45:48 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-503

Osmotica Pharmaceutical Corp.
Attention: Mark S. Aikman
1205 Culbreth Drive, Suite 200
Wilmington, NC 28405

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated January 11, 2007 and your correspondence dated January 11, 2007.

NAME OF DRUG: Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg and 15 mg

DATE OF APPLICATION: October 20, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 23, 2006

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301)827-0503.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Leigh Ann Matheny
Project Manager
301-827-5727

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
1/19/2007 11:53:06 AM
Signing for Wm Peter Rickman

Osmotica Pharmaceutical

February 16, 2007

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN 4, HFD-600
7519 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

PRE-ASSIGNED ORIGINAL ANDA APPLICATION 078503
OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS
5 MG , 10 MG, AND 15 MG

Dear Mr. Buehler,

Osmotica Pharmaceutical Corp is submitting a Patent Amendment to the abbreviated new drug application (ANDA) for Oxybutynin Extended-release Tablets 5 mg, 10 mg, and 15 mg. The reference listed drug (RLD) product for this ANDA is Ditropan XL® Tablets (Application 020897, ALZA). Reference is made to the Acknowledgement Letter dated on January 19, 2007.

Osmotica is submitting the following documentation:

- Copy of notice which was sent to ALZA Corporation and Johnson & Johnson
- Certification that the notice was sent to each person identified under 314.95(a)
- Copy of the return receipt

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

BIOEQUIVALENCY AMENDMENT

ANDA 78-503

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Osmotica Pharmaceutical Corp. TEL: 910-509-0114

ATTN: Mark S. Aikman, Pharm.D. FAX: 910-509-0115

FROM: Beth Fabian-Fritsch PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on October 20, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxybutynin Chloride Extended Release Tablets, 5 mg, 10 mg, and 15 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-503 APPLICANT: Osmotica Pharmaceuticals

DRUG PRODUCT: Oxybutynin Chloride Extended Release Tablets,
5 mg, 10 mg, and 15 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. We acknowledge that you have conducted dissolution testing in simulated gastric fluid using apparatus VII and water using paddle at 50 rpm for the test and reference products. In addition, please conduct comparative dissolution testing on each strength of the test and reference products in water and in at least three different media at pH 1.2, 4.5, and 6.8 using USP Apparatus 1 (Basket) at 100 rpm. Please also submit dissolution data for the reference products using paddle at 50 rpm in the three different pH media.

2. In order to improve the review process, the Division of Bioequivalence requests that you provide electronic summary tables that can be found under the sub-heading "Model Bioequivalence Data Summary Tables" at the following web address: http://www.fda.gov/cder/ogd/index.htm. Please provide this information for any other applications pending in the Division and in applications to be submitted in the future.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Dale Conner

3/9/2007 05:50:45 PM

MINOR AMENDMENT

ANDA 78-503

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Osmotica Pharmaceutical Corp. TEL: 910-509-0114

ATTN: Mark Aikman FAX: 910-509-0115

FROM: Leigh Ann Matheny PROJECT MANAGER: (301) 827-5727

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 20, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxybutynin Chloride Extended Release Tablets, 5 mg, 10 mg, and 15 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__4__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Following this page, 2 pages withheld in full - (b)(4)

12 (b) (4)

13

14

15

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all current stability data; and ensure that the stability data sheets include all current specifications.

2. The review of the labeling portions of your application is pending. Deficiencies, if any, will be conveyed to you under a separate cover.

3. Please be informed that when reporting the acceptable levels of excipients in a drug product formulation based on the Inactive Ingredients Guide (IIG), the Total Daily Intake (TDI) of the ingredients should be taken into account.

4. Please clearly describe the drug release mechanism, specifically how the proposed design promotes constant release of the drug.

5. With respect to the dissolution specifications, please provide the revised specifications and method based on any recommendations made by the Division of Bioequivalence (DBE). Also, stability data should be provided using the recommended method and criteria to justify the proposed expiry date.

6. To help facilitate the review process, when future applications are submitted in the Question-based Review format, please include the standard questions in the Quality Overall Summary (QOS) and please submit a MS-Word version of the QOS.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Devinder Gill
4/18/2007 11:28:14 AM
for Vilayat Sayeed, Ph.D.

Osmotica Pharmaceutical

April 24, 2007

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN 4, HFD-600
7519 Standish Place
Rockville, MD 20855

BIOEQUIVALENCY AMENDMENT

ANDA 078503-OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS
5 MG , 10 MG, AND 15 MG

Dear Mr. Buehler,

Osmotica Pharmaceutical Corp is submitting a response to the Bioequivalency Amendment dated March 9, 2007 and received by fax on March 12, 2007. The in vitro data that was requested was later revised by Beth Fabian-Fritsch during a teleconference on March 22, 2007 which was in response to a faxed question from Osmotica dated March 16, 2007. The revised request consisted of submitting the in vitro results of the reference product (all three strengths, 3 medias (pH 1.2, pH 4.5, and pH 6.8), using Apparatus 2 at 50 rpm).

Additionally the summary tables in section 2.7 have been revised according to your request. Section 2.7 was revised with the new in vitro data and revised tables. This revised Section replaces Section 2.7 in the original application.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

Osmotica Pharmaceutical

May 17, 2007

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN 4, HFD-600
7519 Standish Place
Rockville, MD 20855

PATENT AMENDMENT

ANDA 078503-OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS
5 MG , 10 MG, AND 15 MG

Dear Dr. Buehler,

Please refer to Osmotica's ANDA 078503 for Oxybutynin Chloride Extended-release Tablets 5mg, 10 mg, and 15 mg. Also, please refer to the Acknowledgement letter of receipt for filing dated January 19, 2007 from the Agency.

In a Patent Amendment dated February 16, 2007, Osmotica provided evidence to the Agency that notifications were provided to the sponsor of the reference listed drug product, Alza Corporation and also to its parent company Johnson & Johnson. Alza Corporation is the assignee of the patents 5,674,895; 5,840,754; 5,912,268; 6,124,355; 6,262,115; and 6,919,092 for which the Paragraph IV certifications were made. The notification was received by Alza and J&J on February 1, 2007 and February 5, 2007, respectively. The 45-day period has ended. As of the date of this letter, Osmotica is not aware of any legal action taken by either party related to our submission of this ANDA.

Please contact me should you have any questions or concerns regarding this information.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

BIOEQUIVALENCY AMENDMENT

ANDA 78-503

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Osmotica Pharmaceutical Corp. TEL: 910-509-0114

ATTN: Mark Aikman FAX: 910-509-0115

FROM: Beth Fabian-Fritsch PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on April 24, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCES TO BE PROVIDED TO THE APPLICANT

ANDA: 78-503

APPLICANT: Osmotica Pharmaceuticals

DRUG PRODUCT: Oxybutynin Chloride Extended Release Tablets,
5 mg, 10 mg, and 15 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. We acknowledge that you have submitted dissolution testing data for the 5-mg and 15-mg strengths of the test product in 3 different pH media. Please submit the dissolution data for the 10-mg strength of the test product in the 3 different pH media as well.

2. Please submit all individual tablet data for the data already submitted and for the data requested in the deficiency comment above.

3. In all your dissolution summary tables that include testing with simulated gastric fluid, please indicate whether the testing was done with or without enzyme.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit
6/5/2007 09:23:11 AM

Osmotica Pharmaceutical

July 5, 2007

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN 4, HFD-600
7519 Standish Place
Rockville, MD 20855

BIOEQUIVALENCY AMENDMENT

ANDA 078503-OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS
5 MG , 10 MG, AND 15 MG

Dear Mr. Buehler,

Osmotica Pharmaceutical Corp is submitting a response to the Bioequivalency Deficiency Letter dated June 5, 2007 and received by fax on June 6, 2007.

In addition to the responses to the specific comments, Section 2.7 was revised with the new in vitro data and revised tables. This revised Section replaces Section 2.7 in the original application and previous Amendment.

1. **We acknowledge that you have submitted dissolution testing data for the 5-mg and 15-mg strengths of the test product in 3 different pH media. Please submit the dissolution data for the 10-mg strength of the test product in the 3 different pH media as well.**
   The data is provided in 2.7.1.4 Appendix, Table 5.
2. **Please submit all individual tablet data for the data already submitted and for the data requested in the deficiency comment above.**
   The individual tablet data for the data already submitted and the data requested in the deficiency comment above are provided in Table 17.
3. **In all your dissolution summary tables that include testing with simulated gastric fluid, please indicate whether the testing was done with or without enzyme.**
   The profiles were performed without using enzyme. The tables have been updated to include this information.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

BIOEQUIVALENCY AMENDMENT

ANDA 78-503

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Osmotica Pharmaceutical Corp. TEL: 910-509-0114

ATTN: Mark Aikman FAX: 910-509-0115

FROM: Keri Suh PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on October 20, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxybutynin Chloride Extended-release Tablets, 5 mg, 10 mg, and 15 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DIFICIENCIES

ANDA: 78-503 APPLICANT: Osmotica Pharmaceutical Corp.

DRUG PRODUCT: Oxybutynin Chloride Extended Release Tablets USP, 5 mg, 10 mg and 15 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Oxybutynin Chloride Extended-Release Tablets is currently a USP product. Your proposed dissolution method is the same as the USP method and it is acceptable. However, your proposed dissolution specifications are not acceptable. The dissolution testing should be conducted as specified in USP 30, in 50 ml of simulated gastric fluid without enzymes at 37°C, using USP apparatus 7, 30 cycles per minutes; 2- to 3-cm amplitude. The test product should meet the following specification:

4 hr: NMT 25%,
10 hr: 40-65%,
24 hr: NLT 75%

Your dissolution data meet the FDA-recommended specification listed above. Please acknowledge the acceptance of the FDA-recommended dissolution method and specification.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit
8/9/2007 03:17:19 PM
Signing for Dale P Conner

Osmotica Pharmaceutical

August 29, 2007

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN 4, HFD-600
7519 Standish Place
Rockville, MD 20855

BIOEQUIVALENCY AMENDMENT

ANDA 078503-OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS
5 MG , 10 MG, AND 15 MG

Dear Mr. Buehler,

Reference is made to the Bioequivalency Amendment dated August 9, 2007. Osmotica agrees with the specifications specified in the Agency's letter. Osmotica is currently revising the specifications to address other CMC requirements. Once the specification has been revised the specification will be submitted to the Agency. The dissolution specification will be as follows:

4 hr: NMT 25%
10 hr: 40-65%
24 hr: NLT 75%

If you have any questions please feel free to call at 910.509.0114.

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

Osmotica Pharmaceutical

October 19, 2007

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN 4, HFD-600
7500 Standish Place
Rockville, MD 20855

CMC AMENDMENT

ANDA 078503-OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS
5 MG , 10 MG, AND 15 MG

Dear Dr. Buehler,

Osmotica Pharmaceutical Corp is submitting a response to the CMC deficiency letter classified as a Minor Amendment dated April 18, 2007. All deficiencies have been addressed.

Additionally, a cGMP letter from Osmotica and a revised reconciliation table for the executed batch records for Table R.1.P.1-3 are provided. This was requested by Saundra Middleton during the checklist review for the original ANDA. This information was originally submitted by email on January 11, 2007.

If you have any questions please feel free to call (910.509.0114)

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

Telephone Fax

ANDA 78-503

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-7347

TO: Osmotica Pharmaceutical Corp TEL: 910-509-0114

ATTN: Mark Aikman FAX: 910-509-0115

FROM: Postelle Birch-Smith, Pharm. D.

Dear Sir:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxybutinin Chloride Extended-release Tablets, 5 mg, 10 mg and 15 mg.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-503 Date of Submission: October 20, 2006

Applicant's Name: Osmotica Pharmaceutical Corp.

Established Name: Oxybutinin Chloride Extended-release Tablets USP, 5 mg, 10 mg and 15 mg

---

1. CONTAINER (All strengths in bottles 30, 100, 500 and 1000)

Satisfactory in draft. We encourage the use of boxing, contrasting colors or other means to differentiate the 10 mg and 15 mg strengths of your product.

2. INSERT

a. In the DESCRIPTION section revise "lactose" to read "anhydrous lactose and lactose monohydrate" and "dextrose" to read "anhydrous dextrose".
b. Insert the following as inactive ingredients: (b) (4).
c. In the Table 2 of the CLINICAL PHARMACOLOGY section revise "5.0" to read "5"
d. In the CONTRAINDICATIONS section the second sentence should begin a new paragraph.
e. In the first sentence of the second paragraph of the PRECAUTIONS: Drug Interactions subsection revise "was" to read "were"
f. Throughout the insert revise the sentences that read, "Oxybutynin Chloride Extended-release Tablets (oxybutynin chloride) is…" to read "Oxybutynin chloride extended-release tablets are…"

3. GENERAL COMMENT

Revise the established name on all labeling to read "Oxybutynin Chloride Extended-Release Tablets USP".

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
11/14/2007 10:24:45 AM
for Wm Peter Rickman

Osmotica Pharmaceutical

December 11, 2007

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN 4, HFD-600
7500 Standish Place
Rockville, MD 20855

LABELING AMENDMENT

ANDA 078503-OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS
5 MG , 10 MG, AND 15 MG

Dear Dr. Buehler,

Osmotica Pharmaceutical Corp is submitting a response to the labeling deficiency letter received via Telephone Fax dated November 15, 2007. All deficiencies for the Container and Insert have been addressed.

Please note according to a call with Ms. Birch on December 6, 2007, the SPL can be submitted post approval. Osmotica commits to submitting the SPL post approval within 14 days of the "Approval Letter".

Contained in this amendment are the insert (pdf and Word files), side be side comparison of the insert with the original draft insert submitted in the original application, and bottle labels and a listing of changes. The insert (pdf) and bottle labels are considered as Final Printed Labeling.

If you have any questions please feel free to call (910.509.0114)

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

Osmotica Pharmaceutical

July 24, 2008

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN 4, HFD-600
7500 Standish Place
Rockville, MD 20855

CMC AMENDMENT

ANDA 078503-OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS
5 MG , 10 MG, AND 15 MG

Dear Dr. Buehler,

Osmotica Pharmaceutical Corp is submitting an amendment to address the USP change in Organic Volatile Impurities and Residual Solvents (USP<467>). Provided in this amendment are updated specifications and certificate of analysis for all excipients. No changes were required for (b) (4).

Regarding the drug substance, an updated certificate of analysis was submitted in the CMC minor amendment dated October 19, 2007. Osmotica is providing an updated specification in this amendment. The specification was updated to remove the footnote regarding the residual solvents testing. The CMC minor amendment is pending review. Osmotica's expectation is that the Agency reviews the CMC minor amendment along with this amendment regarding the residual solvents.

Osmotica commits to re-assessing compliance with USP<467> if ingredient suppliers change or if current suppliers change their process.

If you have any questions please feel free to call (910.509.0114).

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

Osmotica Pharmaceutical

January 7, 2009

RECEIVED
JAN 08 2009
CDER CDR

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN 4, HFD-600
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/A M

CMC AMENDMENT

ANDA 078503-OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS
5 MG , 10 MG, AND 15 MG

Dear Dr. Buehler,

Reference is made to the Telephone Conference Fax dated November 18, 2008 and Osmotica's fax dated November 24, 2008. Osmotica Pharmaceutical Corp is submitting an amendment to further explain the stability data. A fax of the information in this amendment was sent on December 15, 2008.

If you have any questions please feel free to call (910.509.0114).

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

RECEIVED
JAN 09 2009
OGD

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

Osmotica Pharmaceutical

January 13, 2009

Gary J. Buehler
Director, Office of Generic Drugs
CDER, FDA
MPN 4, HFD-600
7500 Standish Place
Rockville, MD 20855

LABELING AMENDMENT - Expedited Review Requested

ANDA 078503-OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS
5 MG , 10 MG, AND 15 MG

Dear Dr. Buehler,

Osmotica Pharmaceutical Corp is submitting an amendment to provide labeling changes in compliance with the revision to the RLD label. It is our understanding that this is needed to receive approval for our ANDA 078503. This is the only outstanding item for approval. Osmotica requests that this review is expedited.

If you have any questions please feel free to call (910.509.0114)

Sincerely,

Mark S. Aikman, Pharm.D.
Vice President, Regulatory Affairs and Quality Assurance

1205 Culbreth Dr., Suite 200, Wilmington, NC 28405
Phone: 910-509-0114 • **Facsimile:** 910-509-0115
info@osmotica.com • www.osmotica.com

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-503 Applicant Osmotica Pharmaceutical Corp.
Drug Oxybutynin Chloride ER Strength(s) 5 mg, 10 mg, and 15 mg

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 7 January 2009 Date 2/4/09
Chief, Reg. Support Branch Initials MHS Initials rlw
Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = Ditropan XL NDA# 20-897
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 10/23/2006, BOS=Ditropan XL NDA 20-897, PIV to '895, '754, '355, '268, '092, and '115 patents. ANDA ack for filing with PIV on 10/23/2006 (LO dated 1/19/2007). XP rec'd on 2/20/2007 RR from J and J signed and dated 2/5/2007, RR from Alza signed and dated 2/1/2007. On 5/17/07 the sponsor stated that they were not sued within 45 days. Mylan's eligibility for 180 day exclusivity on the 5 and 10 mg products expired on 5/10/2007. IMPAX's eligibility for 180 day exclusivity on the 15 mg strength expired on 5/9/2007. There are no patent or legal barriers to the approval of this ANDA. ANDA may be Fully Approved.

2. Project Manager, Leigh Ann Bradford Team 4 Date 1/07/09 Date _____
Review Support Branch Initials LB Initials _____

Original Rec'd date 10/20/06 EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing 10/23/06 Date of EER Status 1/29/07
Patent Certification (type) PIV Date of Office Bio Review 9/13/07
Date Patent/Exclus.expires 11/22/15 Date of Labeling Approv. Sum 1/16/08
Citizens' Petition/Legal Case Yes ☐ No ☐ Date of Sterility Assur. App. n/a
(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes ☐ No ☐
First Generic Yes ☐ No ☒ MV Commitment Rcd. from Firm Yes ☐ No ☐
Priority Approval Yes ☐ No ☒ Modified-release dosage form: Yes ☐ No ☐
(If yes, prepare Draft Press Release, Email it to Cecelia Parise) Interim Dissol. Specs in AP Ltr: Yes ☐
Acceptable Bio reviews tabbed Yes ☐ No ☐
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date _____ Date 2/4/09
Name/Initials _____ Name/Initials rlw/for
Comments:
Final-printed labeling (FPL) found acceptable for approval 1/23/09.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 9Jan09
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials DTR
Comments: Changes to AP ltr saved to V drive.

5. Div. Dir./Deputy Dir. Date 1/30/09
Chemistry Div. III Initials DSG

Comments: cmc ok.

6. Frank Holcombe **First Generics Only** Date 2/4/09
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. ANDAs from IMPAX and Mylan have been approved for this drug product.

7. Vacant Date _____
Deputy Dir., DLPS Initials _____
RLD = Ditropan XL Extended-release Tablets 5 mg, 10 mg and 15 mg
Alza Corporation NDA 20-897

8. Peter Rickman Date 2/4/09
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Bioequivalence studies (fasting and non-fasting) on the 15 mg tablet strength found acceptable. In-vitro dissolution testing for all three strengths also found acceptable. Waivers granted to the 5 mg and 10 mg capsule strengths under 21 CFR 320.22(d)(2). Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 8/6/07 and 9/13/07.

Final-printed labeling (FPL) found acceptable for approval 1/23/09.

CMC found acceptable for approval (Chemistry Review #2) 1/6/09.

OR

8. Robert L. West Date 2/4/09
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 1/29/07 (Verified 2/4/09). No "OAI" Alerts noted.

Osmotica provided paragraph IV certifications to each of the patents currently listed in the "Orange Book", but was not sued within the 45-day period. There are no exclusivities currently listed in the "Orange Book" for this drug product.

This ANDA is recommended for approval.

9. Gary Buehler Date 2/4/09
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Leigh Ann Bradford Team 4 Date 2/04/09

Review Support Branch Initials LB
N/a Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:08 pm Time notified of approval by phone
3:10 pm Time approval letter faxed

FDA Notification:
2/04/09 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
2/04/09 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 020897 Product 003 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
020897	003	5674895	May 22, 2015				
020897	003	5674895*PED	Nov 22, 2015				
020897	003	5840754	May 22, 2015				
020897	003	5840754*PED	Nov 22, 2015				
020897	003	5912268	May 22, 2015				
020897	003	5912268*PED	Nov 22, 2015				
020897	003	6262115	May 22, 2015			U-393	
020897	003	6262115*PED	Nov 22, 2015			U-393	
020897	003	6919092	May 22, 2015		Y	U-667	
020897	003	6919092*PED	Nov 22, 2015				

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes

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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

- Orange Book Data - **Monthly**
- Generic Drug Product Information & Patent Information - **Daily**
- Orange Book Data Updated Through December, 2008
- Patent and Generic Drug Product Data Last Updated: February 03, 2009

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/s/

Leigh Ann Bradford

2/4/2009 03:24:40 PM