

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 078293Orig1s000

Name: Oxybutynin Chloride Extended-release
Tablets, 15 mg

Sponsor: Mylan Pharmaceuticals, Inc.

Approval Date: May 10, 2007

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ANDA 078293Orig1s000

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APPLICATION NUMBER:
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APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-293

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 2, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxybutynin Chloride Extended-release Tablets, 15 mg.

Reference is also made to the tentative approval letter issued by this office on February 5, 2007, and to your amendments dated March 5, and April 17, 2007.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved. The Division of Bioequivalence has determined your Oxybutynin Chloride Extended-release Tablets, 15 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Ditropan XL Extended-release Tablets of Alza Corporation (Alza). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, Alza's Ditropan XL Extended-release Tablets, 15 mg, is subject to periods of patent protection. The following patents and 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"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
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
6,124,355 (the '355 patent)	November 22, 2015
6,262,115 (the '115 patent)	November 22, 2015
6,919,092 (the '092 patent)	November 22, 2015

Your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Oxybutynin Chloride Extended-release Tablets, 15 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Mylan Pharmaceuticals Inc. (Mylan) for infringement of one or more of the patents that were the subjects of the paragraph IV certifications. This action must have been brought against Mylan prior to the expiration of 45 days from the date the notice you provided under section 505(j)(2)(B)(i) was received by the NDA/patent holder(s). You have notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act, and within the statutory 45-day period litigation for infringement of the '355 patent was brought against Mylan in the United States District Court for the Northern District of West Virginia (Alza Corporation v. Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc., Civil Action No. 1:06-cv-125). Mylan was not sued within the 45-day period on any of the other listed patents. You informed the agency that the case regarding the '355 patent was dismissed. Moreover, the 180-day exclusivity period of another applicant, discussed in our tentative approval letter of February 5, 2007, has expired. Therefore, under section 505(j)(5)(B)(iii)(I), your ANDA is eligible for approval.

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.

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(s) 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.

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/

Gary Buehler
5/10/2007 02:47:39 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 078293Orig1s000

TENTATIVE APPROVAL LETTER



ANDA 78-293

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 2, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxybutynin Chloride Extended-release Tablets, 15 mg.

Reference is also made to your amendments dated September 29, November 16, and December 14, 2006.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the generic drug exclusivity issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The listed drug product referenced in your ANDA, Ditropan XL Extended-release Tablets, 15 mg, of Alza Corporation, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

<u>U.S. Patent Number</u>	<u>Expiration Date*</u>
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
6,124,355 (the '355 patent)	November 22, 2015
6,262,115 (the '115 patent)	November 22, 2015
6,919,092 (the '092 patent)	November 22, 2015

*with pediatric exclusivity

Your ANDA contains paragraph IV patent certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, sale, offer for sale, or importation of Oxybutynin Chloride Extended-release Tablets, 15 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless an action was brought against Mylan Pharmaceuticals, Inc. (Mylan) for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. This action must have been brought against Mylan prior to the expiration of 45 days from the date the notice you provided under section 505(j)(2)(B) was received by the NDA/patent holder(s). You have notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act. As a result, litigation for infringement of the '355 patent was brought against Mylan in the United States District Court for the Northern District of West Virginia (Alza Corporation v. Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc., Civil Action No. 1:06-cv-125). You informed the agency that Mylan prevailed in the district court with respect to the finding that Mylan did not infringe the asserted claims of the '355 patent. Therefore, under section 505(j)(5)(B)(iii)(I), this court decision renders the ANDA eligible for approval. Furthermore, you informed the agency that on October 11, 2005, Alza appealed the district court decision, and that on September 8, 2006, the U.S. Court of Appeals for the Federal Circuit affirmed the district court's holding that Mylan's product does not infringe the asserted claims of the patent and that the asserted claims are invalid.

The agency recognizes that Mylan was not sued within the 45-day period on any of the other listed patents.

However, we are unable at this time to grant final approval to your ANDA. This is because IMPAX Pharmaceuticals, Inc.'s ANDA 76-745 for Oxybutynin Chloride Extended-release Tablets, 15 mg, approved on November 9, 2006, and containing paragraph IV certifications to the patents listed above, was submitted to the agency prior to the submission of your ANDA. IMPAX's ANDA is entitled to 180-day generic drug exclusivity for Oxybutynin Chloride Extended-release Tablets, 15 mg. Accordingly, your ANDA will be eligible for final approval on May 9, 2007, the date that is 180 days after the date that IMPAX began commercial marketing as identified in section 505(j)(5)(B)(iv) of the Act.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the expiration of IMPAX's exclusivity. This amendment should provide the legal/regulatory basis for your request for final approval. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved; i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay of the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under

section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book".

For further information on the status of this application, or prior to submitting additional amendments, please contact Leigh Ann Matheny, Project Manager, at (301)-827-5727.

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
2/5/2007 09:10:58 AM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 078293Orig1s000

LABELING

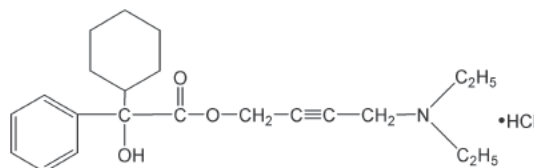
OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, USP 15 mg

R only

DESCRIPTION: Oxybutynin chloride is an antispasmodic, anticholinergic agent. Each oxybutynin chloride extended-release tablet contains 15 mg of oxybutynin chloride USP, formulated as a once-a-day controlled-release tablet for oral administration. Oxybutynin chloride is administered as a racemate of R- and S- enantiomers.

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

Its structural formula is:



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

Oxybutynin chloride extended-release tablets, USP contain the following inactive ingredients: colloidal silicon dioxide, dibasic calcium phosphate (anhydrous), hypromellose, magnesium stearate, methacrylic acid copolymer dispersion, polydextrose, polyethylene glycol, polysorbate 80, povidone, sodium hydroxide, talc, titanium dioxide, triacetin and triethyl citrate. In addition, oxybutynin chloride extended-release tablets may also contain imprinting ink consisting of either black pigment and natural resin or black iron oxide and propylene glycol.

System Components and Performance: Oxybutynin chloride extended-release tablets are formulated to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The dosage form is comprised of a hydrophilic cellulose polymer matrix tablet surrounded by an enteric coating system. The enteric coat is insoluble in the low pH environment of the stomach. As the tablet passes through the stomach and enters the higher pH environment of the small intestine, the enteric coating dissolves and/or erodes to expose the polymer matrix tablet which swells and releases drug at a controlled rate via diffusion and/or erosion.

USP Dissolution Test pending.

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

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

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

Pharmacokinetics: Absorption: Following the first dose of oxybutynin chloride extended-release tablets, oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter steady concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with oxybutynin.

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

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

Parameters (units)	R-Oxybutynin	S-Oxybutynin
C _{max} (ng/mL)	1.0 (0.6)	1.8 (1.0)
T _{max} (h)	12.7 (5.4)	11.8 (5.3)
t _{1/2} (h)	13.2 (6.2)	12.4 (6.1)
AUC ₍₀₋₄₈₎ (ng•h/mL)	18.4 (10.3)	34.2 (16.9)
AUC _{inf} (ng•h/mL)	21.3 (12.2)	39.5 (21.2)

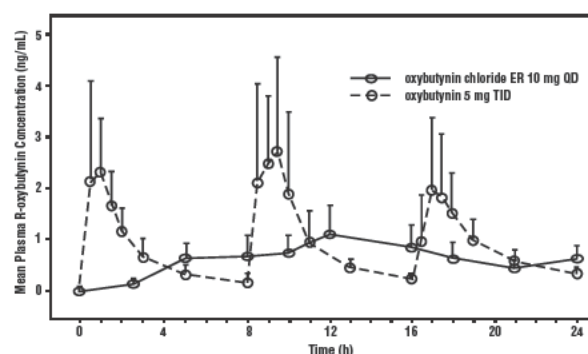


Figure 1. Mean R-oxybutynin plasma concentrations following a single dose of oxybutynin chloride ER 10 mg and oxybutynin 5 mg administered every 8 hours (n = 23 for each treatment).

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

Oxybutynin chloride extended-release steady-state pharmacokinetics was studied in 19 children aged 5 to 15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida). The children were on oxybutynin chloride extended-release total daily dose ranging from 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, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 2. The plasma-time concentration profiles for R- and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are 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 to 15 Following
Administration of 5 to 20 mg Oxybutynin Chloride Extended-Release
Once Daily (n = 19) All Available Data Normalized to an Equivalent of
Oxybutynin Chloride Extended-Release 5 mg Once Daily

	R-Oxybutynin	S-Oxybutynin	R-Desethyloxybutynin	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	23.7 ± 14.4	125.1 ± 66.7	73.6 ± 47.7

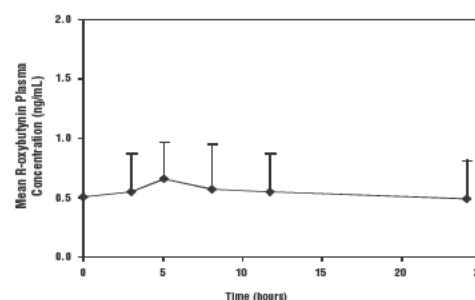


Figure 2. Mean steady-state (±SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg oxybutynin chloride extended-release once daily in children aged 5 to 15. Plot represents all available data normalized to an equivalent of oxybutynin chloride extended-release 5 mg once daily.

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

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

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

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

Dose Proportionality: Pharmacokinetic parameters of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of 5 to 20 mg of oxybutynin chloride extended-release tablets are dose proportional.

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

Pediatric: The pharmacokinetics of oxybutynin chloride extended-release were evaluated in 19 children aged 5 to 15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida). The pharmacokinetics of oxybutynin chloride extended-release in these pediatric patients were consistent with those reported for adults (see Tables 1 and 2, and Figures 1 and 2 above).

Gender: There are no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following administration of oxybutynin chloride extended-release.

Race: Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of oxybutynin chloride extended-release.

Renal Insufficiency: There is no experience with the use of oxybutynin chloride extended-release in patients with renal insufficiency.

Hepatic Insufficiency: There is no experience with the use of oxybutynin chloride extended-release in patients with hepatic insufficiency.

Drug-Drug Interactions: See PRECAUTIONS: Drug Interactions.

Clinical Studies: Oxybutynin chloride extended-release was evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (89%) and female (91.9%) with a mean age of 59 years (range, 18 to 98 years). Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge) as evidenced by ≥ 6 urge incontinence episodes per week and ≥ 10 micturitions per day. Study 1 was a 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 improvement of incontinence symptoms and tolerability of side effects. Controlled studies included patients known to be responsive to oxybutynin or other anticholinergic medications, and these patients were maintained on a final dose for up to 2 weeks.

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

Number of Urge Urinary Incontinence Episodes Per Week

Study 1	N	Oxybutynin Chloride ER	N	Placebo
Mean Baseline	34	15.9	16	20.9
Mean (SD) Change from Baseline†	34	-15.8 (8.9)	16	-7.6 (8.6)
95% Confidence Interval for Difference (oxybutynin chloride ER - Placebo)				(-13.6, -2.8)*

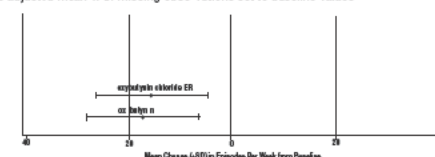
*The difference between oxybutynin chloride ER and placebo was statistically significant.

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



Study 2	N	Oxybutynin Chloride ER	N	Oxybutynin
Mean Baseline	53	27.6	52	23.0
Mean (SD) Change from Baseline†	53	-17.6 (11.9)	52	-19.4 (11.9)
95% Confidence Interval for Difference (oxybutynin chloride ER - oxybutynin)				(-2.8, 6.5)

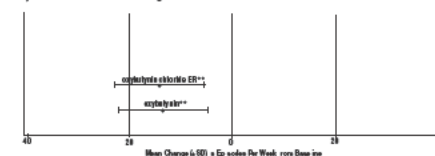
†Covariate adjusted mean w/ missing observations set to baseline values



Study 3	N	Oxybutynin Chloride ER	N	Oxybutynin
Mean Baseline	111	18.9	115	19.5
Mean (SD) Change from Baseline†	111	-14.5 (8.7)	115	-13.8 (8.6)
95% Confidence Interval for Difference (oxybutynin chloride ER - oxybutynin)				(-3.0, 1.6)**

**The difference between oxybutynin chloride ER and oxybutynin fulfilled the criteria for comparable efficacy.

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



INDICATIONS AND USAGE: Oxybutynin chloride extended-release tablets are once daily controlled-release tablets indicated for the treatment of overactive

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

Oxybutynin chloride extended-release tablets are also indicated in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida).

CONTRAINDICATIONS: Oxybutynin chloride extended-release tablets are contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride extended-release is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS: General: Oxybutynin chloride extended-release should be used with caution in patients with hepatic or renal impairment and in patients with myasthenia gravis due to the risk of symptom aggravation.

Urinary Retention: Oxybutynin chloride extended-release should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see CONTRAINDICATIONS).

Gastrointestinal Disorders: Oxybutynin chloride extended-release should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see CONTRAINDICATIONS).

Oxybutynin chloride extended-release, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal atony.

Oxybutynin chloride extended-release should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

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

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

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

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

Patients should be informed that oxybutynin chloride extended-release tablets should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush tablets.

Oxybutynin chloride extended-release tablets should be taken at approximately the same time each day.

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

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 2-fold higher when oxybutynin chloride extended-release tablets were administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are coadministered.

Concurrent ingestion of antacid (20 mL of antacid containing aluminum hydroxide, magnesium hydroxide, and simethicone) did not significantly affect the exposure of oxybutynin or desethyloxybutynin.

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

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

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

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

Nursing Mothers: It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxybutynin chloride extended-release is administered to a nursing woman.

Pediatric Use: The safety and efficacy of oxybutynin chloride extended-release were studied in 60 children in a 24 week, open-label trial. Patients were aged 6 to 15 years, all had symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride. Study results demonstrated that administration of oxybutynin chloride extended-release 5 to 20 mg/day was associated with an increase from baseline in mean urine volume per catheterization from 108 mL to 136 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 189 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 51%.

Oxybutynin chloride extended-release tablets are not recommended in pediatric patients who cannot swallow the tablet whole without chewing, dividing or crushing, or in children under the age of 6 years.

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

ADVERSE REACTIONS: Adverse Events with Oxybutynin Chloride Extended-release Tablets: The safety and efficacy of oxybutynin chloride was evaluated in a total of 580 participants who received oxybutynin chloride extended-release tablets in four clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5 to 30 mg/day for up to 4.5 months. Three of these studies 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. Adverse events from two additional fixed dose, active controlled, 12 week treatment duration, post-marketing studies, in which 576 patients were treated with oxybutynin chloride extended-release tablets 10 mg/day, are also listed in Table 3 (second column). The adverse events are reported regardless of causality.

Table 3 Incidence (%) of Adverse Events Reported by ≥ 5% of Patients Using Oxybutynin Chloride Extended-release Tablets (5 to 30 mg/day) and % of Corresponding Adverse Events in Two Fixed Dose (10 mg/day) Studies			
Body System	Adverse Event	Oxybutynin Chloride ER Tablets 5 to 30 mg/day (n = 429)	Oxybutynin Chloride ER Tablets 10 mg/day (n = 576)
General	headache	10	6
	asthenia	7	3
	pain	7	4
Digestive	dry mouth	61	29
	constipation	13	7
	diarrhea	9	7
	nausea	9	2
	dyspepsia	7	5
Nervous	somnolence	12	2
	dizziness	6	4
Respiratory	rhinitis	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 patients receiving 5 to 30 mg/day oxybutynin chloride extended-release tablets were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose related.

The discontinuation rate for all adverse events was 6.8% in the 429 patients from the four studies of efficacy and safety who received 5 to 30 mg/day. The most frequent adverse event causing early discontinuation of study medication was nausea (1.9%), while discontinuation due to dry mouth was 1.2%.

In addition, the following adverse events were reported by 2 to < 5% of the 429 patients who received 5 to 30 mg/day of oxybutynin chloride extended-release tablets in the four efficacy and safety studies. *General:* abdominal pain, dry nasal and sinus mucous membranes, accidental injury, back pain, flu syndrome; *Cardiovascular:* hypertension, palpitation, vasodilatation; *Digestive:* flatulence, gastroesophageal reflux; *Musculoskeletal:* arthritis; *Nervous:* insomnia, nervousness, confusion; *Respiratory:* upper respiratory tract infection, cough, sinusitis, bronchitis, pharyngitis; *Skin:* dry skin, rash; *Urogenital:* impaired urination (hesitancy), increased post void residual volume, urinary retention, cystitis.

Additional rare adverse events reported from worldwide post-marketing experience with oxybutynin chloride extended-release tablets include: peripheral edema, cardiac arrhythmia, tachycardia, hallucinations, convulsions, and impotence.

Additional adverse events reported with some other oxybutynin chloride formulations include: cycloplegia, mydriasis, and suppression of lactation.

OVERDOSAGE: The continuous release of oxybutynin from oxybutynin chloride extended-release tablets should be considered in the treatment of overdosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

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

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

DOSAGE AND ADMINISTRATION: Oxybutynin chloride extended-release tablets must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

Oxybutynin chloride extended-release tablets may be administered with or without 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 tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.

Pediatric Patients Aged 6 Years of Age and Older: Pediatric patients aged 6 years of age and older: The recommended starting dose of oxybutynin chloride extended-release tablets is 5 mg once daily. Dosage may be adjusted in 5 mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

HOW SUPPLIED: Oxybutynin Chloride Extended-release Tablets, USP are available containing 15 mg of oxybutynin chloride, USP.

The 15 mg tablets are gray film-coated, round, unscored tablets with **M** over **O 15** imprinted in black ink on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-6615-01
bottles of 100 tablets
NDC 0378-6615-05
bottles of 500 tablets

Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]

Protect from moisture and humidity.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.



MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED APRIL 2007
OXYBT:R2



Each extended-release
tablet contains:
Oxybutynin
chloride, USP 15 mg

15 mg



MYLAN®

NDC 0378-6615-01

**OXYBUTYNIN CHLORIDE
EXTENDED-RELEASE**

TABLETS, USP

15 mg

**NEW FORMULATION AND
PRODUCT APPEARANCE**

100 TABLETS



Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication
out of the reach of children.

Store at 20° to 25°C (68° to 77°F).
[See USP for Controlled Room
Temperature.]

Protect from moisture and
humidity.

Usual Dosage: See accompanying
prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM6615A1

3 N
0378-6615-05
9



Each extended-release
tablet contains:
Oxybutynin
chloride, USP 15 mg

15 mg



MYLAN®

NDC 0378-6615-05

**OXYBUTYNIN CHLORIDE
EXTENDED-RELEASE**

TABLETS, USP

15 mg

**NEW FORMULATION AND
PRODUCT APPEARANCE**

500 TABLETS



Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication
out of the reach of children.

Store at 20° to 25°C (68° to 77°F).
[See USP for Controlled Room
Temperature.]

Protect from moisture and
humidity.

Usual Dosage: See accompanying
prescribing information.

This container is not intended for
dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM6615B1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 078293Orig1s000

LABELING REVIEWS

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

ANDA Number: 78-293 Date of Submission: May 2, 2006

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Oxybutinin Chloride Extended-release Tablets, 15 mg

1. CONTAINER

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

2. INSERT

- a. The listing of inactive ingredients in the DESCRIPTION section of the package insert IS NOT consistent with the listing of inactive ingredients found in the statement of components and composition i.e. (b) (4)

Please explain.

- b. Your tablet imprintings are the same as the RLD. Please refer to CFR 206.10.

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

Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505-2730
(Vol. A1.1, p 5424)

4. STORAGE CONDITIONS:

NDA - Store at controlled room temperature 15 ° to 25 °C (59 ° to 77 °F).

ANDA - Store at 20 ° to 25 °C (68 ° to 77 °F) [See USP for Controlled Room Temperature]

USP- Preserve in tight, light-resistant containers.

5. DISPENSING RECOMMENDATIONS:

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

ANDA - Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

6. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert IS NOT consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 000060 (Volume 1.1). There ingredients listed in the DESCRIPTION SECTION not listed in the C & C section of the submission.

7. PACKAGING CONFIGURATIONS:

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

ANDA- The 15 mg tablets will be packaged in bottles of 100's (75cc) and 500's (200cc) tablets only.

8. CONTAINER/CLOSURE SYSTEM:

1) **The bottles of 100's will be packaged using a 75mL round beige HDPE bottle from (b) (4) (DMF (b) (4))** The bottle will be molded using the (b) (4) (DMF (b) (4)) .

The closure will be a 38mm beige plastic CRC from (b) (4) (DMF (b) (4)) and consists of clear (b) (4) (DMF (b) (4)) and a beige HDPE outer shell.

The inner seal is a common (b) (4)

The desiccant is manufactured by (b) (4) (DMF (b) (4)) and consists of a (b) (4) canister containing black activated carbon and silica gel granules.

2) **The bottles of 500's will be packaged using a 200 mL round beige HDPE bottle from (b) (4) (DMF (b) (4))** The bottle will be molded using the (b) (4) (DMF (b) (4)) .

The closure will be a 45 mm fine-ribbed beige plastic CRC from (b) (4) (DMF (b) (4)) and it consists of clear (b) (4) (DMF (b) (4)) shell.

The inner seal is the common (b) (4)

The desiccant is manufactured by (b) (4) and consists of a (b) (4) canister containing black activated carbon and silica gel granules. This is the same as in the 75mL bottle. (p. 5706)

9. The 15 mg tablets are gray, film-coated, round, unscored tablets (b) (4) (b) (4) . This is the same as the RLD. Explanation requested.

10. Mylan also has 5 mg (76-702) and 10 mg (76-644) extended release tablets.

Date of Review: November 28, 2006 Date of Submission: May 2, 2006

Primary Reviewer: Postelle Birch

Team Leader: John Grace

cc: ANDA: 78-293
DUP/DIVISION FILE

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/s/

Postelle Birch
12/1/2006 02:08:15 PM
MEDICAL OFFICER

John Grace
12/3/2006 11:30:16 AM
MEDICAL OFFICER

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

ANDA Number: 78-293 Date of Submission: December 14, 2006

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Oxybutinin Chloride Extended-release Tablets, 15 mg

BASIS OF APPROVAL:

APPROVAL SUMMARY

CONTAINER LABELS: (bottles of 100 and 500)
Satisfactory in FPL as of December 14, 2006 e-submission.

PROFESSIONAL PACKAGE INSERT:
Satisfactory in FPL as of December 14, 2006 e-submission.

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: side-by-side
Basis of Approval for the Carton Labeling: side-by-side
Other Comments

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	IV

			incontinence	
6919092*PED	Nov 22, 2015			

Exclusivity Data -

There is no unexpired exclusivity.

3. MANUFACTURING FACILITY

Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505-2730
(Vol. A1.1, p 5424)

4. STORAGE CONDITIONS:

NDA - Store at controlled room temperature 15 ° to 25 °C (59 ° to 77 °F).
ANDA - Store at 20 ° to 25 °C (68 ° to 77 °F) [See USP for Controlled Room Temperature]
USP- Preserve in tight, light-resistant containers.

5. DISPENSING RECOMMENDATIONS:

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

6. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert IS NOT consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 000060 (Volume 1.1). There ingredients listed in the DESCRIPTION SECTION not listed in the C & C section of the submission.

7. PACKAGING CONFIGURATIONS:

NDA- The 5 mg, 10 mg and 15 mg tablets are packaged in bottles of 100 tablets.
ANDA- The 15 mg tablets will be packaged in bottles of 100's (75cc) and 500's (200cc) tablets only.

8. CONTAINER/CLOSURE SYSTEM:

1) The bottles of 100's will be packaged using a 75mL round beige HDPE bottle from (b) (4) (DMF (b) (4)). The bottle will be molded using the (b) (4) (DMF (b) (4)).

The closure will be a 38mm beige plastic CRC from (b) (4) (DMF (b) (4)) and consists of clear (b) (4) (b) (4), DMF (b) (4)) and a beige HDPE outer shell.

The inner seal is a common (b) (4)

The desiccant is manufactured by (b) (4) (DMF (b) (4)) and consists of a (b) (4) canister containing black activated carbon and silica gel granules.

2) The bottles of 500's will be packaged using a 200 mL round beige HDPE bottle from (b) (4) (b) (4). The bottle will be molded using the (b) (4) (DMF (b) (4)).

The closure will be a 45 mm fine-ribbed beige plastic CRC from (b) (4) (DMF (b) (4)) and it consists of clear (b) (4), DMF (b) (4) shell.

The inner seal is the common (b) (4)

(b) (4)

The desiccant is manufactured by (b) (4) and consists of a (b) (4) canister containing black activated carbon and silica gel granules. This is the same as in the 75mL bottle. (p. 5706)

9. The 15 mg tablets are gray, film-coated, round, unscored tablets with M over O 15 imprinted in black ink on one side of the tablet and blank on the other side.
10. Mylan also has 5 mg (76-702) and 10 mg (76-644) extended release tablets.

Date of Review:	January 8, 2007	Date of Submission:	December 14, 2006
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Primary Reviewer:	Postelle Birch-Smith
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Team Leader:	John Grace
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cc: ANDA: 78-293
DUP/DIVISION FILE

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this page is the manifestation of the electronic signature.**

/s/

Postelle Birch
1/9/2007 05:36:34 PM
MEDICAL OFFICER

John Grace
1/10/2007 10:46:43 AM
MEDICAL OFFICER

This approval summary supersedes the December 14, 2006 approval summary.

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

ANDA Number: 78-293

Dates of Submission: May 2, 2007 and April 17, 2007

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Oxybutynin Chloride Extended-release Tablets USP, 15 mg

BASIS OF APPROVAL:

APPROVAL SUMMARY

CONTAINER LABELS: (bottles of 100 and 500)
Satisfactory in FPL as of April 17, 2007 e-submission.

PROFESSIONAL PACKAGE INSERT:
Satisfactory in FPL as of May 2, 2007 e-submission.

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: Oxybutynin 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: side-by-side
Basis of Approval for the Carton Labeling: side-by-side
Other Comments

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 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

Mylan Pharmaceuticals, Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505-2730
(Vol. A1.1, p 5424)

4. STORAGE CONDITIONS:

NDA - Store at controlled room temperature 15 ° to 25 °C (59 ° to 77 °F).
ANDA - Store at 20 ° to 25 °C (68 ° to 77 °F) [See USP for Controlled Room Temperature]
USP- Preserve in tight, light-resistant containers.

5. DISPENSING RECOMMENDATIONS:

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

6. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert IS NOT consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 000060 (Volume 1.1). There ingredients listed in the DESCRIPTION SECTION not listed in the C & C section of the submission.

7. PACKAGING CONFIGURATIONS:

NDA- The 5 mg, 10 mg and 15 mg tablets are packaged in bottles of 100 tablets.
ANDA- The 15 mg tablets will be packaged in bottles of 100's (75cc) and 500's (200cc) tablets only.

8. CONTAINER/CLOSURE SYSTEM:

1) The bottles of 100's will be packaged using a 75mL round beige HDPE bottle from (b) (4) (DMF (b) (4)). The bottle will be molded using the (b) (4) (DMF (b) (4)).

The closure will be a 38mm beige plastic CRC from (b) (4) (DMF (b) (4)) and consists of clear (b) (4) DMF (b) (4) and a beige HDPE outer shell.

The inner seal is a common (b) (4)

The desiccant is manufactured by (b) (4) (DMF (b) (4)) and consists of a (b) (4) canister containing black activated carbon and silica gel granules.

2) The bottles of 500's will be packaged using a 200 mL round beige HDPE bottle from (b) (4) (DMF (b) (4)). The bottle will be molded using the (b) (4) (DMF (b) (4)).

The closure will be a 45 mm fine-ribbed beige plastic CRC from (b) (4) (DMF (b) (4)) and it consists of clear (b) (4) DMF (b) (4) shell.

The inner seal is the common (b) (4)

(b) (4)

The desiccant is manufactured by (b) (4) and consists of a (b) (4) canister containing black activated carbon and silica gel granules. This is the same as in the 75mL bottle. (p. 5706)

9. The 15 mg tablets are gray, film-coated, round, unscored tablets with M over O 15 imprinted in black ink on one side of the tablet and blank on the other side.
10. Mylan also has 5 mg (76-702) and 10 mg (76-644) extended release tablets.

Date of Review: May 1, 2007

Dates of Submission: May 2, 2007 and April 17, 2007

Primary Reviewer: Postelle Birch-Smith

Team Leader: John Grace

cc: ANDA: 78-293
DUP/DIVISION FILE

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this page is the manifestation of the electronic signature.**

/s/

Postelle Birch
5/7/2007 05:20:13 PM
MEDICAL OFFICER

John Grace
5/8/2007 11:37:41 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 078293Orig1s000

CHEMISTRY REVIEWS

ANDA # 78-293

**Oxybutynin Chloride Extended Release Tablets,
15 mg**

Mylan Pharmaceuticals, Inc.

**Robert Iser
Office of Generic Drugs
Division of Chemistry III
Team 4**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. **ANDA #:** 78-293
2. **REVIEW #:** 1
3. **REVIEW DATE:** 9-6-2006; revised 9-18-06; revised 10-3-2006; revised 12-14-06
4. **REVIEWER:** Robert Iser
5. **PREVIOUS DOCUMENTS:** N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	May 3, 2006
Telephone Amendment	Sept. 29, 2006
Gratuitous Amendment	Nov. 16, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Pharmaceuticals, Inc.
Address:	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504 – 4310
Representative:	S. Wayne Talton
Telephone:	304-599-2595, ext. 6551
Fax:	304-285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug:	Ditropan XL ® Extended Release Tablets
RLD Company:	Alza, NDA # 20-897
Patent Certification:	Paragraph IV, Section III
Exclusivity:	Yes, Section III

10. PHARMACOLOGICAL CATEGORY: Anti-spasmodic**11. DOSAGE FORM:** Extended Release Tablets (MDD: 30 mg daily)**12. STRENGTH/POTENCY:** 15 mg**13. ROUTE OF ADMINISTRATION:** Oral**14. Rx/OTC DISPENSED:** X Rx OTC

Chemistry Review Data Sheet

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

_____ SPOTS product – Form Completed
 X Not a SPOTS product

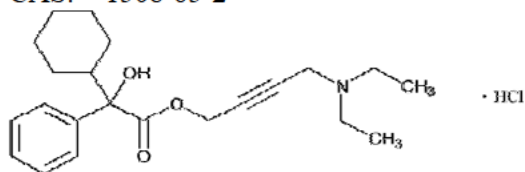
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: (see also firm's info for more chemical names, Section VIII, page 5206)Oxybutynin Chloride USP

(±)-α-cyclohexyl-α-hydroxy-Benzeneacetic acid 4-(diethylamino)-2-butynyl ester hydrochloride

C₂₂H₃₁NO₃·HCl

MW = 393.95

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)	(b) (4)	1	Adequate	9-21-06	Reviewed by R. Iser
	IV			4	N/A		
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4	N/A		
	III		4	N/A		

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: This is a Sister Application to Tentatively Approved ANDAs, 76-702 (5 mg) and 76-644 (10 mg)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	7-10-06	S. Ferguson
Methods Validation	N/A		
Labeling	Acceptable	1/10/07	P. Birch
Bioequivalence	Dissol. - Acceptable Bio Review – Acceptable	11/30/06	B. Davit
EA	Satisfactory	9-6-06	R. Iser
Radiopharmaceutical	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:

Executive Summary Section

The Chemistry Review for ANDA 78-293**The Executive Summary**

Product: Oxybutynin Chloride Extended Release Tablets, 15 mg

Firm: Mylan Pharmaceuticals, Inc.

I. Recommendations

- A. Recommendation and Conclusion on Approvability**
CMC Approvable.
- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A**

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)****Drug Product:**

The proposed drug product, Oxybutynin Chloride Extended Release Tablets is a non-sterile, non-USP product (Note: a proposed PF monograph exists for the ER tablets, to become official in USP 30 – NF 25 as of May 1, 2007).

The tablets are described as white, film-coated, round, biconvex, beveled edged tablets with **M** over **O 15** imprinted in black ink on one side and blank on the other side. Note: Neither the ANDA tablets nor the RLD tablets are scored.

The inactive ingredients for the drug product are: Povidone USP, Hypromellose USP, Dibasic Calcium Phosphate USP, Magnesium Stearate NF, Colloidal Silicon Dioxide NF, Methacrylic Acid Copolymer Dispersion (b) (4) NF, Talc USP, Triethyl Citrate NF, Polysorbate 80 NF, Sodium Hydroxide NF, (b) (4) Black (b) (4) Imprinting Ink (b) (4) Propylene Glycol NF (b) (4).

The proposed manufacturing process includes (b) (4)

As per the review of the sister ANDAs 76-644 and 76-702; and as included in the proposed labeling the firm has provided information regarding the product's enteric coating and extended release mechanism as follows:

Oxybutynin chloride extended-release tablets are formulated to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The dosage form is comprised of a hydrophilic cellulose polymer matrix tablet surrounded by an enteric coating system. The enteric coat is insoluble in the low pH

Executive Summary Section

environment of the stomach. As the tablet passes through the stomach and enters the higher pH environment of the small intestine, the enteric coating dissolves and/or erodes to expose the polymer matrix tablet which swells and releases drug at a controlled rate via diffusion and/or erosion. (Also see additional explanation in this review).

Drug Substance:

Oxybutynin Chloride drug substance is provided by (b) (4). The firm's specifications are based on the USP and the manufacturer's specifications. The drug substance is freely soluble in water, (b) (4).

Drug Product has a MDD of 30 mg per day for Oxybutynin Chloride. The drug substance impurity identification threshold is 0.10% and qualification threshold is 0.15% by ICH Q3A; and drug product degradation product identification threshold is 0.2% and the qualification threshold is 0.5% by ICH Q3B.

Batch Size:

The ANDA batch was produced at (b) (4) tablets and the proposed commercial batch size is (b) (4) tablets.

B. Description of How the Drug Product is intended to be used

The drug product will be marketed with an indication for treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, with a proposed tablet strength of 15 mg; and commercial packaging in 100 and 500 count packages (bottle).

The proposed expiration dating for the product is 24 months; based on three month accelerated data and the recommended storage conditions are Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.] Protect from moisture and humidity. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. The RLD storage is listed as store at 25 °C (77 °F); with excursions permitted to 15-30°C (59-86 °F); and protect from humidity and moisture.

C. Basis for Approvability or Not-Approval Recommendation

CMC recommendation Approvability is based information provided and responses to deficiencies.

The bio review and labeling reviews are still pending; and the EES is acceptable.

Chemistry Assessment Section

(b) (4)

Post Approval Commitment:**Satisfactory**

The firm commits to the following:

- Performing stability studies as outlined in ANDA and as approved by the FDA.
- Reporting of stability results as the become available in periodic reports or as requested.
- Withdrawing from market any lots that fall outside specifications; and if there is evidence of a deviation that is a single occurrence which does not affect product safety or efficacy, Mylan will discuss these facts with the FDA as justification for continued marketing.
- Reporting any changes or deterioration in distributed product to the FDA as required.

Post Approval Stability Protocol:**Satisfactory**

Stability protocol is provided and states that the first three production lots will be packaged in the smallest and largest container – closure will be placed on RT ($25 \pm 2^\circ \text{C}$ / $60 \pm 5\% \text{RH}$) at 3, 6, 9, 12, 18, and 24 months' and yearly thereafter to extend expiry date. Yearly, thereafter, at least one batch will be added in smallest and largest container – closure. The expiry date may be extended based on RT stability data for a minimum of three production lots studied by the approved protocol. The specifications are the same as used for exhibit batch.

Expiry date:**Satisfactory**

The firm proposes a 24 month expiration date based on the available stability data. The proposed date is appropriate based on provided data.

30. MICROBIOLOGY:**N/A****31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS:****N/A****32. LABELING: -****Acceptable, 1/10/07****33. ESTABLISHMENT INSPECTION: -****Acceptable, 7/10/06****34. BIOEQUIVALENCE: -****Dissolution -
BE/BA -****Acceptable, 11/30/06
Acceptable, 11/30/16**

Chemistry Assessment Section

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Satisfactory - Included Section XIX. Exclusion from requirement for environmental assessment statement is provided and is satisfactory.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT: None

cc: ANDA 78-293
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630 / R. Iser- Review Chemist /9-6-06; revised 9-18-06
revised 10-3-06; revised 12-14-06/12/14/06

HFD-630 / D. Gill - Team Leader /12/14/06
HFD-617 / L. Matheny - Project Manager /12/15/06

F/T by: LM 1/30/07

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TYPE OF LETTER: CMC APPROVABLE

**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
1/31/2007 04:20:02 PM
CHEMIST

Devinder Gill
1/31/2007 05:46:38 PM
CHEMIST

Leigh Matheny
1/31/2007 06:31:02 PM
CSO

ANDA # 78-293

**Oxybutynin Chloride Extended Release Tablets USP,
15 mg**

Mylan Pharmaceuticals, Inc.

**Robert Iser
Office of Generic Drugs
Division of Chemistry III
Team 4**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. ANDA #: 78-293

2. REVIEW #: 1

There appears to be a numbering error. This should be review #2

3. REVIEW DATE: April 23, 2007

4. REVIEWER: Robert Iser

5. PREVIOUS DOCUMENTS:

Previous Submission(s)

Original

Telephone Amendment

Gratuitous Amendment

Document Date

May 3, 2006

Sept. 29, 2006

Nov. 16, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Minor Amendment (Full Approval Request)

Telephone Amendment

Document Date

March 5, 2007

April 17, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:

Mylan Pharmaceuticals, Inc.

Address:

781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504 – 4310

Representative:

S. Wayne Talton

Telephone:

304-599-2595, ext. 6551

Fax:

304-285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:

N/A

b) Non-Proprietary Name (USAN):

Oxybutynin Chloride Extended Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug:

Ditropan XL ® Extended Release Tablets

RLD Company:

Alza, NDA # 20-897

Patent Certification:

Paragraph IV, See review #1

Exclusivity:

Yes, See Review #1

10. PHARMACOLOGICAL CATEGORY: Anti-spasmodic

11. DOSAGE FORM:

Extended Release Tablets (MDD: 30 mg daily)

12. STRENGTH/POTENCY:

15 mg

Chemistry Review Data Sheet

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: (see review #1 for more chemical names)

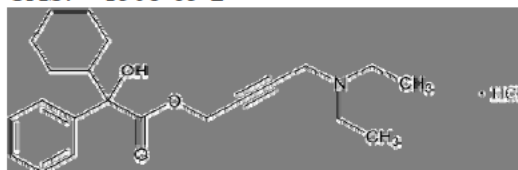
Oxybutynin Chloride USP

(±)-α-cyclohexyl-α-hydroxy-Benzeneacetic acid 4-(diethylamino)-2-butynyl ester hydrochloride

C₂₂H₃₁NO₃·HCl

MW = 393.95

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)	(b) (4)	1	Adequate	9-21-06	Reviewed by R. Iser
	IV		(b) (4)	4	N/A		
	IV		(b) (4)	4	N/A		
	III		(b) (4)	4	N/A		
	III		(b) (4)	4	N/A		
	III		(b) (4)	4	N/A		
	III		(b) (4)	4	N/A		
	III		(b) (4)	4	N/A		
	III		(b) (4)	4	N/A		
	III		(b) (4)	4	N/A		
	III		(b) (4)	4	N/A		
	III		(b) (4)	4	N/A		

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4	N/A		
	III		4	N/A		
	III		4	N/A		

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: This is a Sister Application to ANDAs, 76-702 (5 mg) and 76-644 (10 mg)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	7/10/06	S. Ferguson
Methods Validation	N/A		
Labeling	Acceptable	5/8/07	P. Birch
Bioequivalence	Dissol. - Acceptable Bio Review – Acceptable	11/30/06	B. Davit
EA	Satisfactory	9/6/06	R. Iser
Radiopharmaceutical	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:

Executive Summary Section

The Chemistry Review for ANDA 78-293**The Executive Summary**

Product: Oxybutynin Chloride Extended Release Tablets USP, 15 mg

Firm: Mylan Pharmaceuticals, Inc.

I. Recommendations

- A. Recommendation and Conclusion on Approvability**
CMC Approvable.
- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A**

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)****Drug Product:**

The proposed drug product, Oxybutynin Chloride Extended Release Tablets is a non-sterile, USP product (Note: USP monograph for the ER tablets to become official in USP 30 – NF 25 as of May 1, 2007).

The tablets are described as white, film-coated, round, biconvex, beveled edged tablets with **M** over **O 15** imprinted in black ink on one side and blank on the other side. Note: Neither the ANDA tablets nor the RLD tablets are scored.

The inactive ingredients for the drug product are: Povidone USP, Hypromellose USP, Dibasic Calcium Phosphate USP, Magnesium Stearate NF, Colloidal Silicon Dioxide NF, Methacrylic Acid Copolymer Dispersion (b) (4) NF, Talc USP, Triethyl Citrate NF, Polysorbate 80 NF, Sodium Hydroxide NF, (b) (4) Black (b) (4) Imprinting Ink (b) (4) Propylene Glycol NF (b) (4).

The proposed manufacturing process includes a (b) (4)

As per the review of the sister ANDAs 76-644 and 76-702; and as included in the proposed labeling the firm has provided information regarding the product's enteric coating and extended release mechanism as follows:

Oxybutynin chloride extended-release tablets are formulated to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The dosage form is comprised of a hydrophilic cellulose polymer matrix tablet surrounded by an enteric coating system. The enteric coat is insoluble in the low pH environment of the stomach. As the tablet passes through the stomach and enters the higher pH

Executive Summary Section

environment of the small intestine, the enteric coating dissolves and/or erodes to expose the polymer matrix tablet which swells and releases drug at a controlled rate via diffusion and/or erosion. (Also see additional explanation in this review).

Drug Substance:

Oxybutynin Chloride drug substance is provided by (b) (4). The firm's specifications are based on the USP and the manufacturer's specifications. The drug substance is freely soluble in water, (b) (4).
(b) (4)

Batch Size:

The ANDA batch was produced at (b) (4) tablets and the proposed commercial batch size is (b) (4) tablets.

B. Description of How the Drug Product is intended to be used

The drug product will be marketed with an indication for treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, with a proposed tablet strength of 15 mg; and commercial packaging in 100 and 500 count packages (bottle).

The proposed expiration dating for the product is 24 months; based on three month accelerated data and the recommended storage conditions are Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.] Protect from moisture and humidity. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. The RLD storage is listed as store at 25 °C (77 °F); with excursions permitted to 15-30°C (59-86 °F); and protect from humidity and moisture.

C. Basis for Approvability or Not-Approval Recommendation

CMC sections are Approvable. The bio review, labeling and EES are currently acceptable.

Chemistry Assessment Section

(b) (4)

Post Approval Protocol & Commitment:**Satisfactory per review #1**

Review details and assessment are provided in review #1.

Expiry date:**Satisfactory per review #1**

The firm proposed a 24 month expiration date based on the available stability data. The proposed date is appropriate based on provided data.

30. MICROBIOLOGY:**N/A****31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS:****N/A****32. LABELING: -****Acceptable 5/8/07****33. ESTABLISHMENT INSPECTION: -****Acceptable 7/10/06****34. BIOEQUIVALENCE: -****Dissolution -****Acceptable 11/30/06****BE/BA -****Acceptable****35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:****Satisfactory per review #1****36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT: None**

cc: ANDA 78-293

ANDA DUP

DIV FILE

Field Copy

Endorsements (Draft and Final with Dates):

HFD-630 / R. Iser- Review Chemist /4-23-07/

HFD-630 / D. Gill - Team Leader /4/25/07

HFD-617 / L. Matheny - Project Manager /4/26/07

F/T by: LM 5/9/07

V:\FIRMSAM\MYLAN\LTRS&REV\78293R02.doc

TYPE OF LETTER: CMC APPROVABLE

**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
5/9/2007 11:53:10 AM
CHEMIST
approvable

Devinder Gill
5/9/2007 01:02:13 PM
CHEMIST

Leigh Matheny
5/11/2007 09:03:47 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 078293Orig1s000

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-293
Drug Product Name	Oxybutynin Chloride Extended-Release Tablets
Strength	15 mg
Applicant Name	Mylan Pharmaceuticals Inc.
Address	781 Chestnut Ridge Road, Morgantown, WV 26504
Contact Person	S. Wayne Talton
	Phone (304) 599-2595
	Fax (304) 285-6407
Submission Date(s)	May 2, 2006
Amendment Date(s)	October 12, 2006 (Dissolution)
Reviewer	Sarah M. Robertson, Pharm.D.
First Generic	No

I. Executive Summary

The firm previously received approval for Oxybutynin Cl Extended-Release Tablets, 5 mg (ANDA 76-702) and 10 mg (ANDA 76-644) on Nov. 9, 2006, based on acceptable results of fasted and fed bioequivalence studies. This submission consists of one fasting bioequivalence (BE) study and dissolution data for the 15 mg strength tablet. The firm requests a biowaiver for the fed BE study requirement.

The two-way crossover fasting BE study comparing Oxybutynin Cl Extended-Release Tablets, 15 mg to the reference listed drug (RLD), Ditropan[®] XL (Alza Corp.) was conducted in healthy adult males and females (n = 77). The firm measured plasma levels of both oxybutynin and the active metabolite, desethyloxybutynin. However, only oxybutynin is considered in order to establish bioequivalence. The results (point estimate, 90% CI) for oxybutynin are LAUCt of 0.99, 90.7 – 107.0%; LnAUCi of 0.98, 89.9 – 106.2%; and LnCmax of 0.92, 85.0 – 100.0%. The fasting study is acceptable. A waiver of BE is granted for the fed study requirement.

The dissolution data submitted by the firm is acceptable. The application is complete.

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III. Submission Summary

A. Drug Product Information

Test Product	Oxybutynin Cl Extended-Release Tablets, 15 mg
Reference Product	Ditropan [®] XL 15 mg Tablets
RLD Manufacturer	Alza Corporation
NDA No.	20-897
RLD Approval Date	Dec 16, 1998
Indication	Treatment of Overactive Bladder

B. PK/PD Information

Bioavailability	6%
Food Effect	None
T_{max}	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)
Relevant OGD or DBE History	There is one approved generic for the 15 mg strength tablet (76-745, Impax). Mylan Pharmaceuticals Inc. received approval of their 10 mg and 5 mg strength tablets Nov. 9, 2006 (76-644, 76-702) following resolution of a pending Citizen Petition filed by Ortho Urology. This is currently the only pending ANDA submission.

The Division has responded to 13 control documents (99-276, (b) (4); 00-025, (b) (4); 00-496 (b) (4); (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, Ortho Urology - Citizen Petition; 06-0282, (b) (4); 06-0822, (b) (4).

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, in bioequivalence studies of Oxybutynin HCl Extended Release Tablets.

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. This recommendation is consistent with the CDER Guidance, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, March, 2003.

The DBE recommends the same dissolution method as used for the firm's 5 mg and 10 mg strength tablets:

Medium: Row 1 – pH 1.2 Simulated Gastric Fluid w/out enzymes.
 Row 2 - 4 – pH 6.8 Simulated Intestinal Fluid w/out enzymes.
 Apparatus: Apparatus 3 (reciprocating cylinder)
 Volume: 250 mL
 Temp.: 37°C ± 0.5°C
 Speed: 25 dips per min.
 Spec.: (b) (4)

Agency Guidance

Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, March, 2003.

Drug Specific Issues (if any)

None

B. Contents of Submission

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

C. Pre-Study Bioanalytical Method Validation

	Parent	Metabolite
Analyte name	Oxybutynin	N-Desethoxybutynin
Internal Standard	(b) (4)	(b) (4)
Method description	LC/MS	LC/MS
QC range	150.84 – 7039.20 pg/mL	299.28 – 13966.00 pg/mL
Standard curve range	50.16 – 10032.00 pg/mL	100.24 – 20048.00 pg/mL
Limit of quantitation	50.16 pg/mL	100.24 pg/mL
Inter-assay precision of analytical standards (CV%)	2.11 – 4.40	2.30 – 6.12
Inter-assay accuracy of analytical standards (%)	97.76 – 102.63	95.43 – 102.14
Linearity	$r^2 > 0.9984$	$r^2 > 0.9983$
Average recovery of Drug (%)	65.06, 61.31, 66.05%	72.81, 68.35, 72.89%
Average Recovery of Int. Std (%)	75.86	75.86
QC Intraday precision range (%)	1.61 – 3.35	2.92 – 7.18
QC Intraday accuracy range (%)	96.86 – 101.05	96.95 – 103.12
QC Interday precision range (%)	3.26 – 4.07	3.26 – 4.07
QC Interday accuracy range (%)	100.60 – 104.44	98.32 – 100.80
Bench-top stability (hrs)	110 min. at RT	110 min. at RT
Processed stability (hrs)	76 hrs. at RT	76 hrs. at RT
Freeze-thaw stability (cycles)	4	4
Stock Solution Stability	202 days at -20°C, and 6 hours at RT	202 days at -20°C, and 6 hours at RT
Long-term storage stability	166 days at -80°C	166 days at -80°C
Dilution integrity	2 x (CV% 1.39) 20 x (CV% 2.39)	2 x (CV% 3.04) 20 x (CV% 2.88)
Specificity	No interfering peaks noted in blank plasma samples	No interfering peaks noted in blank plasma samples

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	OXYB-05129
Study Design	Single-dose, two-way crossover study conducted in healthy volunteers under fasting conditions.
No. of subjects enrolled	80
No. of subjects completing	77 (Subj#15 withdrew prior to Period 2 for personal reasons, Subj#37 and #52 were withdrawn prior to Period 2 due to adverse events)
No. of subjects analyzed	77
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Males 42; Females 35
Test product	Oxybutynin Chloride Extended-Release Tablets
Reference product	Ditropan [®] XL Tablets
Strength tested	15 mg
Dose	1 x 15 mg

Summary of Statistical Analysis Metaxalone (N=77)		
Parameter	Point Estimate	90% Confidence Interval
AUC _{0-t}	0.99	90.68 – 107.02
AUC _∞	0.98	89.86 – 106.16
C _{max}	0.92	85.01 – 100.03

Table 1. Reanalysis of Study Samples

OXYB-05129-Fasted Study Oxybutynin Additional Information in Attachment 3, Table 4, pages 372-381 and Table 6, page 386								
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%	0%	0	0	0%	0%
Reason A	4	8	0.14%	0.27%	4	8	0.14%	0.27%
Reason B	22	6	0.76%	0.21%	22	6	0.76%	0.21%
Reason C	3	1	0.10%	0.03%	3	1	0.10%	0.03%
Reason D	1	2	0.03%	0.07%	1	2	0.03%	0.07%
Reason E	0	1	0%	0.03%	0	1	0%	0.03%
Reason F	0	0	0%	0%	0	0	0%	0%
Total	30	18	1.03%	0.62%	30	18	1.03%	0.62%

OXYB-05129-Fasted Study N-Desethyloxybutynin Additional Information in Attachment 3, Table 5, pages 382-385 and Table 7, page 387								
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%	0%	0	0	0%	0%
Reason A	4	6	0.14%	0.21%	4	6	0.14%	0.21%
Reason B	2	1	0.07%	0.03%	2	1	0.07%	0.03%
Reason C	1	1	0.03%	0.03%	1	1	0.03%	0.03%
Reason D	84	80	2.88%	2.75%	56	45	1.92%	1.54%
Reason E	0	1	0%	0.03%	0	1	0%	0.03%
Reason F	28	35	0.96%	1.20%	28	35	0.96%	1.20%
Total	119	124	4.09%	4.26%	91	89	3.12%	3.06%

- A Unacceptable internal standard response
 B Loss of sample during processing
 C Internal standard response is $\leq 5\%$ of the mean internal standard response
 D Sample concentration above the upper limit of quantification
 E Sample reanalyzed to obtain confirming value
 F Rejected sample dilution

F. Formulation

Location in appendix	Section B
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored?	No
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	N/A
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA
Medium	Row 1: pH 1.2 Simulated Gastric Fluid w/out enzymes. Row 2 – 4: pH 6.8 Simulated Intestinal Fluid w/out enzymes.
Volume (mL)	250
USP Apparatus type	3 (reciprocating cylinder)
Rotation	25 dpm
Firm's proposed specifications	2 hr: (b) (4) 4 hr: (b) (4) 8 hr: (b) (4) 16 hr: (b) (4)
FDA-recommended specifications	2 hr: (b) (4) 4 hr: (b) (4) 8 hr: (b) (4) 16 hr: (b) (4)
F2 metric calculated?	No
If no, reason why F2 not calculated	
Is method acceptable?	Yes
If not then why?	

Comment: The firm accepts the use of the same dissolution method for its 15 mg tablets that the DBE found acceptable for the 5 mg and 10 mg tablets. However, in the original submission, the firm proposed (b) (4)

The dissolution testing is complete.

H. Waiver Request(s)

The firm requests a biowaiver for the fed study requirement based on the following: (1) Acceptable results for the fed BE study conducted with 10 mg strength tablets included in ANDA 76-644, (2) Proportionality of formulation for the 10 mg and 15 mg strength tablets, and (3) Acceptable comparative dissolution

The dissolution is acceptable, and the 10 mg and 15 mg formulations are proportional. The waiver is granted.

I. Deficiency Comments

None

J. Recommendations

1. The BE study conducted by Mylan Pharmaceuticals Inc. on the test product Oxybutynin Cl Extended-Release Tablets, 15 mg, Lot #R1N3882, comparing it to the RLD Ditropan[®] XL Tablets, 15 mg, Lot #0531572, under fasting conditions, is acceptable. A waiver is granted for the fed BE study requirement.
2. The dissolution testing conducted by the firm on its drug product Oxybutynin Cl Extended-Release Tablets, 15 mg, is acceptable. The dissolution testing should be conducted in 250 mL of pH 1.2 Simulated Gastric Fluid without enzymes (Row 1) and 250 mL of pH 6.8 Simulated Intestinal Fluid without enzymes (Rows 2-4), at 37°C, using Apparatus III (reciprocating cylinder) at 25 dpm.

The test products should meet the following specifications:

2 hours:	Between 0% and 10%
4 hours:	Between 10% and 30%
8 hours:	Between 35% and 60%
16 hours:	NLT 75%

Sarah M. Robertson, Pharm.D.
Review Branch III

Date

Chandra S. Chaurasia, Ph.D.
Acting Team Leader, Review Branch III

Date

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Date

IV. Appendix
A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	OXYB-05129
Study Title	Single-Dose Fasting Bioequivalence Study of Oxybutynin Chloride Extended-Release Tablets (15 mg; Mylan) to Ditropan [®] XL Tablets (15 mg; ALZA) in Healthy Volunteers.
Clinical Site	PRACS Institute, Ltd., East Grand Forks, MN
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	Period I: January 20 – 24, 2006 Period II: January 27 – 31, 2006
Analytical Site	(b) (4)
Analytical Director	(b) (6) Ph.D.
Analysis Dates	February 10 – March 20, 2006
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	59 Days

Treatment ID	Test	Reference
Test or Reference	A	B
Product Name	Oxybutynin Chloride Extended-Release Tablet	Ditropan [®] XL Tablet
Manufacturer	Mylan Pharmaceuticals Inc.	ALZA Corporation
Batch/Lot No.	R1N3882	0531572
Manufacture Date	12/14/2005	N/A
Expiration Date	N/A	03/2007
Strength	15 mg	15 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	97.9%	99.4%
Content Uniformity (mean, %RSD)	98.4% (1.5% RSD)	99.9% (2.3% RSD)
Formulation	See Appendix B	
Dose Administered	1 x 15 mg	1 x 15 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 Days
Randomization Scheme	AB: 3, 4, 5, 6, 10, 11, 14, 16 – 18, 23, 24, 26, 28, 30, 32, 33, 36 – 38, 41, 42, 46, 47, 49, 50, 53, 55, 58, 59, 61, 63, 66, 67, 70, 71, 74, 75, 78, 80 BA: 1, 2, 7 – 9, 12, 13, 15, 19 – 22, 25, 27, 29, 31, 34, 35, 39, 40, 43 – 45, 48, 51, 52, 54, 56, 57, 60, 62, 64, 65, 68, 69, 72, 73, 76, 77, 79
Blood Sampling Times	0 and at 1, 2, 4, 5, 6, 8, 10, 12, 14, 16, 18, 21, 24, 28, 36, 48, 60, and 72 hrs post dose.
Blood Volume Collected/Sample	1 x 10 mL
Blood Sample Processing/Storage	Plasma samples separated and stored at $-70^{\circ}\text{C} \pm 15^{\circ}\text{C}$
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hrs prior to drug administration and until 4 hrs after
Length of Confinement	10 hrs prior to drug administration and until 24-hr blood draw
Safety Monitoring	Yes, vital signs were measured prior to and at 12 and 24 h after dosing

Comments on Study Design: Acceptable

b) Clinical Results

Table 1. Demographics of Study Subjects

Fasting Bioequivalence Study R05-1459		
	Treatment Groups	
	Test Product N=77 ¹	Reference Product N=77 ¹
Age (years)		
Mean ± SD	24.86 ± 9.78	24.86 ± 9.78
Range	18 - 58	18 - 58
Groups		
<18	-	-
18-39	68 (88.31%)	68 (88.31%)
40-64	9 (11.69%)	9 (11.69%)
65-75	-	-
>75	-	-
Sex		
Female	35 (45.45%)	35 (45.45%)
Male	42 (54.55%)	42 (54.55%)
Hispanic or Latino		
Race		
N	1 (1.30%)	1 (1.30%)
A	-	-
B	-	-
I	-	-
W	2 (2.60%)	2 (2.60%)
Not Hispanic or Latino		
Race		
N	3 (3.90%)	3 (3.90%)
A	3 (3.90%)	3 (3.90%)
B	-	-
I	1 (1.30%)	1 (1.30%)
W	67 (87.01%)	67 (87.01%)

RACE:	
American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W
*Subjects Used in Final Statistical Report	

Table 2. Dropout Information

Subject No	Reason	Period	Replaced?
15	Withdrew consent due to personal reasons	Prior to Period 2	No
37	Withdrawn from study by investigator due to adverse event (vomiting)	Prior to Period 2	No
52	Withdrawn from study by investigator due to adverse event (vomiting)	During Period 1	No

Table 3. Study Adverse Events

Body System/Adverse Event ¹	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study R05-1459	
	Test N=78 ²	Reference N=79 ²
	n (%) ³	n (%) ³
Gastrointestinal disorders		
Abdominal pain lower	1 (1.28%)	-
Nausea	-	1 (1.27%)
Vomiting	1 (1.28%)	1 (1.27%)
General disorders and administration site conditions		
Pallor	-	1 (1.27%)
Injury, poisoning and procedural complications		
Ligament injury	1 (1.28%)	-
Puncture site pain	1 (1.28%)	-
Vessel puncture site bruise	-	1 (1.27%)
Musculoskeletal and connective tissue disorders		
Myalgia	1 (1.28%)	-
Nervous system disorders		
Dizziness	-	2 (2.53%)
Headache	3 (3.85%)	5 (6.33%)
Syncope vasovagal	-	1 (1.27%)
Respiratory, thoracic and mediastinal disorders		
Pharyngolaryngeal pain	-	1 (1.27%)
Rhinorrhoea	-	1 (1.27%)
Sinus congestion	1 (1.28%)	-
Skin and subcutaneous tissue disorders		
Herpes simplex	1 (1.28%)	-
Total Subjects Reporting at Least One Adverse Event		
	8 (10.26%)	10 (12.66%)

¹ MedDRA Version 8.1² N = Number of subjects dosed for each treatment³ n = Number of subjects reporting at least one incidence of respective adverse event; (%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)**Table 4. Protocol Deviations**

Two subjects reported medication use during the study:

Subject No.	Drug	Dose	Start Date	Stop Date
68	Acetaminophen	2 x 325 mg	1/30/06	1/30/06
75	Acetaminophen	2 x 325 mg	1/22/06	1/22/06

Deviations to the blood-draw schedule are shown in Section 16.2.6. (Volume 1.7, page 3195).

Comments on Dropouts/Adverse Events/Protocol Deviations:

As judged by the investigator the adverse events and protocol deviations did not compromise the integrity of the study.

c) Bioanalytical Results

Table 5. Assay Quality Control – Within Study

	Parent				Metabolite			
QC Conc. (pg/mL)	150.84	1508.4	3016.8	7039.2	299.28	2992.8	5985.6	13966.0
Inter-day Precision (%CV)	14.98	10.11	2.12	3.03	17.66	12.23	5.47	5.80
Inter-day Accuracy (%)	103.57	97.48	97.93	99.15	108.09	102.56	101.25	100.63
Cal. Standards Conc. (pg/mL)	50.16 – 10032.00				100.24 – 20048.00			
Inter-day Precision (%CV)	1.79 – 4.62				4.32 – 6.45			
Inter-day Accuracy (%)	97.47 – 103.70				98.51 – 100.81			
Linearity Range (range of R² values)	R ² > 0.9966				R ² > 0.99885			

Comments on Study Assay Quality Control: The high %CV for QC1 for the metabolite (17.66%) was noted by the firm to be due to an outlier value (per the MNR test). Exclusion of this value gives a %CV of 5.94%.

The Study Assay Quality Control is Acceptable.

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

Comments on Chromatograms: Acceptable

Table 6. SOPs dealing with analytical repeats of study samples

The following SOPs were submitted by the firm:

SOP Title	SOP#	Effective Date
Preparation, Identification, Acceptance Criteria of Stock, Calibration Standards, QCs, Reference Solutions	ANI 153.09	11/02/2005
Sample Reassays and Reporting of Final Concentrations	ANI 156.09	09/23/2005
Application of Chromatographic Methods to Routine Drug Analysis	ANI 157.06	01/09/2006
Chromatographic Acceptance Criteria and Verification of Chromatograms	ANI 167.05	06/30/2005

Table 7. 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	N/A

Summary/Conclusions, Study Assays: The study assay results are acceptable.

A total of 48 of 2913 samples analyzed for oxybutynin (1.65%) were repeated: 12 for unacceptable I.S. response, 28 for loss of sample during processing, 4 for I.S. response $\leq 5\%$ of mean I.S. responses, 3 for sample concentrations $> \text{ULQ}$, and 1 sample was reanalyzed to confirm the value.

A total of 243 of 2913 samples analyzed for the metabolite were repeated (8.34%): 10 for unacceptable I.S. response, 3 for loss of sample during processing, 2 for I.S. response $\leq 5\%$ of mean I.S. responses, 164 for sample concentration $> \text{ULQ}$, 63 for sample dilution rejection, and 1 sample was reanalyzed to confirm the value.

Thirteen study samples were not analyzed due to insufficient volume or empty aliquot tube.

d) Pharmacokinetic Results

Table 8. Arithmetic Mean Pharmacokinetic Parameters of Oxybutynin (N=77)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
PARAMETER					
AUCT	63.41	49.59	63.54	49.85	1.00
AUCI	65.91	50.20	66.31	51.05	0.99
C _{MAX}	3.30	57.54	3.50	52.19	0.94
T _{MAX}	14.43	71.70	10.16	47.62	1.42
KE	0.06	33.01	0.06	32.50	1.06
THALF	13.17	39.81	13.57	30.04	0.97

Table 9. Arithmetic Mean Pharmacokinetic Parameters of N-Desethyloxybutynin (N=77)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
PARAMETER					
AUCT	354.80	41.69	348.57	38.07	1.02
AUCI	361.59	42.31	354.32	38.64	1.02
C _{MAX}	21.29	41.34	19.40	34.44	1.10
T _{MAX}	8.23	98.79	7.99	45.62	1.03
KE	0.10	39.11	0.09	42.65	1.07
THALF	8.25	43.97	8.91	42.43	0.93

Table 10. Oxybutynin Geometric Means and 90% Confidence Intervals (N=77)

	Test LS Mean	Ref LS Mean	Ratio LS Means	Lower 90% CI	Upper 90% CI
LAUCT	56.28	57.13	0.99	90.68	107.02
LAUCI	58.30	59.70	0.98	89.86	106.16
LCMAX	2.90	3.15	0.92	85.01	100.03

Table 11. N-Desethyloxybutynin Geometric Means and 90% Confidence Intervals (N=77)

	Test LS Mean	Ref LS Mean	Ratio LS Means	Lower 90% CI	Upper 90% CI
LAUCT	327.84	326.60	1.00	94.67	106.44
LAUCI	334.42	332.15	1.01	94.81	106.93
LCMAX	19.58	18.43	1.06	98.31	114.90

Table 12. Additional Study Information

Root mean square error, AUC_{0-t}	0.308576 (parent); 0.218295 (metabolite)
Root mean square error, AUC_{∞}	0.306326 (parent); 0.221168 (metabolite)
Root mean square error, C_{max}	0.303078 (parent); 0.290352 (metabolite)
Ke and AUCi determined for how many subjects?	All subjects
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C_{max}	None
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis: Acceptable

Table 13. Mean Oxybutynin Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (N=77)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
Time (hr)					
0	0.00	.	0.00	.	.
1	0.11	295.75	0.03	131.70	3.40
2	1.09	124.22	0.31	112.73	3.56
4	1.37	69.68	1.45	81.87	0.94
5	1.96	55.42	2.56	56.67	0.77

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
6	1.46	57.35	2.28	60.08	0.64
8	1.40	98.45	2.25	78.50	0.62
10	1.43	107.15	1.96	55.41	0.73
12	2.20	76.79	2.71	54.36	0.81
14	1.84	74.80	2.29	52.87	0.81
16	1.51	68.18	1.81	46.20	0.83
18	1.23	61.22	1.39	45.70	0.88
21	1.19	58.03	1.14	56.37	1.04
24	1.62	73.55	1.35	64.06	1.20
28	1.67	81.42	1.39	73.54	1.20
36	0.81	73.83	0.63	79.73	1.29
48	0.43	103.61	0.34	86.65	1.26
60	0.20	85.48	0.17	82.00	1.19
72	0.12	101.00	0.12	164.75	0.96

Unit = pg/mL

Table 14. Mean N-Desethoxybutynin Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (N=77)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
Time (hr)					
0	0.00	.	0.00	.	.
1	0.55	240.20	0.31	48.91	1.76
2	7.75	100.39	1.76	49.52	4.40
4	15.58	59.68	12.05	29.11	1.29
5	17.85	48.48	16.70	32.74	1.07
6	13.92	46.40	15.58	36.97	0.89
8	10.46	54.74	15.03	44.72	0.70
10	9.24	68.13	13.37	47.19	0.69
12	10.78	66.42	14.39	47.43	0.75
14	10.84	67.35	13.31	44.68	0.81
16	9.48	61.28	11.59	41.36	0.82
18	8.19	54.02	9.58	39.82	0.85
21	7.38	53.86	7.33	48.12	1.01
24	8.21	58.17	6.92	51.42	1.19
28	7.78	67.09	6.34	64.80	1.23
36	3.52	80.11	2.58	86.09	1.37
48	1.50	115.12	1.07	105.22	1.40
60	0.53	129.23	0.41	130.43	1.27
72	0.30	155.55	0.26	178.00	1.12

Unit = pg/mL

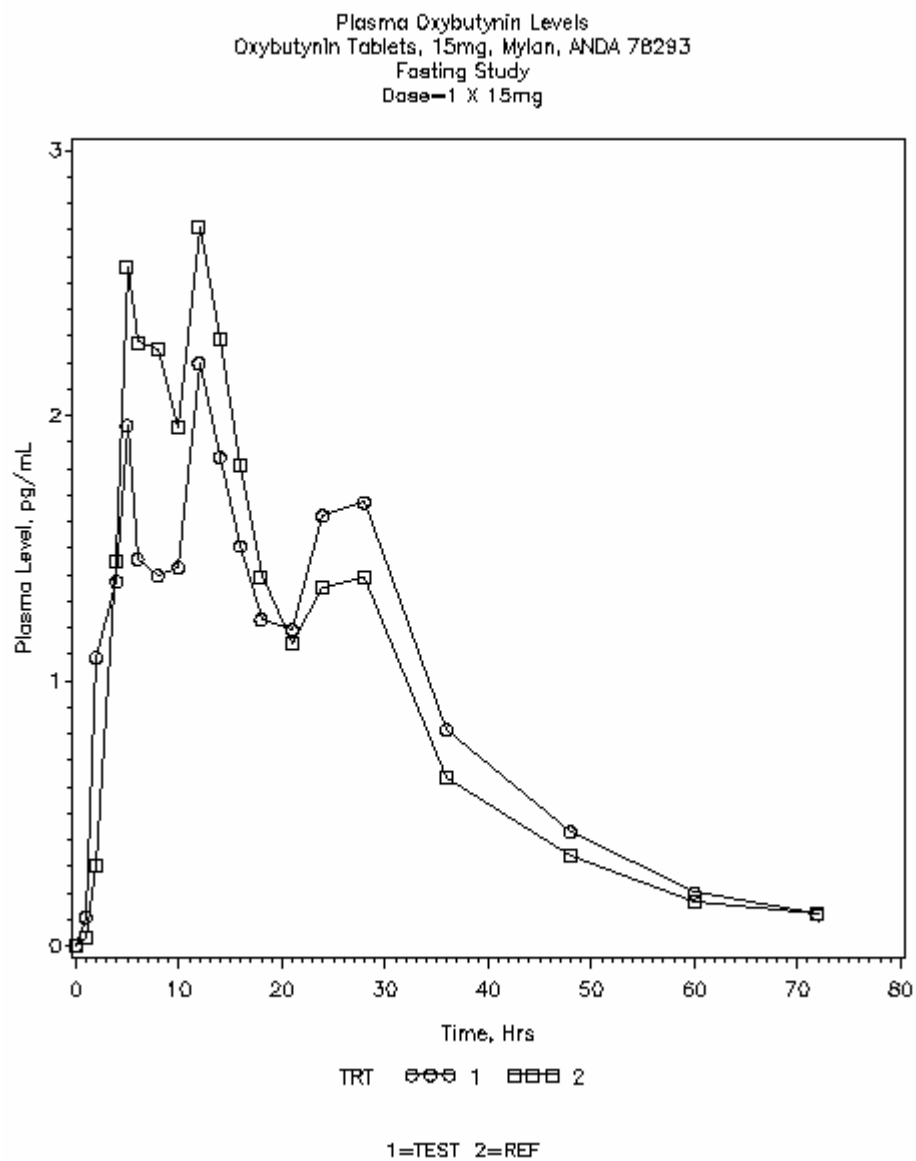
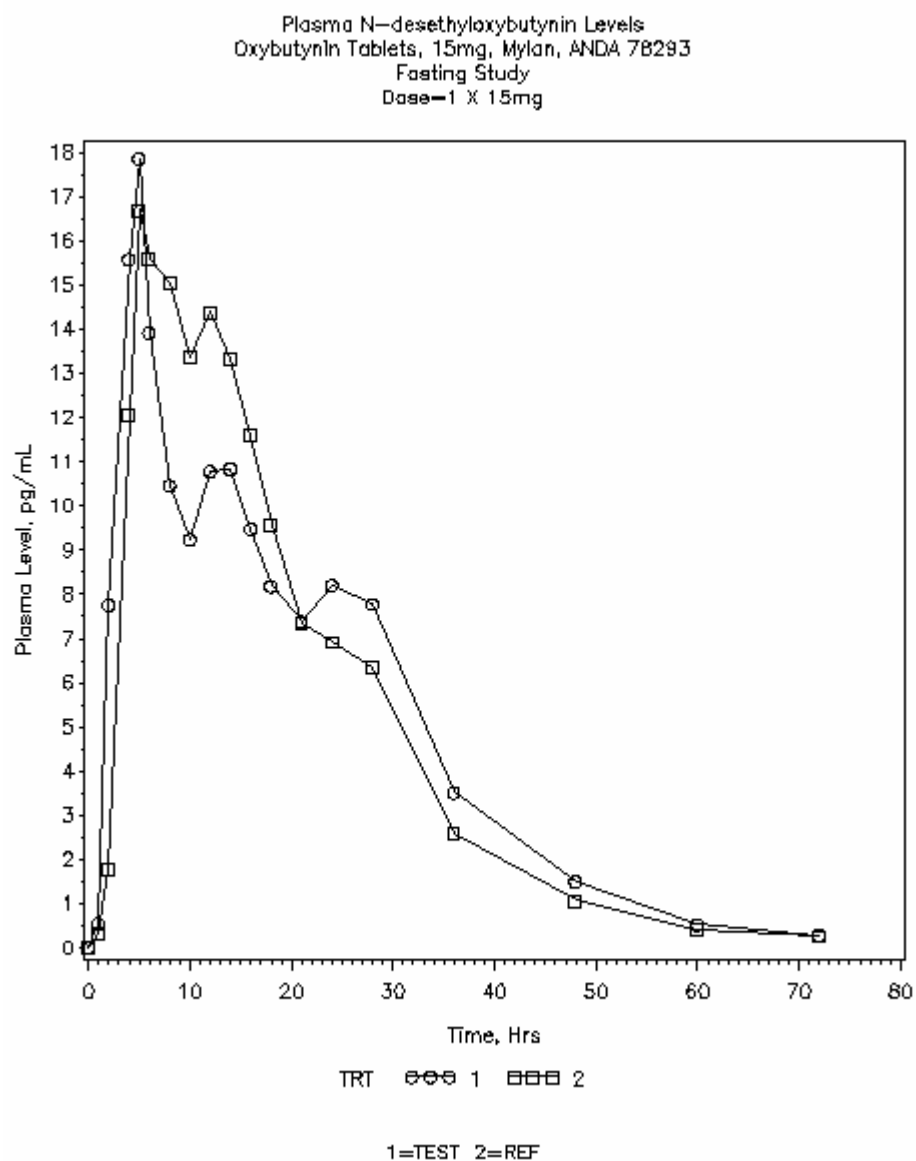
Figure 1. Mean Plasma Concentration-Time Plot (Parent)

Figure 2. Mean Plasma Concentration-Time Plot (Metabolite)



Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
The study is acceptable.

B. Formulation Data

Table 1. Components and Composition

Ingredient	Amount (mg)/ Tablet		Amount (%) Tablet	
	10mg	15mg	10mg	15mg
(b) (4)				
Oxybutynin Chloride	10.0	15.0	4.5	6.8
Povidone, USP (b) (4)	(b) (4)			
Hypromellose, USP (b) (4)				
Dibasic Calcium Phosphate USP, Anhydrous (b) (4)				
(b) (4)				
Magnesium Stearate, NF				
Colloidal Silicon Dioxide, NF (b) (4)				
(b) (4)				
(b) (4) Methacrylic Acid Copolymer Dispersion, NF (b) (4)				
Talc, USP, (b) (4)				
Triethyl Citrate, NF (b) (4)				
Polysorbate 80, NF				
Sodium Hydroxide, NF				
(b) (4)				
(b) (4)				
(b) (4)				
Total	220.5	220.5	100	100
(b) (4)				

C. Dissolution Data

Source of Method

FDA

Medium

Row 1: pH 1.2 Simulated Gastric Fluid without enzymes

Rows 2-4: pH 6.8 Simulated Intestinal Fluid without enzymes

Volume (mL)

250 mL @ 37 °C ± 0.5°C

USP Apparatus type

Apparatus 3 (reciprocating cylinder)

Rotation

25 dpm (dips per minute)

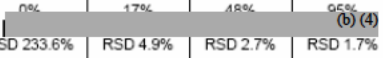
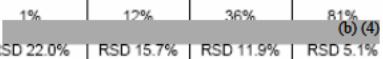
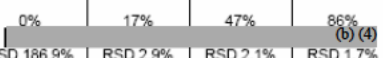

Profile Time

2 hr, 4 hr, 8 hr, 16 hr

Firm's proposed specifications

2 hr: (b) (4)
4 hr: (b) (4)
8 hr: (b) (4)
16 hr: (b) (4)

Table 2. Dissolution Profiles*

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)				Study Report Location
					2 hour	4 hour	8 hour	16 hour	
N/A	Oxybutynin Chloride Extended-release Tablets Lot R1K0797	10mg tablet	Apparatus: 3 Speed: 25dpm Medium: (Row 1) pH 1.2 Simulated Gastric Fluid, without enzymes (Rows 2-4) pH 6.8 Simulated Intestinal Fluid, without enzymes Volume: 250mL Temperature: 37°C ± 0.5°C	12	 0% 17% 18% 95% RSD 233.6% RSD 4.9% RSD 2.7% RSD 1.7% (b) (4)				ANDA Submitted January 21, 2003 Volume 6, pages 4962-4976
N/A	Ditropan XL® Tablets Lot 0112638	10mg tablet		12	 1% 12% 36% 81% RSD 22.0% RSD 15.7% RSD 11.9% RSD 5.1% (b) (4)				
N/A	Oxybutynin Chloride Extended-release Tablets Lot R1N3882	15mg tablet		12	 0% 17% 47% 86% RSD 186.9% RSD 2.9% RSD 2.1% RSD 1.7% (b) (4)				Volume 10, pages 5165-5188
N/A	Ditropan XL® Tablets Lot 0531572	15mg tablet		12	 3% 12% 37% 83% RSD 26.2% RSD 7.9% RSD 9.0% RSD 3.7% (b) (4)				

*The tablet is automatically transferred by the apparatus to the next set of vessels for each time point that is programmed. Therefore, Row 1 corresponds to the 2-hour time point, Row 2 corresponds to the 4-hour time point, Row 3 corresponds to the 8-hour time point, and Row 4 corresponds to the 16-hour time point.

Comment: In the October 12, 2006 amendment, the firm accepts the DBE-recommended specifications for the 2-, 4-, and 16-hour time points, but does not agree with the DBE-recommended specification for the 8-hour time point (b) (4). The firm proposes (b) (4)

. The dissolution testing is complete.

(b) (4)



BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-293

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Oxybutynin Chloride Extended Release Tablets, 15 mg

The Division of Bioequivalence (DBE) has completed its review of your submission and has no further questions at this time.

We agree with your proposed dissolution method and specifications as follows:

The dissolution testing should be conducted in 250 mL of pH 1.2 Simulated Gastric Fluid without enzymes (Row 1) and 250 mL of pH 6.8 Simulated Intestinal Fluid without enzymes (Rows 2-4), at 37°C, using Apparatus III (reciprocating cylinder) at 25 dpm.

The test product should meet the following specifications:

2 hours:	Between 0% and 10%
4 hours:	Between 10% and 30%
8 hours:	Between 35% and 60%
16 hours:	NLT 75%

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely Yours,

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

CC: ANDA 78-293

BIOEQUIVALENCE – Acceptable

Submission dates: May 2, 2006

1. FASTING STUDY (STF)

Strength: 15 mg

Clinical: PRACS Institute, Ltd., East Grand Forks, MN

Analytical: (b) (4)

Outcome: AC

OUTCOME DECISIONS: The fasting BE study is acceptable. A waiver of is granted for the fed BE study requirement.

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


/s/

Sarah M. Robertson
11/29/2006 02:02:48 PM
BIOPHARMACEUTICS

Chandra S. Chaurasia
11/29/2006 02:18:29 PM
BIOPHARMACEUTICS


Barbara Davit
11/30/2006 01:14:57 PM
BIOPHARMACEUTICS


DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	78-293
Drug Product Name	Oxybutynin Chloride Extended-Release Tablets
Strength	15 mg
Applicant Name	Mylan Pharmaceuticals, Inc.
Submission Date(s)	October 12, 2006
First Generic	No
Reviewer	Sheryl D. Gunther
Clinical Site	PRACS Institute, Ltd. 625 East DeMers Avenue East Grand Forks, MN 56721
Analytical Site	 (b) (4)

DISSOLUTION AMENDMENT**EXECUTIVE SUMMARY**

This is a review of the dissolution amendment only.

The firm previously submitted dissolution testing on its 15 mg tablets using the same method as recommended for its 5 mg (ANDA 76-702) and 10 mg (ANDA 76-644) strengths. However, the firm proposed  (b) (4)

 . The dissolution testing is **complete**.

The DBE will review the fasted BE study and waiver request at a later date.

TABLE 2: IN VITRO DISSOLUTION DATA, DBE-RECOMMENDED METHOD





Reviewer's Note: The firm included data for its 10 mg strength submitted in ANDA 76-644 in the following table as the firm is requesting a waiver of the fed BE study requirements in the current application. The current submission includes a fasting study on the proposed 15 mg strength and references the fed study conducted on the 10 mg strength in ANDA 76-644. The firm's waiver request will be evaluated by the in-depth reviewer at the time of the full ANDA review.

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)				Study Report Location
					2 hour	4 hour	8 hour	16 hour	
N/A	Oxybutynin Chloride Extended-release Tablets Lot R1K0797	10mg tablet	Apparatus: 3 Speed: 25dpm Medium: pH 1.2 Simulated Gastric Fluid, without enzymes (Row 1) pH 6.8 Simulated Intestinal Fluid, without enzymes (Rows 2-4) Volume: 250mL Temperature: 37°C ± 0.5°C	12	0% RSD 233.6%	17% RSD 4.9%	48% RSD 2.7%	95% RSD 1.7% (b) (4)	ANDA Submitted January 21, 2003 Volume 6, pages 4962-4976
N/A	Ditropan XL® Tablets Lot 0112638	10mg tablet		12	1% RSD 22.0%	12% RSD 15.7%	36% RSD 11.9%	81% RSD 5.1% (b) (4)	
N/A	Oxybutynin Chloride Extended-release Tablets Lot R1N3882	15mg tablet		12	0% RSD 186.9%	17% RSD 2.9%	47% RSD 2.1%	86% RSD 1.7% (b) (4)	Volume 10, pages 5165-5188
N/A	Ditropan XL® Tablets Lot 0531572	15mg tablet		12	3% RSD 26.2%	12% RSD 7.9%	37% RSD 9.0%	83% RSD 3.7% (b) (4)	

Firm's **current** proposed specifications for the 15 mg strength:

2 hours: (b) (4)
 4 hours: (b) (4)
 8 hours: (b) (4)
 16 hours: (b) (4)

DBE METHOD RECOMMENDED FOR THE 5 MG (ANDA 76-702) AND 10 MG (ANDA 76-644) STRENGTHS

Medium*	Row 1: pH 1.2 Simulated Gastric Fluid without enzymes Rows 2-4: pH 6.8 Simulated Intestinal Fluid without enzymes
Volume	250 mL
Temperature	37 °C ± 0.5°C
Apparatus	Apparatus 3 (reciprocating cylinder)
Rotational Speed	25 dpm (dips per minute)
Specifications (5 and 10 mg strengths only)	2 hr: 
	4 hr: 
	8 hr: 
	16 hr: 

*The tablet is automatically transferred by the apparatus to the next set of vessels for each time point that is programmed. Therefore, Row 1 corresponds to the 2-hour time point, Row 2 corresponds to the 4-hour time point, Row 3 corresponds to the 8-hour time point, and Row 4 corresponds to the 16-hour time point.

COMMENT:

The firm accepts the use of the same dissolution method for its 15 mg tablets that the DBE found acceptable for the 5 mg and 10 mg tablets. However, in the original submission, the firm proposed (b) (4)

. The DBE-recommended specifications and the firm's **current** proposed specifications are provided below.

Time (hours)	DBE-Recommended Specifications	Firm's Current Proposed Specifications
2*	(b) (4)	(b) (4)
4		
8		
16		

*The firm incorrectly referred to the first time point as the "1 hr" time point in the letter. However, the firm's revised finished product specifications and pre- and post-approval stability protocols correctly identify this time point as the "2 hr" time point.

(b) (4)

The dissolution testing is complete.

DEFICIENCY COMMENT:

None

RECOMMENDATIONS:

The *in vitro* dissolution testing conducted by Mylan Pharmaceuticals, Inc. on its test product, Oxybutynin Chloride Extended-Release Tablets, 15 mg, comparing it to Alza Corporation's Ditropan XL[®] Tablets, 15 mg, is **complete**.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-293

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Oxybutynin Chloride Extended-Release
Tablets, 15 mg

The Division of Bioequivalence has completed its review of dissolution testing data submitted in the application and has no further questions at this time. The review of the bioequivalence study and waiver request will be conducted later.

We agree with your proposed dissolution method and specifications as follows:

The dissolution testing should be conducted in 250 mL of pH 1.2 Simulated Gastric Fluid without enzymes (Row 1) and 250 mL of pH 6.8 Simulated Intestinal Fluid without enzymes (Rows 2-4), at 37°C, using Apparatus III (reciprocating cylinder) at 25 dpm.

The test products should meet the following specifications:

2 hours:	Between 0% and 10%
4 hours:	Between 10% and 30%
8 hours:	Between 35% and 60%
16 hours:	NLT 75%

Sincerely yours,

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

BIOEQUIVALENCE –ACCEPTABLE

Submission Date: 10/12/2006

[NOTE: The in vitro testing is complete. The fasted BE study and waiver request are pending review.]

1. BDI

Strength: 15 mg

Outcome Decisions: AC – Acceptable
WinBio Comments: AC

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

/s/

Sheryl Gunther
12/14/2006 01:30:24 PM
BIOPHARMACEUTICS

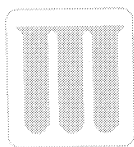
Diem-Kieu Ngo
12/14/2006 01:33:00 PM
BIOPHARMACEUTICS

Barbara Davit
12/18/2006 10:17:53 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 078293Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

May 2, 2006

ORIGINAL ABBREVIATED NEW DRUG APPLICATION (ELECTRONIC DATA AND BIOEQUIVALENCE DATA ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 15MG

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None

Established Name: Oxybutynin Chloride Extended-release Tablets

Reference Listed Drug: Ditropan XL® Extended-release Tablets, NDA 20-897

This application consists of a total of 26 volumes and one CD-Rom.

Archival Copy - 12 volumes.

Review Copy - 12 volumes.

Technical Section For Chemistry - 2 volumes.

Technical Section For Pharmacokinetics - 10 volumes.

Analytical Methods - 2 extra copies; 1 volume each.

CD-Rom - eCover Letter, e356h, eTOC, eLabeling Components, Bioequivalence

Summary Tables and data listings for the bioequivalence study conducted in support of this application.

This application provides for the manufacture of Oxybutynin Chloride Extended-release Tablets, 15mg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.

Department of Prescription Drugs
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 285-6482
Human Resources (304) 598-5406

IS-OAT-TH-03, 04, 05, 06, 07, 08, 09, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 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820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000, 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 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1846, 1847, 1848, 1849, 1850, 1851, 1852, 1853, 1854, 1855, 1856, 1857, 1858, 1859, 1860, 1861, 1862, 1863, 1864, 1865, 1866, 1867, 1868, 1869, 1870, 1871, 1872, 1873, 1874, 1875, 1876, 1877, 1878, 1879, 1880, 1881, 1882, 1883, 1884, 1885, 1886, 1887, 1888, 1889, 1890, 1891, 1892, 1893, 1894, 1895, 1896, 1897, 1898, 1899, 1900, 1901, 1902, 1903, 1904, 1905, 1906, 1907, 1908, 1909, 1910, 1911, 1912, 1913, 1914, 1915, 1916, 1917, 1918, 1919, 1920, 1921, 1922, 1923, 1924, 1925, 1926, 1927, 1928, 1929, 1930, 1931, 1932, 1933, 1934, 1935, 1936, 1937, 1938, 1939, 1940, 1941, 1942, 1943, 1944, 1945, 1946, 1947, 1948, 1949, 1950, 1951, 1952, 1953, 1954, 1955, 1956, 1957, 1958, 1959, 1960, 1961, 1962, 1963, 1964, 1965, 1966, 1967, 1968, 1969, 1970, 1971, 1972, 1973, 1974, 1975, 1976, 1977, 1978, 1979, 1980, 1981, 1982, 1983, 1984, 1985, 1986, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017,

Gary J. Buehler
Page 2 of 2

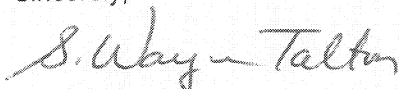
Mylan currently holds Tentatively Approved ANDAs for 5mg (ANDA 76-702) and 10mg (ANDA 76-644) strengths of Oxybutynin Chloride Extended-release Tablets. Final approval of ANDAs 76-702 and 76-644 is dependent upon resolution of an outstanding Citizen Petition (Docket No. 2005P-0352). As discussed with Martin Shimer, of your office, on November 10, 2005, Mylan has chosen to submit our 15mg tablet strength under this separate ANDA since ANDAs 76-702 and 76-644 could be immediately approved upon resolution of the referenced Citizen Petition. Please note that Mylan's Oxybutynin Chloride Extended-release Tablets, 15mg are being manufactured and controlled under similar conditions to those tentatively approved in ANDA's 76-702 and 76-644.

With regards to bioequivalence testing, Mylan has established *in vivo* bioequivalence to the Reference Listed Drug (RLD) by comparing our 15mg formulation to Ditropan XL® Tablets in a fasting *in vivo* bioequivalence study included in Section VI of this application. Mylan's 15mg tablet strength is compositionally similar to our 10mg tablet strength which is subject of ANDA 76-644 that received Tentative Approval on January 12, 2005. As discussed with Steve Mazella, of your office, on November 3, 2005, Mylan wishes to incorporate by reference the post-prandial *in vivo* bioequivalence study included in ANDA 76-644 for the 10mg tablet strength in support of this application for the 15mg tablet strength.

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

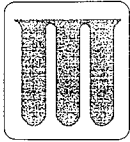
All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6551 and/or facsimile number (304) 285-6407.

Sincerely,



S. Wayne Talton
Vice President
Regulatory Affairs

SWT/np



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 10, 2006

PATENT AMENDMENT

XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 15MG
ANDA 78-293
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to the Agency's letter dated June 30, 2006 notifying us that the ANDA has been found acceptable for filing (refer to Attachment A).

In accordance with 21 CFR 314.95(b) and as detailed in the Agency's June 30th letter, this amendment provides a statement certifying that notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c). A Certification of Notice is provided in Attachment B.

Mylan commits to submit further documentation of receipt of the notice required by 21 CFR 314.95(e), as it pertains to the Paragraph IV patent certification contained in our original application submitted on May 2, 2006 for Oxybutynin Chloride Extended-release Tablets, 15mg.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

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JUL 11 2006

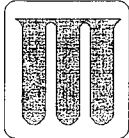
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Department—Fax Numbers
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Administration (304) 599-7284
Business Development (304) 598-5419
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MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

OK
to File
7/28 8-24-06

July 26, 2006

PATENT AMENDMENT

XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 15MG
ANDA 78-293
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. In accordance with 21 CFR 314.95(e), this amendment provides documentation of receipt of the notice required by 21 CFR 314.95(a) and (b), as it pertains to the Paragraph IV patent certification contained in our original application submitted on May 2, 2006 for Oxybutynin Chloride Extended-release Tablets, 15mg. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

The owner of the patents and the holder of the application for the listed drug were served with the required notice. Proof of delivery by Certified Mail evidences receipt by Alza Corporation on July 19, 2006. A copy of the documentation evidencing Mylan's service and receipt is enclosed.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

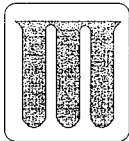
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JUL 27 2006
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MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

August 22, 2006

PATENT AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

WAI
Sued on 355.
CA #1:06CV125
Dated 8/21/06.
JP
CMB
9/5/06.

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 15MG
ANDA 78-293
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Reference is also made to our patent amendments submitted on July 10, 2006 and July 26, 2006 which provided certification of notice and documentation of receipt of the notice, respectively, as it pertains to the Paragraph IV patent certifications contained in our original application submitted on May 2, 2006 for Oxybutynin Chloride Extended-release Tablets, 15mg.

Alza Corporation commenced litigation against Mylan on August 21, 2006. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

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AUG 23 2006

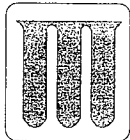
CDER / CDER

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Accounting (304) 285-6403
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Business Development (304) 598-5419
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MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

cc:File
10-2-06

September 14, 2006

PATENT AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 15MG
ANDA 78-293
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Reference is also made to our patent amendments submitted on July 10, 2006, July 26, 2006 and August 22, 2006 which provided certification of notice, documentation of receipt of the notice and notification of the commencement of litigation, respectively, as it pertains to the Paragraph IV patent certifications contained in our original application submitted on May 2, 2006 for Oxybutynin Chloride Extended-release Tablets, 15mg.

On September 6, 2006, the U.S. Court of Appeals for the Federal Circuit held the patent-in-suit to be invalid in a related case. Alza Corporation dismissed the lawsuit against Mylan on September 8, 2006. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

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SEP 15 2006

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MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

September 29, 2006

TELEPHONE AMENDMENT (CHEMISTRY INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

NIAC

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 15MG
ANDA 78-293
RESPONSE TO AGENCY CORRESPONDENCE DATED SEPTEMBER 21, 2006

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the chemistry comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated September 21, 2006 (provided in Attachment C). In response to the Agency's comments of September 21st, Mylan wishes to amend this application as follows:

A. Deficiencies:

FDA COMMENT 1:

(b) (4)

MYLAN RESPONSE:

FDA COMMENT 2:

MYLAN RESPONSE:

Department—Fax Numbers
Accounting (304) 599-2844
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 285-6482
Human Resources (304) 598-5406
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Following this page, 3 pages withheld in full (b)(4)

Gary J. Buehler
Page 5 of 5

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at telephone number (304) 599-2595, extension 6551 and/or facsimile number (304) 285-6407.

Sincerely,

A handwritten signature in black ink that reads "S. Wayne Talton". The signature is written in a cursive, flowing style.

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosure

Desk Copy: Leigh Ann Matheny, Project Manager
Division of Chemistry III, Team 4



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

October 12, 2006

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
NAB

BIOEQUIVALENCE AMENDMENT (CHEMISTRY INFORMATION ENCLOSED)

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 15MG
ANDA 78-293
RESPONSE TO AGENCY CORRESPONDENCE DATED OCTOBER 3, 2006

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated October 3, 2006 (provided in Attachment D). In response to the Agency's comments of October 3rd, Mylan wishes to amend this application as follows:

FDA COMMENT 1: The Division of Bioequivalence has completed its review of dissolution testing submitted in the application. The review of the bioequivalence study and waiver request will be conducted later. The following deficiency has been identified:

The dissolution specifications you proposed are not acceptable. We agree with the use of the following dissolution method:

The dissolution testing should be conducted in 250 mL of pH 1.2 Simulated Gastric Fluid without enzymes (Row 1) and 250 mL of pH 6.8 Simulated Intestinal Fluid without enzymes (Rows 2-4), at 37°C, using Apparatus III (reciprocating cylinder) at 25 dpm.

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OCT 13 2006

OGD / CDER

The test product should meet the following specifications:

2 hours:
4 hours:
8 hours:
16 hours:

(b) (4)

With your response to the above deficiency, please indicate if you accept the above dissolution method and specifications.

MYLAN RESPONSE: The recommended dissolution method and specifications for Oxybutynin Chloride Extended-release Tablets have been evaluated against the initial dissolution data obtained for the exhibit batch. A summary of the initial drug release data for Lot R1N3882 is presented below:

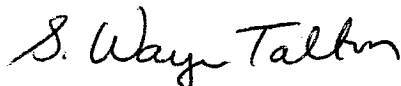
Department—Fax Numbers	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	Legal Services	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	Maintenance & Engineering	(304) 598-5408	Regulatory Affairs	(304) 598-5409
Business Development	Medical Unit	(304) 598-5411	Research & Development	(304) 285-6407
Corporate Services	Product Development	(304) 598-5445	Sales & Marketing	(304) 285-6419
Human Resources		(304) 285-6411		(304) 598-3232

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

Gary J. Buehler
Page 3 of 3

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

A handwritten signature in black ink that reads "S. Wayne Talton". The signature is written in a cursive, flowing style.

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosure

Desk Copy: Christina Thompson, Project Manager
Division of Bioequivalence

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 9, 2006

FROM: Cecelia M. Parise
Regulatory Policy Advisor to the Director
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Robert L. West
Deputy Director
Office of Generic Drugs
Center for Drug Evaluation and Research

TO: ANDAs for Oxybutynin Extended-release Tablets
76-644, Mylan Pharmaceuticals
76-702, Mylan Pharmaceuticals
78-293, Mylan Pharmaceuticals
76-745, Impax Pharmaceuticals

SUBJECT: Enantiomers

Please see the attached memo from the Division of Reproductive and Urologic Drug Products (DRUP). The memo states that there is insufficient evidence to support the notion that R-oxybutynin is the enantiomer primarily responsible for efficacy, and that the absorption of the enantiomers is linear. Therefore, the decision by the Division of Bioequivalence not to apply confidence interval criteria to the enantiomers in order to establish bioequivalence for Oxybutynin Extended-release Tablets for the same reasons outlined in the memo from DRUP still stands and remains correct.

Memorandum

To: Marguerita Sims, J.D.
Office of Regulatory Policy

Through: Mark Hirsch, M.D. *M Hirsch 11/3/06*
Acting Deputy Director, DRUP

George Benson, M.D. *GS Benson 11/3/06*
Medical Team Leader, DRUP

From: Marcea Whitaker, M.D. *M Whitaker 11/2/06*
Medical Officer, DRUP

Ortiz, Stephan, R.Ph., Ph.D. *S Ortiz 11/2/06*
Clinical Pharmacologist, OCPB

Date: October 31, 2006

Re: **Ditropan XL**
Citizen's Petition Response
Second Review

Sponsor: Ortho-McNeil

Background: A Citizen's Petition was filed on August 29, 2005, by Ortho-McNeil (Ortho-Urology) requesting that the Commissioner require the application of standard bioequivalence criteria to oxybutynin and its active metabolite desethyloxybutynin "to ensure that approved generic versions of Ditropan XL ER tablets are both bioequivalent and clinically equivalent to the innovator product." The Petition further requested that these bioequivalence criteria apply to all four enantiomers [(R)- and (S)- oxybutynin and (R)- and (S)- desethyloxybutynin] in both the fed and fasted states. Consultations regarding this Citizen's Petition were completed by both the Office of Generic Drugs and the Division of Reproductive and Urologic Products (DRUP consult sent to ORP on December 5, 2005).

The Office of Regulatory Policy has requested that DRUP provide clarification on several apparently contradictory statements contained in the Ditropan XL® label and in ORP's draft response to the Citizen's Petition. Specifically, the clarification relates to statements relating to the activity of the (R) isomer of oxybutynin in the Office of Generic Drugs consultation versus statements in the Ditropan XL label.

The OGD consultation from 2005 states: "...there are insufficient data to conclude that the primary efficacy and safety activity resides with the minor enantiomer. The sponsor cites an *in vitro* study by Noronha-Blob et al (1990) as demonstrating higher

anticholinergic activity for the R-enantiomer than the S-enantiomer in animal tissues. This study does not offer strong evidence that primary pharmacological activity (safety/efficacy) is determined by the minor enantiomer. First, this study was done in animal tissue and it is not clear how the results can be applied clinically. Second, the authors themselves expressed doubts about any pharmacological advantages offered by the R-oxybutynin enantiomer.”

The Clinical Pharmacology Section of the Ditropan XL label states that:

“Antimuscarinic activity resides predominately in the R-isomer.”

The ORP requested that DRUP clarify this apparent contradiction.

Executive Summary and Comments:

The Division of Reproductive and Urologic Products reviewed the ORP draft response to the Citizen’s Petition which concludes “that relevant scientific information does not support the conclusion that primary safety and effectiveness resides with the minor enantiomer (R-oxybutynin) when administered in humans.” We also reviewed the Ditropan XL labeling that identifies the R-isomer as having the predominant antimuscarinic activity.

The Division’s current comments address only the parent compound and its enantiomers (R- and S-oxybutynin), and not the enantiomers of the metabolite, desethyloxybutynin. The formal position of OGD appears to be that bioequivalence (BE) of the metabolite (and thus, the R- and S- enantiomers of the metabolite) is not required. Therefore, the relative potencies of the R- and S-enantiomers of the metabolite is no longer an issue. We remind ORP that the measurement and the bioequivalence of the metabolite, desethyloxybutynin, were previously addressed in the original consultations from DRUP and OGD.

In regard to the R- and S-enantiomers of the parent compound, oxybutynin, we offer the following three comments:

- 1. The studies cited by the Petitioner to support the notion that R-oxybutynin is the enantiomer primarily responsible for efficacy, specifically, Naronha-Blob et al (1990), and Kachur et al (1988), are *in vitro* animal studies and not studies designed to demonstrate the clinical benefit of R-oxybutynin over S-oxybutynin in man.**
- 2. Since it has not been clinically demonstrated that the major activity of Ditropan XL resides in the minor enantiomer (R-oxybutynin), the Division agrees with the Office of Generic Drugs that there should be no requirement for sponsors to demonstrate separate bioequivalence for the enantiomers of oxybutynin.**
- 3. The statement in Ditropan® and Ditropan XL® labeling that “antimuscarinic activity resides predominately in the R-isomer” is based on statements pertaining to non-clinical information submitted in the original**

Ditropan XL NDA application (1998). The Division currently would recommend that this sentence be removed from the Clinical Pharmacology section of the Ditropan and Ditropan XL labels. Optimally, the sentence would be completely removed from labeling, although it may be possible to add qualifying statements clarifying the source of the information and its unknown clinical relevance. This statement can be modified, deleted, moved, or further addressed when the sponsor submits new labeling to comply with the physician's labeling rule (PLR).

In summary, the Division believes that primary safety and efficacy have not been adequately demonstrated to reside with the R-enantiomer of oxybutynin in humans despite the wording in current labeling.

Discussion:

Herein, we provide a more detailed discussion of the issue in support of the preceding Executive Summary and Final Comments.

Based upon our understanding of the FDA BA/BE Guidance, entitled "*Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*", we believe that all four of the following criteria must be met in order to require separate application of the BE criteria to enantiomers of a racemic mixture:

- 1) The enantiomers exhibit different pharmacodynamic characteristics.
- 2) The enantiomers exhibit different pharmacokinetic characteristics.
- 3) Primary efficacy and safety activity resides with the minor enantiomer, and
- 4) Nonlinear absorption is present for at least one of the enantiomers.

The discrepancy which ORP wishes DRUP to address involves the third criterion, "Primary efficacy and safety activity resides with the minor enantiomer." For Ditropan and Ditropan XL, the minor parent enantiomer is (R)-oxybutynin. The sponsor argues, based upon a preclinical *in vitro* study in guinea pigs (Naronha-Blob et al, 1990), that the (R)-oxybutynin carries both primary efficacy and safety. ORP's draft response to the Citizen's Petition refutes this claim citing lack of human data and applicability. A problem arises because the Clinical Pharmacology section of both Ditropan and Ditropan XL labels states that "antimuscarinic activity resides predominately in the R-isomer." This sentence, with accompanying citation, was present in the sponsor's original proposed labeling for NDA 20-897 (Ditropan XL) in a submission dated November 25, 1997, in section 3.6 *Nonclinical Pharmacology, Toxicology and Metabolism*. The Sponsor stated:

"The predominant mechanism of urodynamic action and systemic toxicity is generally considered to be mediated through oxybutynin's anticholinergic activity (Yarker et al, 1995). An increase in cholinergic activity and the resulting loss of peripheral control has been suggested as the mechanism for idiopathic detrusor instability (Eckford & Keane, 1993), which may be alleviated by the

anticholinergic activity of oxybutynin (Yarker et al, 1995). The spasmolytic, calcium antagonism, or anesthetic properties of oxybutynin may also play a contributing role in its therapeutic efficacy. Oxybutynin exists in two enantiomeric forms, with most of the anticholinergic properties residing in the (R)-isomer (Yarker et al, 1995). The marketed immediate release oxybutynin products (Ditropan® and various generics), and OROS® (oxybutynin chloride) are racemates.”

Reviewer’s comment: The Yarker et al (1995) article was reviewed. No reference to chirality and pharmacodynamic effect was found within the article, suggesting that this section of the sponsor’s submission was not appropriately referenced. The cited reference does not support the sponsor’s claim.

Additional relevant information was located in the archived reviews of the original Ditropan XL NDA. In summarizing the Sponsor’s submission, the Pharmacology/Toxicology reviewer stated:

“In contrast to the anticholinergic activity of oxybutynin, which resides predominately in the R-isomer, its spasmolytic actions are not stereoselective and are 500 times weaker.”

Reviewer’s comments: 1) Despite this statement by the original Pharmacology/Toxicology reviewer, sufficient evidence was not submitted to support the statement that the R-isomer is responsible for the majority of the clinical anticholinergic activity. 2) Therefore, based on this lack of data to support this specific sentence in the labeling, modification of the Clinical Pharmacology section of the Ditropan and Ditropan XL labels would be appropriate.

In discussions with the DRUP Pharmacology/Toxicology review team, it is clear that the data which supported the above statement in labeling came from studies performed *in vitro* and in animals and not from *in vivo* human data.

Additional relevant information is found in the October 11, 2006, consultation from the Office of Generic Drugs to ORP, wherein OGD stated:

- 1) The “...current, relevant scientific information does not provide persuasive support for the assertion that primary safety and efficacy of the drug resides with the R-enantiomer of oxybutynin when administered to humans.”
- 2) “Absent sufficient clinical testing for precise measurements of the drug’s activity (including relative contributions of enantiomers) in humans, we do not think it is appropriate to rely on these animal studies to predict specific drug activity (e.g., relative contributions of enantiomers to safety and effectiveness) or correlation in humans.”
- 3) “In sum, current, relevant scientific information does not provide persuasive support for the conclusion that the primary safety and efficacy of the drug reside with the R-enantiomer of oxybutynin.”

Reviewer's comment: The DRUP review team agrees with the above statements made by OGD.

Conclusions:

1. The current comments address the parent compound, R- and S-oxybutynin, and not the metabolite, desethyxybutynin. The formal position of OGD appears to be that bioequivalence (BE) of the metabolite (and thus, the R- and S- enantiomers of the metabolite) is not required. Therefore, the relative potencies of the R- and S- enantiomers of the metabolite is no longer an issue. We remind ORP that the issues of bioequivalence (BE) and measurement of the metabolite (and the R- and S- enantiomers of the metabolite) were previously addressed in the original consultations from DRUP and OGD.
2. The studies cited by the Petitioner to support the notion that R-oxybutynin is the enantiomer primarily responsible for efficacy, specifically, Naronhia-Blob et al (1990), and Kachur et al (1988) are *in vitro* animal studies and not studies designed to demonstrate the benefit of R-oxybutynin over S-oxybutynin in man.
3. Since there is insufficient evidence that Ditropan XL's major activity has been clinically demonstrated to reside in the minor enantiomer (R-oxbutynin), we agree with the Office of Generic Drugs that there should be no requirement for sponsors to demonstrate separate bioequivalence for the enantiomers of oxybutynin.
4. The statement in Ditropan® and Ditropan XL® labeling that "antimuscarinic activity resides predominately in the R-isomer" is based on statements pertaining to non-clinical information submitted in the original Ditropan XL NDA application. We currently believe that this sentence should be removed from the Clinical Pharmacology section of the Ditropan and Ditropan XL labels, or at minimum, qualified so that the unknown clinical relevance of this nonclinical information is made clear.
5. Finally, even if human data were available which demonstrated that R-oxybutynin is predominately responsible for the anticholinergic activity, the fourth criterion necessary for requiring BE evaluation of enantiomers ("nonlinear absorption is present for at least one of the enantiomers") has not been met.

Reference:

Yarker, Y., Goa, K., & Fitton, A. (1995). Oxybutynin: A Review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapeutic Use in Detrusor Instability. *Drug and Aging*, 6 (3): 243-262.

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

/s/

Patricia L. Downs
11/9/2006 10:09:10 AM
SECRETARY

Cecelia Parise
11/9/2006 10:16:36 AM
CSO

Robert L. West
11/9/2006 10:36:16 AM
CSO



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

November 16, 2006

ORIG AMENDMENT

NIAA

**GRATUITOUS CHEMISTRY AMENDMENT
(CHEMISTRY INFORMATION ENCLOSED)**

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 15MG
ANDA 78-293
(RESPONSE TO AGENCY CORRESPONDENCE DATED OCTOBER 3, 2006 AND TO
PROVIDE FOR REVISIONS TO THE PROPOSED BATCH RECORD)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated October 3, 2006 (refer to Attachment A).

The purpose of this Gratuitous Chemistry Amendment is to update the chemistry portion of our application in accordance with the comments received from the Division of Bioequivalence on October 3, 2006. A Bioequivalence Amendment was submitted on October 12, 2006, under separate cover.

The Division of Bioequivalence recommended that dissolution testing be conducted in 250 mL of pH 1.2 Simulated Gastric Fluid without enzymes (Row 1) and 250 mL of pH 6.8 Simulated Intestinal Fluid without enzymes (Rows 2-4), at 37°C, using Apparatus III (reciprocating cylinder) at 25 dpm.

Agency Recommended Specifications:

2 hours:	(b) (4)
4 hours:	
8 hours:	
16 hours:	

Mylan accepted the proposed dissolution method and the specifications for the 2 hour, 4 hour, and 16 hour time points. We agree to (b) (4)

Mylan's proposed dissolution specifications for Oxybutynin Chloride Extended-release Tablets, 15mg have been incorporated into Mylan's stability and quality control programs. Revised finished product specifications and pre- and post-approval stability protocols are provided in Attachments B and C, respectively.

**RECEIVED
NOV 17 2006
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Please note that the finished product specifications and pre- and post-approval stability protocols have also been revised to reflect the procedural name change from drug release to dissolution in accordance with the compendial Dissolution and Drug Release monographs. Additionally, the finished product dissolution specification was revised to reference Dissolution <711> rather than Drug Release <724> for the acceptance criteria and Identification Test B was revised to reference chromatograms obtained in the Dissolution method rather than the Drug Release method. A corresponding revision was made to the Identification procedure (FP-OXYB15-ID-M), which is provided in Attachment D. The revised Dissolution (formerly Drug Release) procedure (FP-OXYB15-DR-M) is provided in Attachment E.

(b) (4)

The comparative quantitative statement for Oxybutynin Chloride Extended-release Tablets is provided in Attachment I.

Mylan commits to placing the first lot manufactured using (b) (4) in the annual stability program and report long-term stability data in the annual report.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

Gary J. Buehler
Page 3 of 3

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

A handwritten signature in black ink that reads "S. Wayne Talton". The signature is written in a cursive style with a large, stylized "S" and "T".

S. Wayne Talton
Vice President
Regulatory Affairs

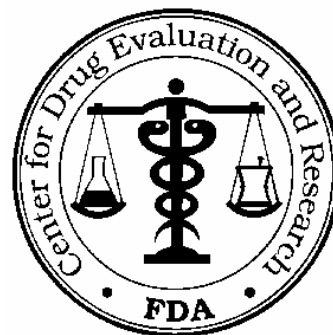
SWT/mj

Enclosure

Telephone Fax

ANDA 78-293

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



TO: Mylan Pharmaceuticals, Inc.

TEL: 304-599-2595

ATTN: S. Wayne Talton

FAX: 304-285-6407

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, 15 mg.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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

ANDA Number: 78-293 Date of Submission: May 2, 2006

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Oxybutinin Chloride Extended-release Tablets, 15 mg

1. CONTAINER

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

2. INSERT

- a. The listing of inactive ingredients in the DESCRIPTION section of the package insert IS NOT consistent with the listing of inactive ingredients found in the statement of components and composition i.e. [REDACTED] (b) (4)

[REDACTED] Please explain.

- b. Your tablet imprintings are the same as the RLD. Please refer to CFR 206.10.

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

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

/s/

John Grace
12/3/2006 11:31:04 AM
for Wm Peter Rickman



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

December 14, 2006

LABELING AMENDMENT (ELECTRONIC LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 15MG
ANDA 78-293
(RESPONSE TO THE AGENCY CORRESPONDENCE DATED DECEMBER 3,
2006)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the labeling comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated December 3, 2006. A copy of the Agency's December 3rd correspondence is provided on the enclosed CD-Rom as Letter.pdf.

In response to the Agency's December 3rd correspondence, Mylan wishes to amend this application with Final Printed labeling which has been revised as follows:

1. CONTAINER:

FDA COMMENT 1.: We encourage you to use boxing, contrasting colors and other means to differentiate the strengths of your product.

MYLAN RESPONSE: Contrasting colors have been used to differentiate this product strength from the 5 mg and 10 mg strengths of Oxybutynin Chloride Extended-release Tablets approved under ANDAs 76-702 and 76-644, respectively.

2. INSERT:

FDA COMMENT 2.a.: The listing of inactive ingredients in the DESCRIPTION section of the package insert IS NOT consistent with the listing of inactive ingredients found in the statement of components and composition i.e. (b) (4)

. Please explain.

MYLAN RESPONSE: As requested by the Agency, Mylan's final printed outsert has been revised to reflect the inactive ingredients consistent with the statement of components and composition included in the original ANDA. Included in Attachment A.pdf is a copy

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of

(b) (4)

FDA COMMENT 2.b.: Your tablet imprintings are the same as the RLD. Please refer to CFR 206.10.

MYLAN RESPONSE: The tablet description included in our original draft labeling was incorrect. Mylan's imprinting for Oxybutynin Chloride Extended-release Tablet, 15 mg is **M** over **O15** in black ink which is different from the tablet imprinting for the RLD.

Please note that Mylan's final printed bottle labeling bears the statement "New Formulation and Product Appearance." Upon approval of our ANDAs for Oxybutynin Chloride Extended-release Tablets, 5 mg and 10 mg, Mylan launched an authorized generic version of Alza's 15 mg tablet strength. We wish to use this statement on our bottle labels for the first six months of commercial distribution of Mylan's formulation to help prevent confusion in the marketplace. Mylan acknowledges that we can only use this statement for six months post approval.

In accordance with the Agency's Guidance *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Oxybutynin Chloride Extended-release Tablets as described in the electronic Table of Contents. As a review aid, Mylan has also included Microsoft Word versions of all proposed labeling components. To access these Word files, bookmarks are provided within the pdf versions.

Since a Structured Product Labeling (SPL) version of the Reference Listed Drug's labeling is available, Mylan commits to submit a SPL version of our generic product labeling post approval or upon Agency request.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,



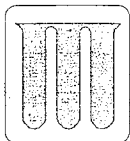
S. Wayne Talton
Vice President
Regulatory Affairs

SWT/rr

Enclosure

Desk Copy:

Postelle Birch-Smith, Labeling Reviewer
Division of Labeling and Program Support



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

March 5, 2007

MINOR AMENDMENT (REQUEST FOR FINAL ANDA APPROVAL)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N. Am

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 15MG
ANDA 78-293
(Request for Final ANDA Approval)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which received Tentative Approval on February 5, 2007. A copy of the February 5, 2007 Tentative Approval letter has been provided in Attachment A for your reference. In accordance with the conditions outlined in the February 5, 2007 tentative approval letter and pursuant to 21 CFR 314.107(b)(3)(i)(A), Mylan hereby requests that final approval of ANDA 78-293 be granted on May 9, 2007 concurrent with the expiration of the 180 day marketing exclusivity period for the first generic drug applicant.

As required by the February 5, 2007 Tentative Approval letter, this amendment also provides notification that no changes to the conditions outlined in the chemistry, manufacturing and controls (CMC) of this application have been made since the date of Tentative Approval.

With respect to labeling, our Final Printed Outsert (code OXYBT:R1; Revised December 2006) and container labels remain the same as those submitted in our Labeling Amendment dated December 14, 2006.

As required by 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or by facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

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MAR 06 2007
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Desk Copy: Leigh Ann Matheny, Project Manager
Division of Chemistry III, Team 4

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MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

April 17, 2007

TELEPHONE AMENDMENT (CHEMISTRY AND ELECTRONIC LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS USP, 15MG
ANDA 78-293
(RESPONSE TO THE AGENCY TELEPHONE CALL RECEIVED APRIL 2, 2007)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Reference is also made to a telephone call received on April 2, 2007 from Robert Iser, of your Office, in which he requested that we make chemistry and labeling revisions in accordance with the compendial monograph for Oxybutynin Chloride Extended-release Tablets, USP which becomes official on May 1, 2007.

As requested by Mr. Iser, Mylan has revised our drug product specifications and stability protocols to reflect the product name change from Oxybutynin Chloride Extended-release Tablets to Oxybutynin Chloride Extended-release Tablets, USP. The revised drug product specifications and stability protocols are provided in Attachments A and B, respectively.

Mylan has adopted the compendial Identification method. Identification Test A is infrared absorption according to the general USP test <197>. Identification Test B is a retention time comparison of the Sample and Standard preparations as obtained in the Assay method. Identification Test C is a retention time comparison of the Sample and Standard preparations as obtained in the Dissolution method. Although Identification Test C is not included in the official USP monograph, Mylan has decided to retain this test as an additional control to ensure that Oxybutynin Chloride, USP is identified in the drug product. The revised Identification procedure (FP-OXY15-ID-M) is provided in Attachment C.

With regards to Dissolution, please note that Mylan is retaining our tentatively approved Dissolution method and tolerances for Oxybutynin Chloride Extended-release Tablets USP, 15mg. Upon final approval of this application, Mylan intends to petition the USP to include our Dissolution method and tolerances in the official drug product monograph.

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Gary J. Buehler
Page 2 of 2

Mylan also wishes to retain our tentatively approved procedures for Assay and Related Compounds. Method comparison studies have been performed to demonstrate equivalency between Mylan's methods and the compendial methods. The results of the comparison studies demonstrate that Mylan's methods provide the same or increased assurance of the quality of the drug product. Mylan acknowledges that the compendial Assay and Related Compounds procedures for Oxybutynin Chloride Extended-release Tablets, USP are the official regulatory analytical procedures and will prevail in the event of a dispute. Refer to Attachment D for copies of the Assay and Related Compounds method comparison reports.

In addition to the specific chemistry updates described herein, Mylan has revised all drug product test procedures to reflect the USP designation in the drug product name. While these updates are considered editorial, the revised analytical procedures for Dissolution, Assay, Uniformity of Dosage Units, Related Compounds, and Water Determination are provided in Attachment E for completeness.

With regards to labeling, Mylan has revised our outsert and bottle labels to reflect the USP designation. In addition, our outsert has been revised to include the statement "USP Dissolution Test Pending" since our dissolution method and tolerances are not currently published in the USP. Mylan commits to remove this statement from our labeling once our dissolution method and tolerances have been officially published in the USP monograph. A side-by-side comparison of Mylan's revised final printed bottle labels and revised final printed outsert to the previously submitted are provided herein. Please refer to the Comp1.pdf and Comp2.pdf files on the enclosed CD-Rom for details. A copy of the electronic labeling Table of Contents is provided in Attachment F.

In accordance with the Agency's Guidance *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Oxybutynin Chloride Extended-release Tablets, USP as described in the electronic Table of Contents. As a review aid, Mylan has also included Microsoft Word versions of all proposed labeling components. To access these Word files, bookmarks are provided within the pdf versions.

Mylan commits to submit a SPL version of our generic product labeling post approval or upon Agency request. Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,



S. Wayne Talton
Vice President
Regulatory Affairs

SWT/as

Desk Copy: Robert Iser, Review Chemist (cover letter only)
Division of Chemistry III



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

May 2, 2007

TELEPHONE AMENDMENT (ELECTRONIC LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS USP, 15MG
ANDA 78-293
(RESPONSE TO THE AGENCY TELEPHONE CALL RECEIVED MAY 1, 2007)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to our Telephone Amendment submitted on April 17, 2007 which contained updated chemistry and labeling information. Reference is also made to a telephone call received on May 1, 2007 from Ms. Postelle Birch, of your Office, in which she requested that we amend our April 17th Telephone Amendment to provide the Final Printed Outsert for Oxybutynin Chloride Extended-release Tablets USP, 15mg.

As requested by Ms. Birch, we enclose a CD-Rom which contains electronic final printed outsert labeling for Oxybutynin Chloride Extended-release Tablets, USP as described in the enclosed electronic Table of Contents. As a review aid, Mylan has also included a Microsoft Word version of the final printed labeling. To access the Word file, a bookmark is provided within the pdf version.

Mylan commits to submit a SPL version of our generic product labeling post approval. Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/rr

Desk Copy: Postelle Birch, Labeling Reviewer
Division of Labeling and Program Support

Department—Fax Numbers

Accounting	(304) 285-6403
Administration	(304) 599-7284
Business Development	(304) 598-5419
Corporate Services	(304) 285-6482
Human Resources	(304) 598-5406

Information Systems

Label Control	(304) 285-6404
Legal Services	(800) 848-0463
Maintenance & Engineering	(304) 598-5408
Medical Unit	(304) 598-5411
Product Development	(304) 598-5445

Purchasing

Quality Assurance	(304) 285-6411
Quality Control	(304) 285-6419
Regulatory Affairs	(304) 598-3232
Research & Development	
Sales & Marketing	

(304) 598-5401

(304) 598-5407
(304) 598-5409
(304) 285-6407
(304) 285-6419
(304) 598-3232

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-293 Applicant Mylan Pharmaceuticals, Inc.

Drug Oxybutynin Chloride Extended Release Tablets USP Strength(s) 15 mg

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

REVIEWER:

DRAFT Package

FINAL Package

1. **Martin Shimer**
 Chief, Reg. Support Branch
 Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐
 (required if sub after 6/1/92) Pediatric Exclusivity System
 RLD = _____ NDA# _____
 Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked _____
 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: Mylan filed PIV certifications to all listed patents. Alza initiated suit against Mylan[1:06CV-125-IMK] in the Northern District of WV on 8/21/2006. This suit was withdrawn by Alza on September 8, 2006. Ergo, there is no remaining 30 month stay prohibiting approval of this ANDA. IMPAX ANDA 76-745 holds 180 day exclusivity for this drug product until 5/9/2007. This ANDA will be eligible for Full Approval on 5/9/2007.

2. **Project Manager**, Leigh Ann Matheny Team 4
 Review Support Branch
 Date 4/26/07 Date _____
 Initials LM Initials _____
 Original Rec'd date 5/2/06 EER Status Pending ☐ Acceptable ☒ OAI ☐
 Date Acceptable for Filing 5/3/06 Date of EER Status 7/10/06
 Patent Certification (type) IV Date of Office Bio Review 11/30/06
 Date Patent/Exclus. expires 5/22/2012 Date of Labeling Approv. Sum _____
 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 Interim Dissol. Specs in AP Ltr: Yes ☐
 it to Cecelia Parise)
 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 2/5/07
 Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
 Comments:

3. **Labeling Endorsement**
 Reviewer: _____ Labeling Team Leader: _____
 Date 5/8/07 Date 5/8/07
 Name/Initials P.B. Name/Initials J.G.
 Comments:

4. **David Read** (PP IVs Only) Pre-MMA Language included ☐ Date 5/7/07
 OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials DT
 Comments: Changes to Ap Ltr saved to V drive.

5. Div. Dir./Deputy Dir. Date 5/9/07
Chemistry Div. III Initials VAS

Comments:cmc acceptable

6. Frank Holcombe First Generics Only Date _____
Assoc. Dir. For Chemistry Initials _____
Comments: (First generic drug review)

7. Vacant Date _____
Deputy Dir., DLPS Initials _____

8. Peter Rickman Date 5/10/2007
Director, DLPS Initials swpr
Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒
Comments: Mylan filed PIV patents certs to all listed patents. Alza initiated litigation, but withdrew 9/8/2006. No remaining 30 month stay. Eligible for full approval after Impax 180 day exclusivity expires 5/9/2007; W/H exclusivity expired 10/15/2006; labeling acceptable 5/8/2007; bio acceptable 11/30/2006 (single dose fasting); EER acceptable 7/10/2006. okay for full approval

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Press Release Acceptable ☐
Comments:

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

10. Project Manager, Leigh Ann Matheny Team 4 Date 5/10/07
Review Support Branch Initials LK for
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
2:55 PM Time notified of approval by phone
2:58 PM Time approval letter faxed

FDA Notification:
5/10/07 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
5/10/07 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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

/s/

Lisa Kwok
5/10/2007 03:03:53 PM