

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 076702Orig1s000

Name: Oxybutynin Chloride Extended-release
Tablets
5 mg

Sponsor: Mylan Pharmaceuticals, Inc.

Approval Date: November 9, 2006

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 076702Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 076702Orig1s000

APPROVAL LETTER

ANDA 76-702

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 March 28, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Oxybutynin Chloride Extended-release Tablets, 5 mg.

Reference is made to the Tentative Approval letter issued by this office on January 12, 2005, and to your amendments dated March 17, June 9, and July 27, 2004; and September 16, September 21, and October 27, 2005. We also acknowledge receipt of your correspondence dated July 19, August 31, and September 29, 2005, and August 17, 2006, regarding the '092 patent as noted below and informing the agency of the outcome of your patent litigation regarding the '355 patent.

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, 5 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Ditropan XL Extended-release Tablets, 5 mg, of Alza Corporation. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

<u>Time</u>	<u>Percent Dissolved</u>
2 hr:	0 - 10%
4 hr:	10 - 30%
8 hr:	40 - 65%
16 hr:	NLT 80%

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

The listed drug product referenced in your ANDA, Ditropan XL Extended-release Tablets, 5 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, 5 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 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) 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. 1:03-cv-158). Subsequent to your receipt of the tentative approval letter, 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 6, 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.

With respect to 180-day generic drug exclusivity, we note that Mylan was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification for Oxybutynin Chloride Extended-release Tablets, 5 mg, to each of the listed patents. Therefore, with this approval, Mylan is eligible for 180-days of market exclusivity for Oxybutynin Chloride Extended-release Tablets, 5 mg. This exclusivity, which is provided for under section 505(j)(5)(8)(iv) of the Act,¹ will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv). Please submit correspondence to the ANDA informing the agency of the date the exclusivity begins to run.

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.

¹ Because your ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

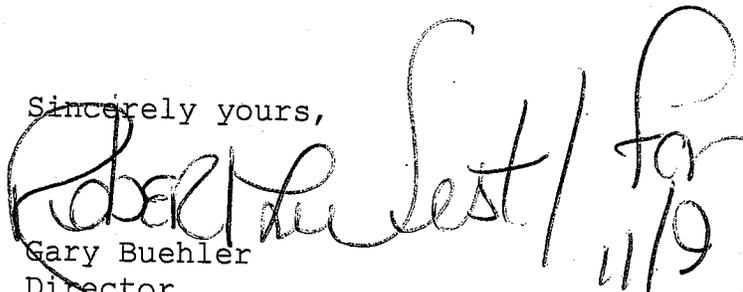
Post-marketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

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

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

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

Sincerely yours,


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

for
11/9/2006

cc: ANDA 76-702
Division File
Field Copy
HFD-610/R. West
HFD-600/C. Parise
HFD-604/D. Hare
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:

HFD-630/M. Darj/ *MD Darj 13 Feb 2006*
HFD-630/D. Gill/ *DS Gill 2-13-06*
HFD-617/S. Park/ *S. Park 2/13/06*
HFD-613/P. Birch/
HFD-613/J. Grace/

Approved Electronic Labeling Located at:

\\Cdseubogd1\76702\N_000\2004-08-20\Labeling\Proposed BL2.pdf
\\Cdseubogd1\76702\N_000\2004-10-13\Labeling\Proposed OT.pdf

V: \FIRMSAM\MYLAN\LTRS&REV\76702.ap.doc

F/T by: EW 2/13/06

APPROVAL

cmc Sabir Jafar
1/14/06
2/14/06

Robert Ford
8/17/2006
pending CR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 076702Orig1s000

TENTATIVE APPROVAL LETTER

ANDA 76-702

JAN 12 2005

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
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 March 28, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxybutynin Chloride Extended-release Tablets, 5 mg.

Reference is also made to your amendments dated December 2, 2003; and July 27, August 20, September 24, and October 13, 2004. We also acknowledge receipt of your correspondence dated September 30, 2003, and March 31, 2004, addressing the patent issues noted below.

We have completed the review of this abbreviated application, 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 application at this time because of the patent issue noted below. Therefore, the application is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your application 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. In addition, this letter does not address notice issues related to the 180-day exclusivity provisions under Section 505(j)(5)(B)(iv) of the Act.

The listed drug product referenced in your application, Ditropan XL Extended-release Tablets, 5 mg, of Alza Corporation, is subject to periods of patent protection. The following patents

and their expiration dates are currently listed in the agency's publication entitled 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
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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

Your ANDA contains paragraph IV patent certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, sale, offer for sale, or importation of Oxybutynin Chloride Extended-release Tablets, 5 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 was brought against Mylan in the United States District Court for the Northern District of West Virginia involving your challenge to the '355 patent (Alza Corporation v. Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc., Civil Action No. 1:03-cv-158). We note that Mylan was not sued within the 45-day period on any of the other listed patents.

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in Section 505(j)(5)(B)(iii)¹ or such shorter or longer period as the court may have ordered, or,

¹ Because information on the '895, '754, '268, '355, and '115 patents was submitted before August 18, 2003, this reference is to a section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101(c)(3).

- b. the date the court decides² that the patent(s) is/are invalid or not infringed [see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act], or,
 - c. the '355 patent has expired, and
2. The agency is assured there is no new information that would affect whether final approval should be granted.

To reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. Your amendment must provide:

1. A copy of a court decision or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and
2.
 - a. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or
 - b. a statement that no such changes have been made to the application since the date of tentative approval.

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, at any time prior to the final date of approval the agency may request 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 application, or may result in a delay in the issuance of the final approval letter.

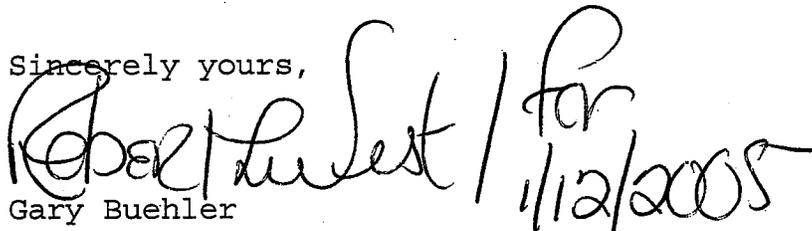
² This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

Any significant changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures 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 before the effective final approval date is prohibited under section 501 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355, and it 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 Sarah Park, Project Manager, at 301-827-9275.

Sincerely yours,


Gary Buehler

Director

Office of Generic Drugs

Center for Drug Evaluation and Research

cc: ANDA 76-702
Division File
Field Copy
HFD-610/R. West
HFD-600/C.Parise
HFD-604/D. Hare
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:

HFD-623/M.Darj/ *W. Darj 08 Sep 2004*
HFD-623/D.Gill/ *DSGill 9-8-04. DSG. 12-7-04*
HFD-617/S.Park/ *Sipadung 9/10/04*
HFD-613/D.Catterson/ *David 11/8/04*
HFD-613/J.Grace/ *Jm 11/8/04*

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F/T by

TENTATIVE APPROVAL

come satisfactory.
Hayat Bayun
12/2/04.

Robert West
1/12/2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 076702Orig1s000

LABELING

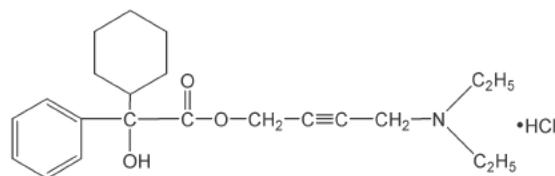
OXYBUTYNYN CHLORIDE EXTENDED-RELEASE TABLETS 5 mg

Rx only

DESCRIPTION: Oxybutynin chloride is an antispasmodic, anticholinergic agent. Each oxybutynin chloride extended-release tablet contains 5 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 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 contain the following inactive ingredients: colloidal silicon dioxide, D&C yellow #10 aluminum lake, dibasic calcium phosphate (anhydrous), FD&C blue #1 aluminum lake, FD&C red #40 aluminum lake, 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 extended-release tablets may also contain imprinting ink consisting of either black pigment and natural resin or black iron oxide, isopropyl alcohol, methanol 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.

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)

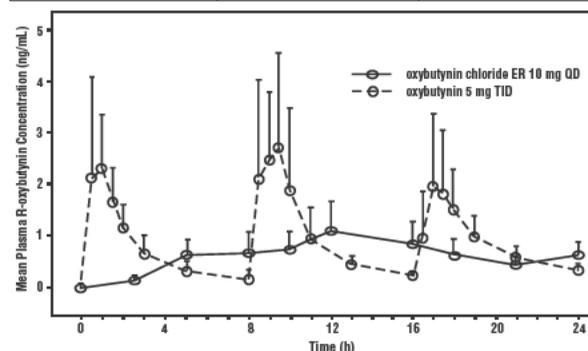


Figure 1. Mean R-oxybutynin plasma concentrations following a single dose of oxybutynin chloride ER 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment).

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.

Pharmacokinetic information for pediatric patients 5 to 15 years of age with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin chloride extended-release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

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: Pharmacokinetic information for pediatric patients 5 to 15 years of age with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin chloride extended-release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

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.

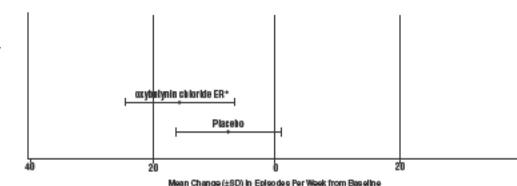
Clinical Studies: Oxybutynin chloride extended-release was evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (89%) and female (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 forced dose escalation design, whereas the other studies used a dose adjustment design in which each patient's final dose was adjusted to a balance between improvement of incontinence symptoms and tolerability of side effects. Controlled studies included patients known to be responsive to oxybutynin or other anticholinergic medications, and these patients were maintained on a final dose for up to 2 weeks.

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

Number of Urge Urinary Incontinence Episodes Per Week

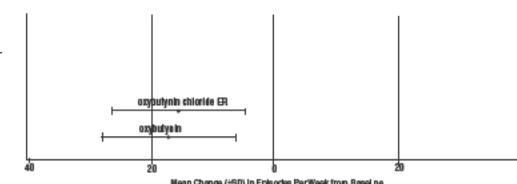
Study 1	N	Oxybutynin Chloride ER	N	Placebo
Mean Baseline	34	15.9	16	20.9
Mean (SD) Change from Baseline [†]	34	-15.8 (8.9)	16	-7.6 (8.6)
95% Confidence Interval for Difference (oxybutynin chloride ER - Placebo)				(-13.6, -2.8)*

*The difference between oxybutynin chloride ER and placebo was statistically significant.
[†]Covariate adjusted mean with missing observations set to baseline values



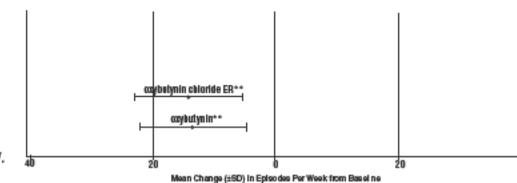
Study 2	N	Oxybutynin Chloride ER	N	oxybutynin
Mean Baseline	53	27.6	52	23.0
Mean (SD) Change from Baseline [†]	53	-17.6 (11.9)	52	-19.4 (11.9)
95% Confidence Interval for Difference (oxybutynin chloride ER - oxybutynin)				(-2.8, 6.5)

[†]Covariate adjusted mean with missing observations set to baseline values

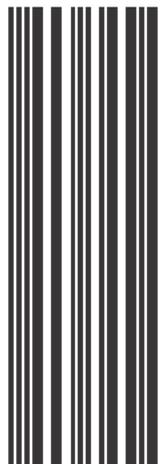


Study 3	N	Oxybutynin Chloride ER	N	oxybutynin
Mean Baseline	111	18.9	115	19.5
Mean (SD) Change from Baseline [†]	111	-14.5 (8.7)	115	-13.8 (8.6)
95% Confidence Interval for Difference (oxybutynin chloride ER - oxybutynin)				(-3.0, 1.6)**

**The difference between oxybutynin chloride ER and oxybutynin fulfilled the criteria for comparable efficacy.
[†]Covariate adjusted mean with missing observations set to baseline values



OXBT R1



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.

Pediatric use information for the treatment of patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin extended-release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

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 co-administered.

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

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 pompholiticiformis*, *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: Clinical study information for pediatric patients 6 to 15 years of age with symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin chloride extended-release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

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 4 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 2 below. Adverse events from two additional fixed dose, active controlled, 12 week treatment duration, postmarketing studies, in which 576 patients were treated with oxybutynin chloride extended-release tablets 10 mg/day, are also listed in Table 2 (second column). The adverse events are reported regardless of causality.

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 4 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 4 efficacy and safety studies. *General:* abdominal pain, dry nasal and sinus mucous membranes, accidental injury, back pain, flu syndrome; *Cardiovascular:* hypertension, palpitation, vasodilation; *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 overdose. 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: Dosing information for pediatric patients aged 6 years and older is approved for Alza Corporation's oxybutynin chloride extended-release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

HOW SUPPLIED: Oxybutynin chloride extended-release tablets are available containing 5 mg of oxybutynin chloride, USP.

The 5 mg tablets are light green, film coated, round, biconvex, beveled edge, unscored tablets with **M** over **O 5** imprinted in black ink on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-6605-01
bottles of 100 tablets
NDC 0378-6605-05
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 Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED SEPTEMBER 2005
OXB:T:R1

3 N
0378-6605-01
9



Each extended-release
tablet contains:
Oxybutynin
chloride, USP 5 mg

5 mg



MYLAN®

NDC 0378-6605-01

**OXYBUTYNIN
CHLORIDE
EXTENDED-RELEASE
TABLETS**

5 mg

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.]

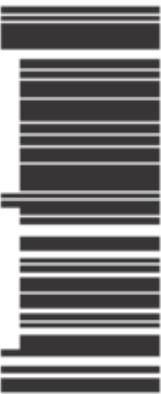
Protect from moisture and humidity.

Usual Dosage: Once daily. See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM 6605A

3 N
0378-6605-05
7



Each extended-release
tablet contains:
Oxybutynin
chloride, USP 5 mg

5 mg



MYLAN®

NDC 0378-6605-05

**OXYBUTYNIN
CHLORIDE
EXTENDED-RELEASE
TABLETS**

5 mg

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: Once daily. See
accompanying prescribing
information.

This container is not intended for
dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM6605B

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 076702Orig1s000

LABELING REVIEWS

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

ANDA Number: 76-702

Dates of Submission: March 28, 2003, August 20, 2004, September 24, 2004 and October 13, 2004

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Oxybutinin Chloride Extended-release Tablets, 5 mg

BASIS OF TENTATIVE APPROVAL:

TENTATIVE APPROVAL SUMMARY

Container Labels:

(bottles of 100)

Satisfactory in draft as of August 20, 2004 submission.

(Vol. 3.1 and \\Cdsesubogd1\76702\W_000\2004-08-20\Labeling\Proposed BL1.pdf)

(bottles of 500)

Satisfactory in draft as of August 20, 2004 submission.

(Vol. 3.1 and \\Cdsesubogd1\76702\W_000\2004-08-20\Labeling\Proposed BL2.pdf)

Professional Package Insert Labeling:

Satisfactory in draft as of September 24, 2004 submission.

(Vol. 5.1 and \\Cdsesubogd1\76702\W_000\2004-10-13\Labeling\Proposed OT.pdf)

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

PATENT/ EXCLUSIVITIES

Patent Data -

No	Expiration	Use Code	Use	File
5674895	May 22, 2015			
5674895*PED	Nov 22, 2015			IV
5840754	May 22, 2015			
5840754*PED	Nov 22, 2015			IV
5912268	May 22, 2015			
5912268*PED	Nov 22, 2015			IV
6124355	May 22, 2015	U-378	Method for treating incontinence	
6124355*PED	Nov 22, 2015	U-378	Method for treating incontinence	IV

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	

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
020897	April 15, 2006	NPP	New Patient Population	
020897	October 15, 2006	PED	Pediatric Exclusivity	

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name			
	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			X
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?			
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	

Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?			
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

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
See table.
3. MANUFACTURING FACILITY
Mylan Pharmaceuticals, Inc.
Morgantown, WV 26505
(Vol. 1.2, p 000165)
4. STORAGE CONDITIONS:
NDA - Store at controlled room temperature 15° to 25° C (59° to 77° F).
ANDA - Store at controlled room temperature (b) (4)
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 is no listing of the ingredients in the (b) (4)
7. PACKAGING CONFIGURATIONS:
NDA- The 5 mg, 10 mg and 15 mg tablets are packaged in bottles of 100 tablets.
ANDA- The 5 mg tablet will be used 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) 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) (DMF (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. (Vol. 1:2, p. 000337-40)

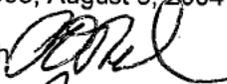
9. In Mylan's original labeling submission, the Systems Components and Performance section was omitted. Email discussion was exchanged to decide whether or not omitting this section would constitute "same-as" labeling. It was decided that the firm could not omit the section and would have to resubmit an amendment which included this section which described the release system for their product. Wayne Talton was called on September 16, 2004 and he stated that Mylan would resubmit labeling. Below is a copy of the final email sent by John Grace on Thursday September 19, 2004 at 8:38 AM stating our position:

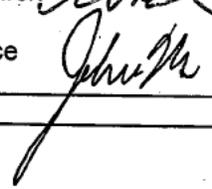
"Mylan's proposal is to eliminate that subsection entirely.
There is no proposed text. -The statement from Wayne Talton is a marketing statement (not a labeling statement) from Mylan's Marketing Department.
I did some checking and found that the approved ANDAs that referenced Procardia XL, which has the same subsection as Ditropan XL, proposed a different statement which would describe the ANDA product. I think this is an "allowable difference" per regs. Eliminating subsection would not meet "same as" requirements.
We will ask Mylan to propose a "System Components and Performance" subsection for their product.

John F. Grace"

Date of Review: October 18, 2004

Dates of Submission: March 28, 2003, August 5, 2004 and September 24, 2004

Primary Reviewer: Postelle Birch  Date: October 18, 2004

Team Leader: John Grace  Date: 10/19/04

cc: ANDA: 76-702
DUP/DIVISION FILE
HFD-613/PBirch/JGrace (no cc)
V:\FIRMSAMMYLAN\LTRS&REV\76-702tap.label.doc
Review

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

ANDA Number: 76-702

Dates of Submission: September 16, 2005

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Oxybutinin Chloride Extended-release Tablets, 5 mg

BASIS OF APPROVAL:

APPROVAL SUMMARY

Container Labels:

(bottles of 100)

Satisfactory in FPL as of September 16, 2005 submission.

(Vol. 3.1 and \\Cdsesub1\76702\W_000\2005-09-16\Labeling\Proposed BL1.pdf)

(bottles of 500)

Satisfactory in FPL as of September 16, 2005 submission.

(Vol. 3.1 and \\Cdsesub1\76702\W_000\2005-09-16\Labeling\Proposed BL2.pdf)

Professional Package Insert Labeling:

Satisfactory in FPL as of September 16, 2005 submission.

(Vol. 5.1 and \\Cdsesub1\76702\W_000\2005-09-16\Labeling\Proposed OT.pdf10)

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

PATENT/ EXCLUSIVITIES

Patent Data –

No	Expiration	Use Code	Use	File
5674895	May 22, 2015			
5674895*PED	Nov 22, 2015			IV
5840754	May 22, 2015			
5840754*PED	Nov 22, 2015			IV
5912268	May 22, 2015			
5912268*PED	Nov 22, 2015			IV
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 -

Code/sup	Expiration	Use Code	Description	Labeling Impact
020897	April 15, 2006	NPP	New Patient Population	
020897	October 15, 2006	PED	Pediatric Exclusivity	

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			X
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)	Yes	No	N.A.
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X

Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?	X		
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

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
See table.
3. MANUFACTURING FACILITY
Mylan Pharmaceuticals, Inc.
Morgantown, WV 26505
(Vol. 1.2, p 000165)
4. STORAGE CONDITIONS:
NDA - Store at controlled room temperature 15° to 25°C (59° to 77°F).
ANDA - Store at controlled room temperature (b) (4)
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 is no listing of the ingredients in the (b) (4)
7. PACKAGING CONFIGURATIONS:

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

ANDA- The 5 mg tablet will be used 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) (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) DMF (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. (Vol. 1.2, p. 000337-40)

Date of Review: December 6, 2005

Dates of Submission: September 16, 2005

Primary Reviewer: Postelle Birch *Postelle Birch* Date: 12/8/05

Team Leader: John Grace *John Grace* Date: 12/12/05

cc: ANDA: 76-702
DUP/DIVISION FILE
HFD-613/PBirch/JGrace (no cc)
Y:\FIRMSAMMYLAN\LTRS&REV\76-702ap.label.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 076702Orig1s000

CHEMISTRY REVIEWS



#1



ANDA #76-702

Oxybutynin Chloride Extended-Release Tablets

Mylan Pharmaceuticals Inc.

Robert W. Trimmer, Ph.D.

Chemistry Division I

Branch IV



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B. Endorsement Block	9
C. CC Block.....	9
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Chemistry Review Data Sheet

1. ANDA #76-702

2. REVIEW #: 01

3. REVIEW DATE: August 22, 2003

4. REVIEWER: Robert W. Trimmer, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

n/a

Document Date

6. SUBMISSION BEING REVIEWED:

Submission Reviewed

Original

Document Date

3-28-2003

7. NAME & ADDRESS of APPLICANT:

Name: Mylan Pharmaceuticals Inc.

Address: PO Box 4310
781 Chestnut Ridge Road
Morgantown, WV 26504-4310

Representative: Mr. S. Wayne Talton



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Telephone: 304-599-2595

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: -

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

9. LEGAL BASIS For SUBMISSION:

505(j)(2)(A)(vii)

Based on RLD: Ditropan Extended Release NDA 20-897 (for 5, 10, & 15 mg tabs)

10. PHARMACOL. CATEGORY: antispasmodic and anti-cholinergic agent

11. DOSAGE FORM: tablets

12. STRENGTH / POTENCY: 5 mg

13. ROUTE of ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

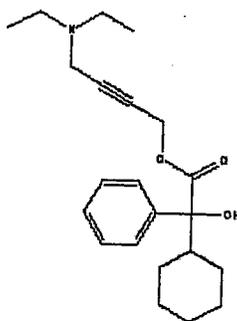
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

Oxybutynin Chloride $C_{22}H_{31}NO_3$. MW 357.49184-(Diethylamino)-2-butylnyl-*alpha*-phenylcyclohexaneglycolate hydrochloride.

HCl salt



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	[REDACTED]	(b) (4)	1	Not adequate	06-30-2003 revised 7-2-03	
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		7				The component has been previously reviewed & found sat. Numerous ANDAs have been approved using this component.
	III		7				"

¹ Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: n/a

DOCUMENT	APPLICATION NUMBER	DESCRIPTION



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	n/a		
EES	acceptable	8-20-2003	
Methods Validation	open		
Labeling	open		D.Catterson
Bioequivalence	open		
Env. Assessment	sat.		
Radiopharmaceutical	n/a		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 76-702

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
Not recommended for approval at this time re DMF, bio and other issues.
- 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 and Drug Substance

Oxybutynin Chloride drug substance is a USP product. Per the applicant, any previously released DS remaining in inventory 1 year after its original release date or its retest date will be sampled and tested prior to further use. The DS can be recontrolled up to 5 years from date of receipt or up to the manufacturer's expiration date. Materials will be retested at least once per year up to the noted time limit.

Chemical name: 4-(Diethylamino)-2-butylanyl-*alpha*-phenylcyclohexaneglycolate hydrochloride. CAS number: 1508-65-2 and MW: 393.97. It is a white to off-white powder melting between 124 to 129°. Extensive testing by Mylan via the literature and testing by (b) (4) showed no evidence of polymorphism. This DS is freely soluble in water, very soluble in methanol, slightly soluble in ether, and very slightly soluble in hexane. In spite of it being very soluble in water, Mylan has developed a particle size method and established spec of (b) (4) NMT (b) (4), (b) (4) NMT (b) (4) and (b) (4) NMT (b) (4). The DS is administered as a racemate of R- and S- enantiomers.

This ER drug product is 5mg per dose and is not a USP drug product. The tablets are light green colored, round, biconvex, beveled edged, unscored tablets with M over 05 imprinted in black ink on one side and blank on the other side.

The DP is available in bottles of 100 and 500 tablets.

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

The labeling should describe its use. The name given by the innovator is Ditropan Tablets (HMR, Inc.).



CHEMISTRY REVIEW



Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

Multiple deficiencies were noted including a non-adequate Type II DMF.

III. Administrative

A. Reviewer's Signature

Robert W. Trimmer

B. Endorsement Block

Chemist Name/Date:

Chemistry Team Leader Name/Date:

Project Manager Name & Date:

Robert W. Trimmer, Ph.D./

Dave S. Gill, Ph.D./

Sarah Kim, PM/

C. CC Block



CHEMISTRY REVIEW



Chemistry Assessment Section

31. **SAMPLES and RESULTS / METHODS VALIDATION STATUS:**
The drug product is not an USP compendial item. Method validation by a FDA district laboratory is therefore required, however, the request will be submitted after the issues on assay, dissolution, and impurity specifications have been resolved.
32. **LABELING:** open
33. **ESTABLISHMENT INSPECTION:** sat.
Per the EER the overall recommendation was found acceptable on **20-August-2003**.
34. **BIOEQUIVALENCE:** pending bio review re dissolution
- a. The request for a waiver of *in-vivo* bioequivalence study is to be granted by our Division of Bioequivalence.
 - b. Dissolution data will be compared with DBE's specs.
35. **ENVIRONMENTAL IMPACT CONSIDERATIONS / CATEGORICAL EXCLUSION:** sat.
The applicant claims a claim for categorical exclusion under an environmental assessment under 21 CFR 25.31.
The request for exclusion from the requirements for the environmental impact analysis statement was signed by Mr. Sisto.

Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-702

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Oxybutynin Chloride Extended-release Tablets, 5 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File ^{(b) (4)} is deficient. The holder of the DMF has been notified of the deficiencies. Please do not submit a MINOR amendment until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.
2. Regarding your ^{component} ~~Drug Substance~~ specifications~~s~~
 - a.  (b) (4)
 - b. 
 - c. 
3. Regarding your Drug Product release specifications:
 - a.  (b) (4)
 - b. 
 - c. 
4. Regarding the analytical methods, please provide the LOD data for the process and degradation impurities.
5. Please provide the data, or state the page number where the data is found, for the ^{(b) (4)} tests. The ^{(b) (4)} specifications are listed on page 5312 of your ANDA.

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

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.
2. Your bioequivalence information (including dissolution data) are pending review by the Division of Bioequivalence (DBE). The final Release and Stability Specifications will be based on the recommendations of DBE.
3. Please note that methods validation will be scheduled after testing issues in this letter are resolved.
4. A review of the Labels and Labeling is pending. Any deficiencies found will be sent to you under separate cover.

Sincerely yours,

DS Gil

f Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/Robert W. Trimmer, Ph.D. /9/5/03

Robert W. Trimmer 9-15-03

HFD-623/ Dave S. Gill, Ph.D. /9/5/03

DSGill 9-16-03

HFD-617/S. Kim, Pharm. D./PM /9/12/03

S. Kim 9/16/03

F/T by /ard/9/15/03

V:\FIRMSam\mylan\ltrs&rev\76702cr1.oxybutynin.doc

TYPE of LETTER: NOT APPROVABLE - MINOR



ANDA #76-702

Oxybutynin Chloride Extended-Release Tablets, 5 mg

Mylan Pharmaceuticals Inc.

**Mike Darj
Office of Generic Drugs
Division of Chemistry III**

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A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block.....	9
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Chemistry Review Data Sheet

1. ANDA #76-702 (First Generic)
2. REVIEW #: 2
3. REVIEW DATE: August 18, 2004
REVISION DATE: September 10, 2004
4. REVIEWER: Mike Darj, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Original

Document Date

28-MAR-2003

6. SUBMISSION BEING REVIEWED:

Submission Reviewed

Amendment

Gratuitous Amendment

Document Date

02-DEC-2003

27-JUL-2004

7. NAME & ADDRESS of APPLICANT:

Name: Mylan Pharmaceuticals, Inc.
Address: 781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504
Representative: S. Wayne Talton
Telephone: (304) 599-2595



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS For SUBMISSION:

505(j)(2)(A)(vii)
Based on RLD: Ditropan Extended Release NDA 20-897 (for 5, 10, & 15 mg tabs)

10. PHARMACOL. CATEGORY: antispasmodic and anti-cholinergic agent

11. DOSAGE FORM: Extended-release tablets

12. STRENGTH / POTENCY: 5 mg

13. ROUTE of ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

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

_____ SPOTS product – Form Completed

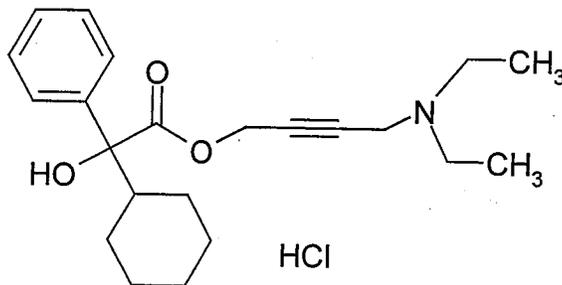
 x Not a SPOTS product

Chemistry Review Data Sheet

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

Oxybutynin Chloride $C_{22}H_{31}NO_3 \cdot HCl$. MW 393.97

4-(Diethylamino)-2-butynyl-*alpha*-phenylcyclohexaneglycolate hydrochloride.





CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	adequate	Dec-02-2004	Reviewed by this reviewer
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		7				The component has been previously reviewed & found sat. Numerous ANDAs have been approved using this component.
	III		7				"

¹ Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: n/a

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	n/a		
EES	acceptable	20Aug2003	
Methods Validation	n/a		
Labeling	Acceptable	19Oct2004	P. Birch
Bioequivalence	Acceptable	13Aug2004	P. Nwakama
Env. Assessment	Acceptable		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 76-702

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is recommended for approval (see section II).

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 and Drug Substance

Oxybutynin Chloride drug substance is a USP product. Per the applicant, any previously released DS remaining in inventory 1 year after its original release date or its retest date will be sampled and tested prior to further use. The DS can be recontrolled up to 5 years from date of receipt or up to the manufacturer's expiration date. Materials will be retested at least once per year up to the noted time limit.

Chemical name: 4-(Diethylamino)-2-butynyl-*alpha*-phenylcyclohexaneglycolate hydrochloride. CAS number: 1508-65-2 and MW: 393.97. It is a white to off-white powder melting between 124 to 129°C. Extensive testing by Mylan via the literature and testing by (b) (4) showed no evidence of polymorphism. This DS is freely soluble in water, very soluble in methanol, slightly soluble in ether, and very slightly soluble in hexane. In spite of it being very soluble in water, Mylan has developed a particle size method and established spec of (b) (4) NMT (b) (4), (b) (4) NMT (b) (4), and (b) (4) NMT (b) (4). The DS is administered as a racemate of R- and S- enantiomers.

This ER drug product is 5mg per dose and is not a USP drug product. The tablets are light green colored, round, biconvex, beveled edged, unscored with **M** over **05** imprinted in black ink on one side and blank on the other side.

The DP is available in bottles of 100 and 500 tablets.

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

The drug product is a tablet that is taken orally.



- C. Basis for Approvability or Not-Approval Recommendation**
All CMC issues have been successfully addressed.

III. Administrative

A. Reviewer's Signature

M. Darj 07 December

B. Endorsement Block

HFD-623/M. Darj, Ph.D., RC/

HFD-623/D. Gill, Ph.D., TL/

F/T by: EW 12/6/04

V:\FIRMSAMMYLAN\LTRS&REV\76702.CR3.DOC

Type of Letter: Approvable

C. CC Block

ANDA 76-702

ANDA DUP

DIV FILE

Field Copy



30. **MICROBIOLOGY:** n/a

31. **SAMPLES and RESULTS / METHODS VALIDATION STATUS:**
n/a

32. **LABELING:** Acceptable 10/19/2004

33. **ESTABLISHMENT INSPECTION:** Acceptable
EER overall recommendation found acceptable on **20-August-2003**

34. **BIOEQUIVALENCE:** Acceptable 8/13/2004

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS / CATEGORICAL EXCLUSION:** sat.
CR1

The applicant claims a claim for categorical exclusion under an environmental assessment under 21 CFR, 25.31.

The request for exclusion from the requirements for the environmental impact analysis statement was signed by Mr. Sisto.



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-702
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/ M. Darj, Ph.D., RC/18Aug2004/10Sep2004/

Michael Darj 07 Dec 2004

HFD-623/D. Gill, Ph.D., TL/9/10/04

DS Gill 12-7-04

HFD-617/S. Park, Pharm. D., PM/9/14/04

S. Park 12/7/04

F/T by: EW 12/6/04

V:\FIRMSAMMylan\LTRS&REV\76702.CR3.doc

TYPE of LETTER: APPROVABLE

#3



ANDA #76-702

Oxybutynin Chloride Extended-Release Tablets, 5 mg

Mylan Pharmaceuticals Inc.

**Mike Darj
Office of Generic Drugs
Division of Chemistry III**

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C. Basis for Approvability or Not-Approval Recommendation	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block.....	9
Chemistry Assessment	10



Chemistry Review Data Sheet

1. ANDA #76-702 (First Generic)

2. REVIEW #: 3

3. REVIEW DATE: October 21, 2005 (Minor Amendment of 16Sep05 and Gratuitous Amendment of 21Sep2005)
November 3, 2005 (Telephone Amendment of 27Oct2005)

4. REVIEWER: Mike Darj, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	28-MAR-2003
Minor Amendment	02-DEC-2003
Gratuitous Amendment	27-JUL-2004
Minor Amendment	16-Sep-2005
Gratuitous Amendment	21-Sep-2005

6. SUBMISSION BEING REVIEWED:

<u>Submission Reviewed</u>	<u>Document Date</u>
Telephone Amendment	27-Oct-2005

7. NAME & ADDRESS of APPLICANT:

Name: Mylan Pharmaceuticals, Inc.
Address: 781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504
Representative: S. Wayne Talton



Chemistry Review Data Sheet

Telephone: (304) 599-2595

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS For SUBMISSION:

505(j)(2)(A)(vii)

Based on RLD: Ditropan Extended Release NDA 20-897 (for 5, 10, & 15 mg tabs)

10. PHARMACOL. CATEGORY: antispasmodic and anti-cholinergic agent

11. DOSAGE FORM: Extended-release tablets

12. STRENGTH / POTENCY: 5 mg

13. ROUTE of ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

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

SPOTS product – Form Completed

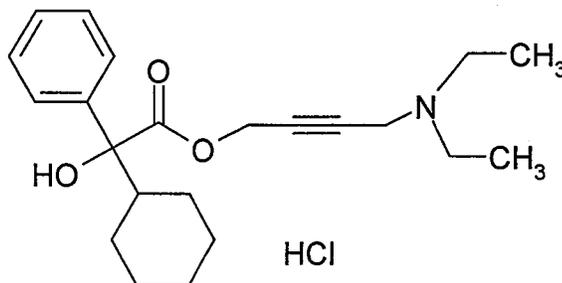
Not a SPOTS product

Chemistry Review Data Sheet

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

Oxybutynin Chloride $C_{22}H_{31}NO_3 \cdot HCl$. MW 393.97

4-(Diethylamino)-2-butynyl-*alpha*-phenylcyclohexanecarboxylate hydrochloride.





17. RELATED/SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	adequate	19Sep2005	Reviewed by M. Darj
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			7			The component has been previously reviewed & found sat. Numerous ANDAs have been approved using this component.
	III			7			"

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1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

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5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: n/a

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	n/a		
EES	acceptable	20Aug2003	
Methods Validation	n/a		
Labeling	Acceptable	12-Dec-2005	P. Birch
Bioequivalence	Acceptable	13Aug2004	P. Nwakama
Env. Assessment	Acceptable		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The review of this minor amendment was expedited as per Sarah Park.



The Chemistry Review for ANDA 76-702

The Executive Summary

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
The ANDA is 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 and Drug Substance

Oxybutynin Chloride drug substance is a USP product. Per the applicant, any previously released DS remaining in inventory 1 year after its original release date or its retest date will be sampled and tested prior to further use. The DS can be recontrolled up to 5 years from date of receipt or up to the manufacturer's expiration date. Materials will be retested at least once per year up to the noted time limit.

Chemical name: 4-(Diethylamino)-2-butynyl-*alpha*-phenylcyclohexaneglycolate hydrochloride. CAS number: 1508-65-2 and MW: 393.97. It is a white to off-white powder melting between 124 to 129°C. Extensive testing by Mylan via the literature and testing by (b) (4) showed no evidence of polymorphism. This DS is freely soluble in water, very soluble in methanol, slightly soluble in ether, and very slightly soluble in hexane. In spite of it being very soluble in water, Mylan has developed a particle size method and established spec of (b) (4) NMT (b) (4), (b) (4) NMT (b) (4) and (b) (4) NMT (b) (4). The DS is administered as a racemate of R- and S- enantiomers.

This ER drug product is 5mg per dose and is not a USP drug product. The tablets are light green colored, round, biconvex, beveled edged, unscored with **M** over **05** imprinted in black ink on one side and blank on the other side.

The DP is available in bottles of 100 and 500 tablets.

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

The drug product is a tablet that is taken orally.



Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Approvability is based on satisfactory resolution of all deficiencies.

Bioequivalence section is acceptable and labeling section is approvable.

The drug product, Oxybutynin Chloride ER Tablets, 5 mg can be classified as safe and effective in this review.

III. Administrative

A. Reviewer's Signature

 13 Feb 2006

B. Endorsement Block

HFD-630/M. Darj, Ph.D., RC/

HFD-630/D. Gill, Ph.D., TL/

F/T by: EW 2/13/06

V:FIRMSAMMYLAN\LTRS&REV\76702.CR3.DOC

Type of Letter: Approvable

C. CC Block

ANDA 76-702

ANDA DUP

DIV FILE

Field Copy



Chemistry Assessment Section

cc: ANDA 76-702
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/ M. Darj, Ph.D., RC/03Nov2005/ *Wd - IACJ 13 Feb 2006*

HFD-630/D. Gill, Ph.D., TL/11-3-05 *DSG:u 2-13-06*

HFD-617/S. Park, Pharm. D., PM/1/10/06 *Span 2/13/06*

F/T by: EW 2/13/06

V:\FIRMSAMMylan\LTRS&REV\76702.CR3.doc

TYPE of LETTER: APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 076702Orig1s000

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-702
Drug Product Name	Oxybutynin Chloride Extended-Release Tablets
Strength	5 mg
Applicant Name	Mylan Pharmaceuticals Inc.
Address	781 Chestnut Ridge Road, Morgantown, WV 26504
Submission Date(s)	March 28, 2003
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	Yes
File Location	V:\firmsAMMylan\ltrs&rev\76702S.0303

I. Executive Summary

This submission consisted of two (fasting and non-fasting), two-way, crossover, bioequivalence (BE) studies and dissolution data on the 5 mg strength. Both studies are conducted in healthy adult males and females (fasting, n = 60; non-fasting, n = 28). Statistical analyses of the plasma concentration data for oxybutynin and N-desethyloxybutynin in both studies demonstrate bioequivalence.

Oxybutynin results in the fasting study are (point estimate, 90% CI): LAUCT of 0.88, 81.1 – 95.2%; LAUCI 0.88, 81.5 – 95.6%; and LCmax 0.95, 87.5 – 103.1%.

N-desethyloxybutynin results in the fasting study are (point estimate, 90% CI): LAUCT of 0.92, 86.4 – 97.2%; LAUCI 0.93, 87.4 – 98.9%; and LCmax 0.99, 93.9 – 104.9%.

Oxybutynin results in the non-fasting study are (point estimate, 90% CI): LAUCT of 1.05, 91.4 – 120.8%; LAUCI 1.05, 91.8 – 119.0%; and LCmax 1.21, 108.2 – **135.4%**.

N-desethyloxybutynin results in the non-fasting study are (point estimate, 90% CI): LAUCT of 0.95, 85.1 – 105.6%; LAUCI 0.95, 85.3 – 105.3%; and LCmax 1.00, 91.6 – 108.7%. The non-fasting study was performed prior to the implementation of the CDER Guidance for Industry: *Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis and Labeling*.

The firm had initially submitted (3/28/2003) ANDA (#76644) for the 10 mg strength consisting of a replicate fasting and a crossover non-fasting BE studies. The studies were acceptable but the ANDA was incomplete because of the dissolution testing. The 5- and 10-mg strengths have the same inactive ingredients but are not proportionally similar. Both strengths were filed under two separate ANDAs since each ANDA contains Paragraph IV Patent Certification statements and each strength is designated as a RLD.

In this ANDA, the dissolution testing is incomplete, because the firm conducted dissolution in a single medium using the method developed in house. From the bioequivalence point of view, the application is incomplete.

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III. Submission Summary

A. Drug Product Information

Test Product	Oxybutynin Chloride ER Tablets, 5 mg
Reference Product	Ditropan® XL Tablets, 5mg
RLD Manufacturer	Alza Pharmaceuticals
NDA No.	20897
RLD Approval Date	December 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 the 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)
Relevant OGD or DBE History	This is the first ANDA submitted to the Agency for oxybutynin ER tablets, 5 mg. The first ANDA (#76644) for oxybutynin ER tablets, 10 mg also filed by Mylan (3/28/2003) was found incomplete by the DBE (11/26/2003) due to a deficiency in dissolution testing.

The Division has responded to 7 control documents [5 CDs (#99-276, (b) (4) 7/12/99; #00-025, (b) (4) 1/14/2000; #00-496 (b) (4) 11/17/2000 and #00-517 (b) (4) 1/28/2000; #01-297, (b) (4) 5/30/2001) on analyte measurement and the remaining 2 inquiries (#02-059, (b) (4) 1/29/2001 and #02-034, (b) (4) 1/11/2002) on *in vivo* bioequivalence and dissolution requirements].

The Division of Bioequivalence (DBE) recommends the measurement in plasma 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.

The Agency's recommendations included that the metabolite, desethyloxybutynin, should be measured because it is formed as a result of presystemic metabolism and contributes meaningfully to efficacy. This is consistent with the CDER Guidance, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, March 2003. Only parent oxybutynin AUC and Cmax data should be analyzed using a confidence interval approach. The metabolite data from the test product should be evaluated for comparability to the metabolite data from the reference product. Since dissolution testing methods for ER products are generally product-specific, firms should establish dissolution methods as a part of product development process. Therefore, firms should conduct dissolution testing using USP apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75, and 100 rpm) in different dissolution media (e.g. water, 0.1N HCl and buffers at pH 4.5 and 6.8).

Agency Guidance

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

Drug Specific Issues (if any)

Oxybutynin exhibits dose-dependent, linear pharmacokinetics. The R- and S-isomers of oxybutynin exhibit different pharmacokinetic and pharmacodynamic characteristics. Activity resides primarily with the R-isomer, which is the minor enantiomer. There is no evidence of nonlinear absorption for either enantiomer (OCPB Review of NDA 20-897, 12/15/98).

C. Contents of Submission

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

D. Pre-Study Bioanalytical Method Validation

Vol. 1.7; pp. 3577 - 3613		
	Parent	Metabolite
Analyte name	Oxybutynin	N-Desethyloxybutynin (b) (4)
Internal Standard		
Method description	LC/MS	LC/MS
QC range	0.20 to 12.0 ng/mL	0.60 to 36.0 ng/mL
Standard curve range	0.20 to 20.0 ng/mL	0.60 to 60.0 ng/mL
Limit of quantitation	0.20 ng/mL	0.60 ng/mL
Average recovery of Drug (%)	92.64	92.00
Average Recovery of Int. Std (%)	90.51	87.58
Intraday precision range (% CV)	0.42 to 3.48%	1.62 to 3.07%
Intraday accuracy range (%)	93.48 to 101.31%	96.16 to 103.46%
Interday precision range (% CV)	4.55 to 6.08%	2.47 to 8.83%
Interday accuracy range (%)	99.69 to 103.86%	99.91 to 104.27%
Bench-top stability (hrs)	4 hours	4 hours
Stock stability (days)	42 days	31 days
Processed stability (hrs)	96 hours	96 hours
Freeze-thaw stability (cycles)	3	3
Long-term storage stability (days)	203 days	203 days
Dilution integrity	1:1; 101.7% to 111.5%	1:1; 95.5% to 111.9%
Specificity	Yes	Yes
SOPs submitted	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes
20% Chromatograms included (Y/N)	Yes	Yes
Random Selection of Serial Chrom	Yes	Yes

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	OXYB-02116
Study Design	Single-dose, randomized, two-way, crossover
No. of subjects enrolled	60
No. of subjects completing	58
No. of subjects analyzed	58
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 36 Female: 24
Test product	Oxybutynin ER Tablets
Reference product	Ditropan® XL Tablets
Strength tested	5 mg
Dose	4 x 5 mg

Summary of Statistical Analysis Additional Information in Appendix, Table 7 and Table 8		
Parameter	Point Estimate	90% Confidence Interval
Oxybutynin		
AUC _{0-t}	0.88	81.1 – 95.2
AUC _∞	0.88	81.5 – 95.6
C _{max}	0.95	87.5 – 103.1
N-desethylOxybutynin		
AUC _{0-t}	0.92	86.4 – 97.2
AUC _∞	0.93	87.4 – 98.9
C _{max}	0.99	93.9 – 104.9

Reanalysis of Study Samples Additional information in Appendix, Table 6									
Reason why assay was repeated (‘Whole Subject’)	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	
Unacceptable QCs (Subj. 5, 25, 35, 40, 46, 60)	114	114	5.20	5.20	114	114	5.20	5.20	
Failure to thaw Samples (Subj. 15 and 57)	38	38	1.73	1.73	38	38	1.73	1.73	
Total	152	152	6.93	6.93	152	152	6.93	6.93	
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	
Abnormal Internal Standard Response	27	31	2.46	2.83	27	31	2.46	2.83	
Entire Sample Lost During Assay Procedure	4	0	0.36	0	4	0	0.36	0	
Value Above Standard Curve Range	4	14	0.36	1.28	4	14	0.36	1.28	
Total	35	45	3.18	4.11	35	45	3.18	4.11	

Did use of recalculated plasma concentration data change study outcome? N/A
The ‘whole subject’ and ‘single sample’ reassay values were reported as the final results in accordance with SOPs #D416-01 and #D400-02, established priori.

Comments on Fasting Study: The fasting study is acceptable.

2. Single-dose Fed Bioequivalence Study

Study No.	OXYB-02109
Study Design	randomized, two-way, single-dose crossover
No. of subjects enrolled	28
No. of subjects completing	28
No. of subjects analyzed	28
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 16 Female: 12
Test product	Oxybutynin ER Tablets
Reference product	Ditropan® XL Tablets
Strength tested	5 mg
Dose	4 x 5 mg

Summary of Statistical Analysis Additional Information in Appendix, Table 17 and Table 18		
Parameter	Point Estimate	90% Confidence Interval
<u>Oxybutynin</u>		
AUC _{0-t}	1.05	91.4 – 120.8
AUC _∞	1.05	91.8 – 119.0
C _{max}	1.21	108.2 – 135.4
<u>N-desethyloxybutynin</u>		
AUC _{0-t}	0.95	85.1 – 105.6
AUC _∞	0.95	85.3 – 105.3
C _{max}	1.00	91.6 – 108.7

Reanalysis of Study Samples Additional information in Appendix, Table 16								
Reason why assay was repeated (‘Whole Subject’)	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
Sample loss during extraction (Subj. 10 and 15)	38	38	3.58	3.58	38	38	3.58	3.58
Atypical recovery (Subj. 8, 9, 17, and 20)	76	76	7.17	7.17	76	76	7.17	7.17
Failure to thaw Samples (Subj. 23)	19	19	1.79	1.79	19	19	1.79	1.79
Total	133	133	12.54	12.54	133	133	12.54	12.54

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
Abnormal Internal Standard Response	3	5	0.28	0.47	3	5	0.28	0.47
Value Above Standard Curve Range	2	4	0.19	0.38	2	4	0.19	0.38
Total	5	9	0.47	0.85	5	9	0.47	0.85

Did use of recalculated plasma concentration data change study outcome? N/A

The 'whole subject' and 'single sample' reassay values were reported as the final results in accordance with SOPs #D416-01 and #D400-02, established priori.

Comments on fed study: The non-fasting study is acceptable based on the point estimates (ratios of geometric means). The study did not pass the 90% CI criteria for LC_{max} (108.2 – 135.4%) but it was initiated prior to the implementation of the CDER Guidance for Industry: *Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis and Labeling*.

F. Formulation

Location in appendix	Section B, Page 25
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored? (yes or no)	No
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test? (yes or no)	N/A
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

Source of Method Firm
Medium Row 1 (2-hour):
 pH 1.2 Simulated Gastric Fluid w/o Enzyme

Row 2 – 4 (4-, 8- and 16-hour):
 pH 6.8 Simulated Intestinal Fluid w/o Enzyme
Volume (mL) 250 mL
USP Apparatus type Apparatus 3 (Reciprocating Cylinder)
Rotation (rpm) 25 dips per minute
Firm's proposed specifications (b) (4)

FDA Method: USP Apparatus VII, Artificial Gastric Fluid w/o Enzyme (37.0 ± 0.5°C), 50 mL, 30 cycles /min; sampling times: 4, 10 and 24 hours.

FDA-recommended specifications (b) (4)

F2 metric calculated (yes or no) Yes
If no, reason why F2 not calculated N/A
Method is acceptable (yes or no) No

F2 metric, other strengths compared to biostudy strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
N/A (one strength)			

F2 metric, test compared to reference	
Strength	F2 metric
5 mg	44.3

H. Waiver Request(s)

Strengths for which waivers requested N/A
 Regulation cited N/A
 Proportional to strength tested in vivo (yes or no) N/A
 Dissolution is acceptable (yes or no) No
 Waiver granted (yes or no) N/A

I. Deficiency Comment

The firm conducted dissolution testing in one medium only. The firm should be requested to perform dissolution testing using USP Apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75 and 100 rpm) in 900 mL of various dissolution media (e.g. Water, 0.1 N HCl, and buffers at pH 4.5 and 6.8). In addition, the firm should conduct dissolution testing using the USP Apparatus VII, Artificial Gastric Fluid

w/o Enzyme ($37.0 \pm 0.5^{\circ}\text{C}$), 50 mL, 30 cycles /minute, sampling times 2, 4, 10 and 24 hours.

J. Recommendations

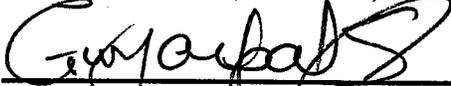
1. The single-dose, fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 5 mg, lot # R1K3865, comparing it to Ditropan® XL Tablets, 5 mg, lot # 0200368 manufactured by Alza Corporation is acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 5 mg, are bioequivalent to the reference product, Ditropan® XL Tablets, 5 mg, manufactured by Alza Corporation.
2. The single-dose, non-fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 5 mg, lot # R1K3865, comparing it to Ditropan® XL Tablets, 10 mg, lot # 0200368 manufactured by Alza Corporation is acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 5 mg, are bioequivalent to the reference product, Ditropan® XL Tablets, 5 mg, manufactured by Alza Corporation.
3. The *in vitro* dissolution testing conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 5 mg, is incomplete because of the deficiency comment mentioned above.



12/11/2003

Patrick Nwakama, Pharm.D., Branch III,

Date signed



12-12-03

Gur Jai Pal Singh, Ph.D., Branch III,

Date signed



12/12/03

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

for

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	OXYB-02116
Study Title	Single-Dose, Fasting Bioequivalence Study
Clinical Site	PRACS Institute, Ltd., Fargo, North Dakota
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	Period 1: December 6 – 10, 2002; Period 2: December 21-24, 2002
Analytical Site	Mylan Pharmaceuticals Inc., Morgantown, West Virginia
Analytical Director	(b) (6) Ph.D.
Analysis Dates	January 24 – February 27, 2003
Storage Period	82 days (long-term stability duration: 203 days)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Oxybutynin ER Tablets	Ditropan® XL Tablets
Manufacturer	Mylan Pharmaceuticals	Alza Corporation
Batch/Lot No.	R1K3865	0200368
Manufacture Date	10/09/02	N/A
Expiration Date	N/A	11/03
Strength	5 mg	5 mg
Dosage Form	Tablets	Tablets
Batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	102.9%	102.6%
Content Uniformity	102.6% (RSD 1.2%)	100.2% (RSD 2.4%)
Formulation	See Appendix Section B	
Dose Administered	4 x 5 mg	4 x 5 mg
Route of Administration		Oral
No. of Sequences	2	
No. of Periods	2	
No. of Treatments	2	
No. of Groups	1	
Washout Period	14 days	
Randomization Scheme	AB: 4,5,6,7,10,11,13,15,18,19,21,22,27,29,31,32,36,37 38, 40,41,43,44,46,49,51,53,54,57,58,59,62 BA: 1,2,3,8,9,12,14,16,17,20,23,24,25,26,28,30,33,34, 35, 39,42,45,47,48,50,52,55,56,60,61,63,64	
Blood Sampling Times	0,1,2,4,5,6,8,10,12,14,16,18,21,24,28,36,48,60 and 72 h	
Blood Volume Collected/Sample	7 mL	
Blood Sample Processing/Storage	- 70°C ± 15°C	
IRB Approval	Yes	

Informed Consent	Yes
Subject Demographics	See Table 1
Length of Fasting	10 hours
Length of Confinement	34 hours
Safety Monitoring	Subjects were monitored throughout the confinement portion of the study. Vital signs were taken prior to dosing and as scheduled post-dosing.

Table 1 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.00	Male	60.0	Caucasian	93.3
Mean	29.1	Mean	63.9	18-40	80.0	Female	40.0	Afr.Amer.	3.3
SD	12.3	SD	7.2	41-64	20.0			Hispanic	0.0
Range	18 - 76	Range	49 - 79.0	65-75	0.00			Asian	1.7
				>75	0.00			Other	1.7

Study Results

Table 2 Dropout Information

Subject No	Subject #13	Subject #20
Reason	Voluntary Withdrawal	Illness
Period	Prior to Period II	Prior to Period II
Replacement	No	No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Vomiting		2
Headache	2	1
Cough		1
Nausea		1
Dizziness	3	1
Diarrhea		1
Total:	5	7

Comments: (on adverse events)

Compared with the reference product, there were a slightly lower number of adverse events with the test product. All events were reported as mild in severity.

Table 4 Protocol Deviations

There were 29 deviations (16 sampling time delays \leq 1 hour and 13 'no show' for blood draws). Actual sampling times were used for statistical and PK analyses. Three subjects (#19, #55 and

#58) took analgesics for headache, within 14 days of dosing in Period I. The deviations are not significant to compromise the integrity of the study.

Table 5 Assay Validation – Within Study

Vol. 1.2, pp 267 – 268; Vol. 1.3, pp 495 – 531		
	Parent	Metabolite
QC Conc. (ng/mL)	0.3 – 12.0 ng/mL	0.9 – 36.0 ng/mL
Inter day Precision (% CV)	3.1 – 17.3 %	3.5 – 8.2%
Inter day Accuracy (%)	94.2 – 102.8%	99.1 – 103.8%
Cal. Standards Conc. (ng/mL)	0.20 – 20.0 ng/mL	0.60 – 60.0 ng/mL
Inter day Precision (% CV)	1.6 – 5.5%	2.4 – 5.9%
Inter day Accuracy (%)	98.5 – 101.2%	97.7 – 100.7%
Linearity Range	0.99613	0.99510

Chromatograms: Any interfering peaks? None

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
D-400-02	8/24/99	Reassay or Reinjection of Clinical Samples
D-416-01	6/18/02	Reassay of Whole Subjects

Comments on repeat assays:

- Did recalculation of plasma concentrations change the study outcome? No
- Does the reviewer agree with the outcome of the repeat assays? Yes
- Provide any other comments about the repeat assays: None.

Comments on Within-Study Validation: The within study validation is complete.

Conclusion: Analytical method is acceptable.

Table 7 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 10 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	% CV	Mean	% CV	
Oxybutynin						
AUC _{0-t}	ng*hr/mL	110.77	58.48	122.41	57.53	0.90
AUC _∞	ng*hr/mL	120.56	57.20	130.61	55.99	0.92
C _{max}	ng/mL	5.67	52.14	5.99	63.84	0.95
T _{max}	hr	14.52	57.51	10.48	32.42	1.38
T _{1/2}	hr	13.48	51.82	14.82	45.51	0.91
kel	hr ⁻¹	0.06	44.82	0.06	44.83	1.13
N-desethyl Oxybutynin						
AUC _{0-t}	ng*hr/mL	552.46	44.52	595.45	45.29	0.93
AUC _∞	ng*hr/mL	581.77	42.51	614.38	44.31	0.95
C _{max}	ng/mL	32.06	34.56	32.43	41.50	0.99
T _{max}	hr	6.57	83.58	8.76	45.63	0.75
T _{1/2}	hr	9.32	63.15	10.20	52.01	0.91
kel	hr ⁻¹	0.10	49.30	0.09	53.35	1.13

Table 8 Least Square Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
Oxybutynin				
AUC _{0-t}	96.70	110.04	0.88	81.1 – 95.2
AUC _∞	103.93	117.71	0.88	81.5 – 95.6
C _{max}	5.06	5.33	0.95	87.5 – 103.1
N-desethyl Oxybutynin				
AUC _{0-t}	508.48	554.85	0.92	86.4 – 97.2
AUC _∞	533.18	573.59	0.93	87.4 – 98.9
C _{max}	30.36	30.58	0.99	93.9 – 104.9

Table 9 Additional Study Information:

Oxybutynin

Root mean square error, AUC _{0-72h}	0.258	
Root mean square error, AUC _∞	0.257	
Root mean square error, C _{max}	0.262	
mean ratio AUC _{0-t} /AUC _∞	T = 0.99	R = 0.94
Range of values, ratio AUC _{0-t} /AUC _∞	T = 0.73 – 0.99	R = 0.79 – 0.99

N-desethyl Oxybutynin

Root mean square error, AUC _{0-72h}	0.191	
Root mean square error, AUC _∞	0.199	
Root mean square error, C _{max}	0.178	
mean ratio AUC _{0-t} /AUC _∞	T = 0.99	R = 0.99
Range of values, ratio AUC _{0-t} /AUC _∞	T = 0.52 – 0.99	R = 0.78 – 0.99

Comments: (on pharmacokinetic analysis)

- Ke and AUC_i were determined for all subjects.
- Measurable drug concentrations at 0 hr: None
- First measurable drug concentration at C_{max}: None
- Were there statistically significant sequence or period effects? No
- The 90% confidence intervals are within the acceptable limits of 80-125% for the ln-transformed parameters of AUC_t, AUC_i, C_{max}.
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.

Conclusion: The single-dose fasting bioequivalence study is acceptable.

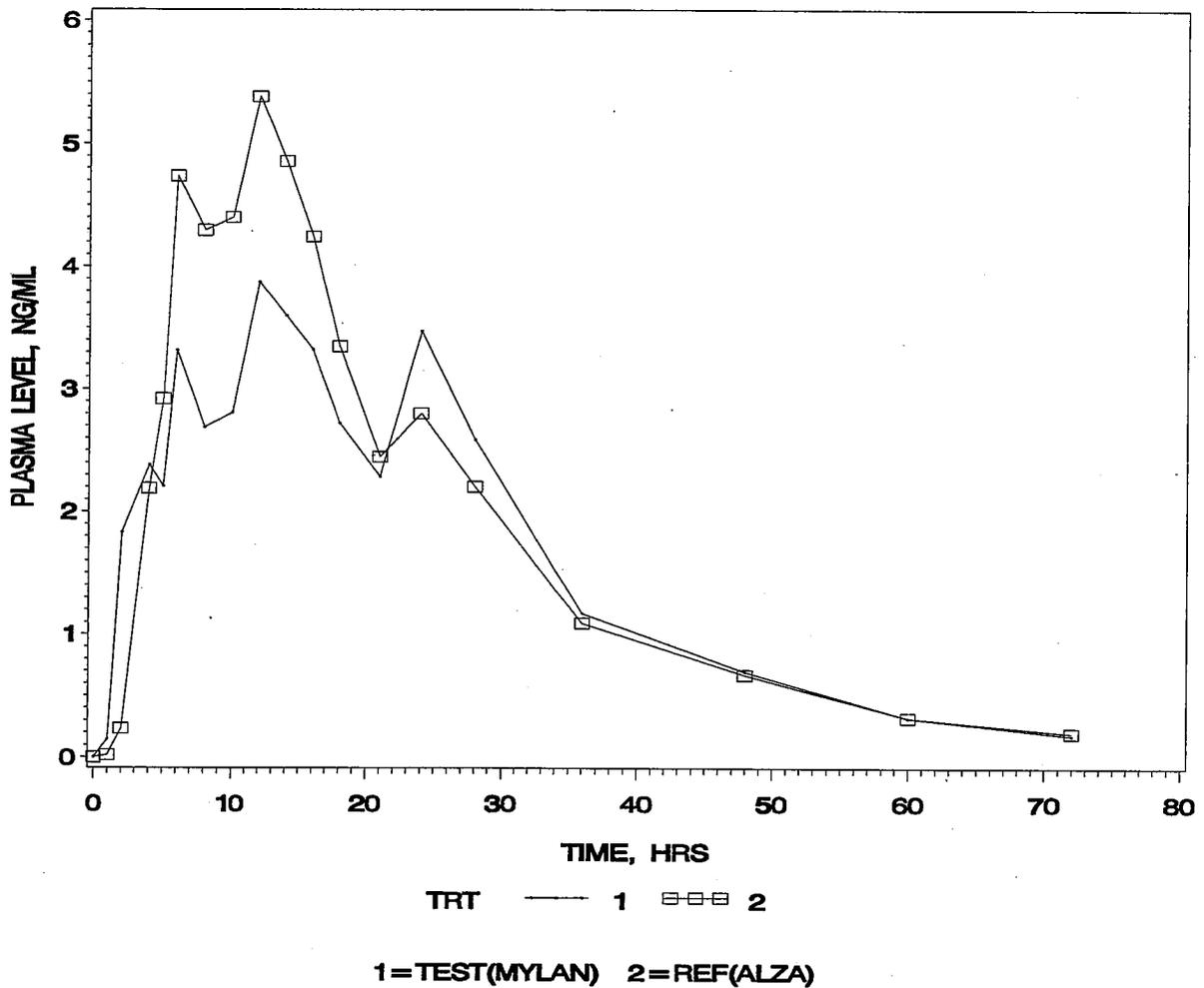
Table 10 Mean Plasma Oxybutynin Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study

Time (hr)	Test (n = 58)		Reference (n = 58)		T/R
	Mean Conc.	% CV	Mean Conc.	% CV	
0	0.00	.	0.00	.	.
1	0.14	274.82	0.02	623.95	8.35
2	1.83	131.68	0.23	111.79	7.85
4	2.38	53.50	2.19	80.04	1.09
5	2.21	51.89	2.92	101.17	0.76
6	3.32	51.12	4.74	55.92	0.70
8	2.69	57.14	4.30	70.80	0.63
10	2.81	73.82	4.40	77.69	0.64
12	3.87	72.73	5.38	69.67	0.72
14	3.60	73.17	4.86	80.09	0.74
16	3.32	77.44	4.24	70.03	0.78
18	2.72	93.13	3.35	72.06	0.81
21	2.28	93.53	2.45	65.97	0.93
24	3.47	76.79	2.80	50.54	1.24
28	2.59	64.85	2.20	52.52	1.17
36	1.17	67.11	1.09	54.24	1.07
48	0.70	89.76	0.67	64.60	1.04
60	0.32	101.11	0.32	94.83	0.99
72	0.18	135.66	0.20	129.55	0.91

Figure 1 Mean Plasma Oxybutynin Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study

PLASMA OXYBUTYNIN LEVELS

OXYBUTYNIN ER TABLETS, 5 MG, ANDA #76-702
UNDER FASTING CONDITIONS
DOSE=4 X 5 MG



2. Single-dose Fed Bioequivalence Study

Study Information	
Study Number	OXYB-02117
Study Title	Single-Dose, Non-Fasting Bioequivalence Study
Clinical Site	PRACS Institute, Ltd., Fargo, North Dakota
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	Period I: December 14 - 17, 2002 Period II: December 28 - 31, 2002
Analytical Site	Mylan Pharmaceuticals Inc., Morgantown, West Virginia
Analytical Director	(b) (6) Ph.D.
Analysis Dates	December 14, 2002 – March 2, 2003
Storage Period	78 days (long-term stability: 203 days)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Oxybutynin ER Tablets	Ditropan® XL Tablets
Manufacturer	Mylan Pharmaceuticals	Alza Corporation
Batch/Lot No.	R1K3865	0200368
Manufacture Date	10/09/02	N/A
Expiration Date	N/A	11/03
Strength	5 mg	5 mg
Dosage Form	Tablets	Tablets
Batch Size	(b) (4)	N/A
Potency	102.9%	102.6%
Content Uniformity	102.6% (RSD 1.2%)	100.2% (RSD 2.4%)
Formulation	See Appendix Section B	
Dose Administered	4 x 5 mg	4 x 5 mg
Route of Administration	Orally (after administration of the OGD-recommended standardized breakfast)	
No. of Sequences	2	
No. of Periods	2	
No. of Treatments	2	
No. of Groups	1	
Washout Period	7 days	
Randomization Scheme	AB: 1,2,6,7,11,12,13,14,18,20,23,24,25,28 BA: 3,4,5,8,9,10,15,16,17,19,21,22,26,27	
Blood Sampling Times	0,1,2,4,5,6,8,10,12,14,16,18,21,24,28,36,48,60 and 72 h	
Blood Volume Collected/Sample	1 x 7 mL	
Blood Sample Processing/Storage	- 70°C ± 15°C	
IRB Approval	Yes	
Informed Consent	Yes	
Subject Demographics	See Table 11	
Length of Fasting	10 hours	

Length of Confinement 34 hours
Safety Monitoring Same as Fasting Study

Table 11 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.00	Male	57.1	Caucasian	96.4
Mean	29.4	Mean	76.6	18-40	78.6	Female	42.9	Afr.Amer.	0.00
SD	11.5	SD	12.1	41-64	21.4			Hispanic	0.00
Range	19 - 60	Range	55.4- 98.5	65-75	0.00			Asian	3.6
				>75	0.00			Other	0.00

Study Results

Table 12 Dropout Information - No dropouts

Table 13 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Headache	0	5
Dry Mouth	0	1
Pharyngitis	1	2
Total:	1	8

Comments: (on adverse events)

Compared with the test product, there were 8 times more adverse events with the reference product but all events were reported as mild in severity.

Table 14 Protocol Deviations

There were 13 deviations (9 sampling time delays \leq 1 hour and 4 'no show' for blood draws). Actual sampling times were used for statistical and PK analyses.

Three subjects (#4, #14 and #21) took topical antifungal, cough preparations, and simple analgesics during the course of the study. The deviations are not significant to compromise the integrity of the study.

Table 15 Assay Validation – Within Study

Vol. 1.7: pp 3152 – 3153, 3316 – 3340		
	Parent	Metabolite
QC Conc. (ng/mL)	0.3 – 12.0 ng/mL	0.9 – 36.0 ng/mL
Inter day Precision (%CV)	0.3 – 7.3 %	1.0 – 7.1%
Inter day Accuracy (%)	100.5 – 112.2%	103.2 – 118.8%
Cal. Standards Conc. (ng/mL)	0.20 – 20.0 ng/mL	0.60 – 60.0 ng/mL
Inter day Precision (%CV)	2.9 – 6.7%	3.1 – 5.7%
Inter day Accuracy (%)	97.3 – 103.5%	98.2 – 101.9%
Linearity Range	0.99353	0.99173

Chromatograms: Any interfering peaks? None

Table 16 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
D-400-02	8/24/99	Reassay or Reinjection of Clinical Samples
D-416-01	6/18/02	Reassay of Whole Subjects

Comments on repeat assays:

- Did recalculation of plasma concentrations change the study outcome? No
- Does the reviewer agree with the outcome of the repeat assays? Yes
- Provide any other comments about the repeat assays: None.

There were no pharmacokinetic repeats reported.

Comments on Within-Study Validation: The within-study validation is acceptable.

Conclusion: Analytical method is acceptable.

Table 17 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 20 and Figure 2

Oxybutynin						
Parameter	Units	Test		Reference		T/R
		Mean	% CV	Mean	% CV	
AUC _{0-t}	ng*hr/mL	122.51	59.44	109.87	51.76	1.12
AUC _∞	ng*hr/mL	130.16	59.17	118.51	53.44	1.10
C _{max}	ng/mL	6.60	58.11	5.16	49.78	1.28
T _{max}	hr	13.04	59.99	11.00	56.09	1.19
T _{1/2}	hr	13.35	30.08	14.30	38.88	0.93
kel	hr ⁻¹	0.06	36.21	0.06	52.94	0.99

N-desethyloxybutynin						
Parameter	Units	Test		Reference		T/R
		Mean	% CV	Mean	% CV	
AUC _{0-t}	ng*hr/mL	608.67	64.81	622.19	67.69	0.98
AUC _∞	ng*hr/mL	629.35	66.64	650.10	73.58	0.97
C _{max}	ng/mL	31.20	42.51	31.23	45.94	1.00
T _{max}	hr	10.18	60.62	8.46	34.85	1.20
T _{1/2}	hr	8.75	41.96	9.80	56.49	0.89
kel	hr ⁻¹	0.09	42.80	0.09	49.41	1.03

Table 18 Geometric Means and 90% Confidence Intervals

Oxybutynin				
Parameter	Test	Reference	T/R	90% CI
AUC _{0-t}	102.29	97.36	1.05	91.4 – 120.8
AUC _∞	109.48	104.75	1.05	91.8 – 119.0
C _{max}	5.62	4.64	1.21	108.2 – 135.4

N-desethyloxybutynin				
Parameter	Test	Reference	T/R	90% CI
AUC _{0-t}	517.48	545.82	0.95	85.1 – 105.6
AUC _∞	534.35	563.88	0.95	85.3 – 105.3
C _{max}	28.80	28.87	1.00	91.6 – 108.7

Table 19 Additional Study Information

Oxybutynin		
Root mean square error, AUC _{0-t}	0.307	
Root mean square error, AUC _∞	0.285	
Root mean square error, C _{max}	0.245	
mean ratio AUC _{0-t} /AUC _∞	T = 0.94	R = 0.93
Range of values, ratio AUC _{0-t} /AUC _∞	T = 0.82 – 0.97	R = 0.86 – 0.97

N-desethyloxybutynin		
Root mean square error, AUC _{0-t}	0.237	
Root mean square error, AUC _∞	0.232	
Root mean square error, C _{max}	0.187	
mean ratio AUC _{0-t} /AUC _∞	T = 0.97	R = 0.97
Range of values, ratio AUC _{0-t} /AUC _∞	T = 0.92 – 0.99	R = 0.88 – 0.99

Comments: (on pharmacokinetic analysis)

- Ke and AUC_i were determined for all subjects.
- Measurable drug concentrations at 0 hr: None
- First measurable drug concentration at C_{max}: None
- Were there statistically significant sequence or period effects? No
- The 90% confidence intervals are within the acceptable limits of 80-125% for the LAUCT and LAUCI. However, the 90% CI for LC_{max} are not within the acceptable limits.
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with those of the firm.

Conclusion: The single-dose fed bioequivalence study is acceptable since the point estimates are within the acceptable limits of 0.80 – 1.25.

Table 20 Mean Oxybutynin Plasma Concentrations (ng/mL), Single-Dose Fed Bioequivalence Study

Time (hr)	Test (n = 28)		Reference (n= 28)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
1	0.00	.	0.00	.	.
2	0.01	529.15	0.23	118.00	0.04
4	0.33	187.21	2.54	60.19	0.13
5	1.65	113.11	3.36	55.48	0.49
6	4.66	78.32	4.59	56.09	1.01
8	2.94	61.64	3.29	50.57	0.89
10	2.74	89.31	3.47	58.81	0.79
12	4.12	77.19	4.05	49.59	1.02
14	3.82	75.37	3.50	46.35	1.09
16	3.97	93.78	3.66	48.51	1.08
18	2.87	75.71	2.78	50.54	1.04
21	2.64	62.02	2.33	56.13	1.13
24	3.75	80.08	2.55	59.43	1.47
28	2.98	66.33	2.08	53.08	1.43
36	1.58	74.05	1.11	59.01	1.42
48	0.85	79.91	0.67	78.51	1.26
60	0.46	92.40	0.37	97.06	1.24
72	0.24	117.38	0.21	140.96	1.15

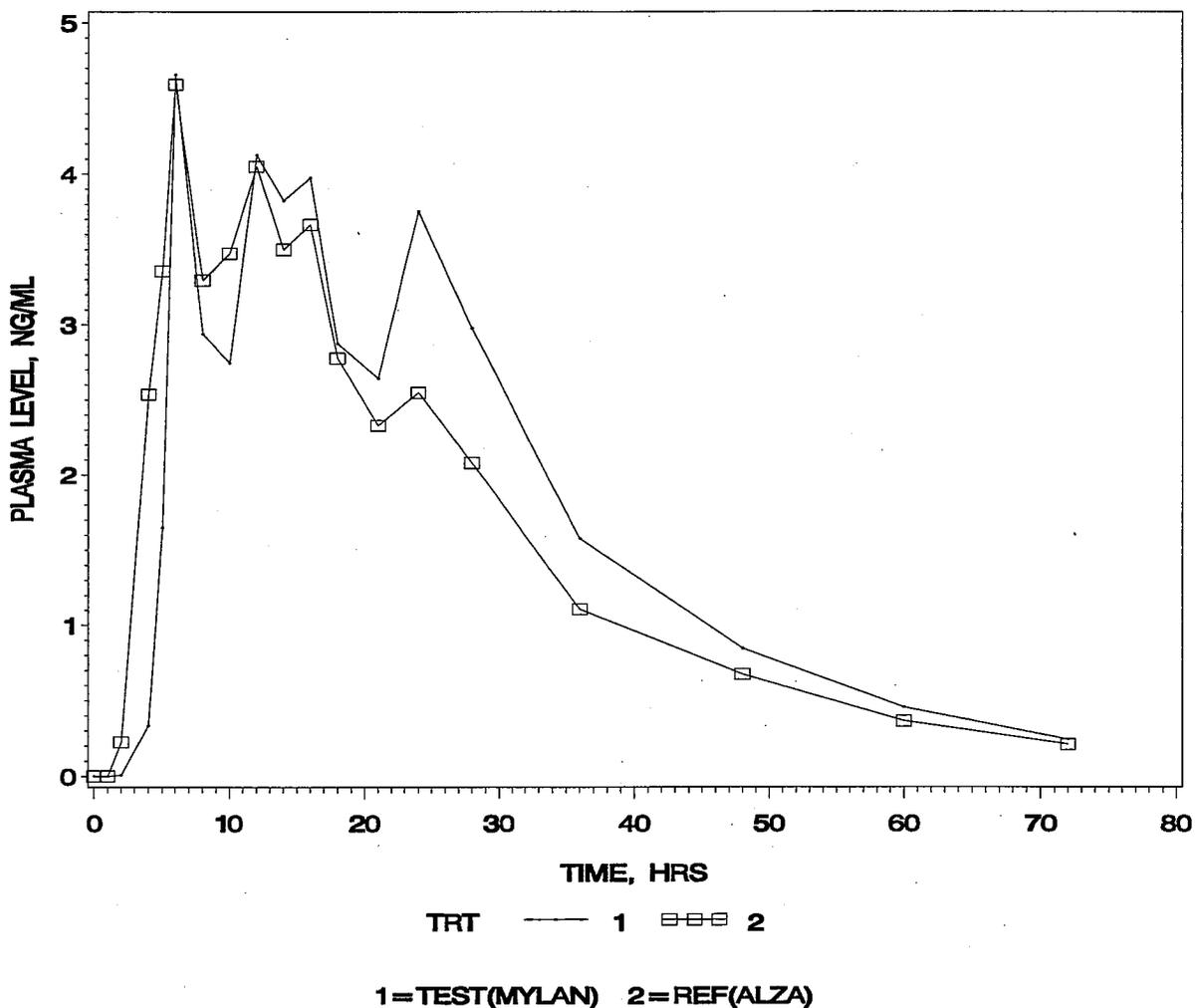
Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

PLASMA OXYBUTYNIN LEVELS

OXYBUTYNIN ER TABLETS, 5 MG, ANDA #76-702

UNDER NON-FASTING CONDITIONS

DOSE=4 X 5 MG



B. Formulation Data

Ingredients	(mg) / tablet	% w/w
Oxybutynin Chloride	5.00	2.37
Povidone, USP		(b) (4)
Dibasic Calcium Phosphate USP, Anhydrous		
Hypromellose, USP		
(b) (4)		
Magnesium Stearate, NF		
Colloidal Silicon Dioxide, NF		
(b) (4)		
Methacrylic Acid Copolymer Dispersion, NF		
Talc USP, (b) (4)		
Triethyl Citrate, NF		
Polysorbate 80, NF		
Sodium Hydroxide, NF		
(b) (4)		
Imprinting Ink (b) (4)		
Total (b) (4) Weight		210.5

C. Dissolution Data

Table 1

Sampling Time (hours)	Oxybutynin ER Tablets 5 mg Lot No. R1K3865			Ditropan® XL Tablets 5 mg Lot No. 0021413		
	Mean	RSD	Range ^{(b) (4)}	Mean	RSD	Range ^{(b) (4)}
2	0	188.8	[REDACTED]	2	21.7	[REDACTED]
4	18	5.6		11	21.8	
8	51	4.7		35	12.2	
16	102	2.0		83	8.1	

Figure 3 Dissolution Profiles (*optional*)

D. Consult Reviews

None

E. SAS Output

	Parent	Metabolite
Fasting	 OXYBUTYNIN7670 2fast_output.txt	 DESETHYLoxybuty nin76702fast_outp
Non-Fasting	 OXYBUTYNIN7670 2fed_output.txt	 DESETHYLoxybuty nin76702fed_outp

F. Additional Attachments (N/A)

BIOEQUIVALENCE DEFICIENCY COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 76-702

APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Oxybutynin Chloride ER Tablets, 5 mg

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

You have conducted dissolution testing in one medium only. Please perform dissolution testing using USP Apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75 and 100 rpm) in 900 mL of various dissolution media (e.g. Water, 0.1 N HCl, and buffers at pH 4.5 and 6.8). It may not be necessary to use the higher paddle speeds with Apparatus II if 50 rpm is adequately discriminatory. In addition, please conduct dissolution testing using USP Apparatus VII, Artificial Gastric Fluid w/o Enzyme ($37.0 \pm 0.5^{\circ}\text{C}$), 50 mL, 30 cycles /minute. We recommend sampling times of 1, 2, 4, 10 and 24 hours, or until at least 80% of the drug is dissolved.

Sincerely yours,

for *(Barbara M Savit)*
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

CC: ANDA 76-702
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P.Nwakama

12/11/2003

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Printed in final on //

Endorsements: (Final with Dates)

HFD-658/ P.Nwakama

HFD-658/ GJP Singh

HFD-650/ S.Mazzella

HFD-650/ D. Conner

dates 12-12-03

Brud 12/2/03

for

BIOEQUIVALENCE - Incomplete Submission Date: March 28, 2003

1. **FASTING STUDY (STF)** Strengths: 5 mg
Clinical: PRACS Institute, Fargo Outcome: ~~AC~~ IC
Analytical: Mylan Pharmaceuticals
2. **FOOD STUDY (STP)** Strength: 5 mg
Clinical: PRACS Institute, Fargo Outcome: ~~AC~~ IC
Analytical: Mylan Pharmaceuticals
- ~~**Dissolution (DIS)** Strength: 5 mg
Outcome: IC~~

Outcome Decisions: IC - Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-702
Drug Product Name	Oxybutynin Chloride Extended-Release Tablets
Strength	5 mg
Applicant Name	Mylan Pharmaceuticals Inc.
Address	781 Chestnut Ridge Road, Morgantown, WV 26504
Submission Date(s)	March 28, 2003
Amendment Date(s)	March 17, 2004
Reviewer	Patrick Nwakama
First Generic	Yes
File Location	V:\firmsAM\Mylan\ltrs&rev\76702a0304

I. Executive Summary

Mylan Pharmaceuticals previously submitted fasting and non-fasting bioequivalence (BE) studies for the 5 mg tablet on March 17, 2003. Both BE studies were found acceptable based on the following results.

Oxybutynin results in the fasting study were (point estimate, 90% CI): LAUCT of 0.88, 81.1 – 95.2%; LAUCI 0.88, 81.5 – 95.6%; and LCmax 0.95, 87.5 – 103.1%. N-desethyloxybutynin results in the fasting study were (point estimate, 90% CI): LAUCT of 0.92, 86.4 – 97.2%; LAUCI 0.93, 87.4 – 98.9%; and LCmax 0.99, 93.9 – 104.9%. Oxybutynin results in the non-fasting study were (point estimate, 90% CI): LAUCT of 1.05, 91.4 – 120.8%; LAUCI 1.05, 91.8 – 119.0%; and LCmax 1.21, 108.2 – 135.4%. N-desethyloxybutynin results in the non-fasting study were (point estimate, 90% CI): LAUCT of 0.95, 85.1 – 105.6%; LAUCI 0.95, 85.3 – 105.3%; and LCmax 1.00, 91.6 – 108.7%. The non-fasting study was performed prior to the implementation of the CDER Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis and Labeling. The study meets the acceptance criteria in place at the time of the study was conducted.

The dissolution testing was found incomplete because only one medium (simulated gastric and intestinal fluids without enzyme) was employed using an in-house dissolution method. In this amendment, the firm has submitted additional dissolution data using the methods requested by the DBE. The test product now meets the FDA dissolution specifications. However, the application is incomplete pending the firm's acceptance of the DBE recommended dissolution method and specification.

Background:

January 21, 2003 - Mylan Pharmaceuticals submitted original ANDA (76644) containing two BE (fasting and non-fasting) studies for its Oxybutynin ER 10 mg Tablets. The BE studies were found acceptable. The dissolution testing was not conducted in at least three dissolution media as requested for modified release drug products. Therefore, the application was found incomplete. A deficiency letter was sent on December 8, 2003, requesting the firm to conduct additional dissolution testing. On February 18, 2004, the firm submitted additional dissolution data as an amendment to the ANDA. The test product now found to meet the FDA dissolution specifications. However, the application is incomplete pending the firm's acceptance of the DBE recommended dissolution method and specification.

March 28, 2003 - Mylan Pharmaceuticals submitted another ANDA (76702) containing two BE (fasting and non-fasting) studies for its Oxybutynin ER 5 mg Tablets. The BE studies were found acceptable. The dissolution testing was not conducted in at least three dissolution media as required for modified release drug products. Therefore, the application was found incomplete. A deficiency letter was sent on December 12, 2003, requesting the firm to conduct additional dissolution testing. In the current submission (3/17/2004), the firm submitted additional dissolution data as an amendment to the ANDA.

FDA Deficiency Comment:

You have conducted dissolution testing only in one medium. Please perform dissolution testing using USP Apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75 and 100 rpm) in 900 mL of various dissolution media (e.g. Water, 0.1 N HCl, and buffers at pH 4.5 and 6.8). It may not be necessary to use the higher paddle speeds with Apparatus II if 50 rpm is adequately discriminating. In addition, please conduct dissolution testing using USP Apparatus VII, Artificial Gastric Fluid w/o Enzyme (37.0 ± 0.5°C), 50 mL, 30 cycles /minute. We recommend sampling times 1, 2, 4, 10 and 24 hours, or until at least 80% of the drug is dissolved.

Firm's Response:

The firm did not conduct dissolution testing with water, 0.1 N HCl, and pH 4.5 buffer on Oxybutynin chloride ER Tablets, 5 mg since, as previously demonstrated with the 10 mg strength, pH 6.8 buffer is the only medium in which the test product exhibited drug release. The firm felt this was expected since the test products (5mg and 10 mg) utilizes identical enteric coating that does not facilitate drug release at pH values less than 5.5. The firm conducted dissolution testing with paddle at 50, 75 and 100 rpm; and basket at 100 rpm (Table I). The firm did not conduct dissolution testing using USP Apparatus VII, Artificial Gastric Fluid w/o Enzyme (37.0 ± 0.5°C), 50 mL, 30 cycles /minute because the test product will not exhibit drug release at pH 1.2.

Mylan claims that dissolution of its test product occurs only in pH 6.8 buffer with paddle or basket because of its unique coating and release mechanism. However, the firm did not propose specifications for percent dissolution.

Reviewer's Comments:

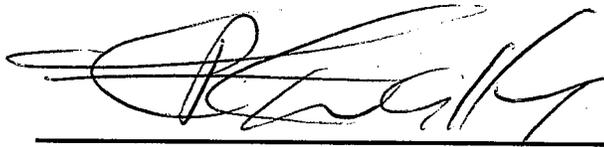
This reviewer and Dr. Tran, the DBE dissolution focal point, agree that the test product exhibited the best dissolution profile in 900 mL phosphate buffer pH 6.8, Basket at 100 rpm (see e-mail attachment).

Recommendations

1. The single-dose, fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 5 mg, lot # R1K3865, comparing it to Ditropan® XL Tablets, 5 mg, lot # 0200368 manufactured by Alza Corporation was previously found acceptable to the Division of Bioequivalence. The study demonstrated that under fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 5 mg, were bioequivalent to the reference product, Ditropan® XL Tablets, 5 mg, manufactured by Alza Corporation.
2. The single-dose, non-fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 5 mg, lot # R1K3865, comparing it to Ditropan® XL Tablets, 5 mg, lot # 0200368 manufactured by Alza Corporation was previously found acceptable to the Division of Bioequivalence. The study demonstrated that under non-fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 5 mg, were bioequivalent to the reference product, Ditropan® XL Tablets, 5 mg, manufactured by Alza Corporation.
3. The *in vitro* dissolution testing conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 5 mg, is now acceptable.

The dissolution testing should be conducted in 900 mL, pH 6.8 phosphate buffer using USP Apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

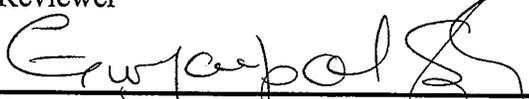
1 hr: NMT	(b) (4)
4 hrs:	(b) (4)
10 hrs	(b) (4)
24 hrs: NLT	(b) (4)



4/5/2004

Patrick Nwakama, Pharm.D., Branch III,
Reviewer

Date signed



4-5-04

Gur Jai Pal Singh, Ph.D., Branch III,
Team Leader

Date signed



4/6/04

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

Table I

***In vitro* Dissolution Testing**

Sampling Times (HOURS)	Test Product: Oxybutynin ER Lot Number: R1K3865 Strength: 5 mg			Reference Product: Ditropan® XL Lot Number: 0332168 Strength: 5 mg		
	MEAN	RANGE	%CV	MEAN	RANGE	%CV
pH 6.8 Phosphate buffer, 900 mL, Basket @ 100 rpm						
1	5	(b) (4)	6.3	0	0	0
2	9	(b) (4)	6.8	0	0	0
4	17	(b) (4)	4.7	10	(b) (4)	19.3
10	41	(b) (4)	3.1	43	(b) (4)	10.3
24	84	(b) (4)	4.5	85	(b) (4)	2.6
pH 6.8 Phosphate buffer, 900 mL, Paddle @ 50 rpm						
1	4	(b) (4)	27.8	0	0	0.0
2	7	(b) (4)	15.5	0	0	0.0
4	13	(b) (4)	16.5	9	(b) (4)	25.5
10	31	(b) (4)	6.9	47	(b) (4)	12.1
24	62	(b) (4)	6.1	89	(b) (4)	3.1
pH 6.8 Phosphate buffer, 900 mL, Paddle @ 75 rpm						
1	2	(b) (4)	9	0	0	0.0
2	6	(b) (4)	5.8	0	0	0.0
4	12	(b) (4)	4.7	10	(b) (4)	28.8
10	31	(b) (4)	5.2	46	(b) (4)	11.7
24	70	(b) (4)	5.4	88	(b) (4)	2.4
pH 6.8 Phosphate buffer, 900 mL, Paddle @ 100 rpm						
1	4	(b) (4)	13.9	0	0	0
2	7	(b) (4)	12.7	0	0	0
4	14	(b) (4)	8.1	9	(b) (4)	24.1
10	33	(b) (4)	5.7	43	(b) (4)	9.2
24	68	(b) (4)	4.1	86	(b) (4)	2.9

E-mail Attachment

-----Original Message-----

From: Tran, Nhan L
Sent: Monday, March 01, 2004 9:27 AM
To: Nwakama, Patrick E
Cc: Singh, Gur J P
Subject: DISSOLUTION METHOD FOR OXYBUTYNIN EXTENDED-RELEASE TABLETS

The firm provided enough information for us to make an informed recommendation. Results submitted by the firm indicated that the following method and conditions can be adopted for Mylan's Oxybutynin ER tablets:

USP Apparatus I (Basket) at 100 RPM
900 ml phosphate buffer pH 6.8

Tolerances:

1 hr: NMT (b) (4)

4 hrs: (b) (4)

10 hrs: (b) (4)

24 hrs: NLT (b) (4)

Remember, this is only a suggestion. Please discuss this with your TL for his opinion and/or concurrence.

Thanks,

ANDA #76-702
Oxybutynin Chloride ER Tablets

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 76-702

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Oxybutynin Chloride ER Tablets, 5 mg

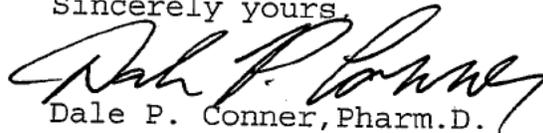
The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiency has been identified.

Please acknowledge that you have accepted the following dissolution method and specifications.

The dissolution testing should be conducted in 900 mL of pH 6.8 Phosphate Buffer using USP apparatus I (Basket) at 100 rpm. The test products should meet the following specifications:

1 hr: NMT (b) (4)
4 hrs: (b) (4)
10 hrs: (b) (4)
24 hrs: NLT (b) (4)

Sincerely yours,



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

ANDA #76-702
Oxybutynin Chloride ER Tablets

CC: ANDA 76-702
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P.Nwakama

pc 4/5/2004

V:\FIRMSAM\Mylan\LTRS&REV\76-702a0304.doc
Printed in final on 3//2004

Endorsements: (Final with Dates)

HFD-658/ P.Nwakama *pc*
HFD-658/ GJP Singh *pc 4-5-04*
HFD-650/ S.Mazzella
HFD-650/ D. Conner *pc 4/6/04*

BIOEQUIVALENCE - DEFICIENCY Submission Date: March 28, 2003 ^{17, 2004}

STUDY AMENDMENT (STA)
Clinical: Kendle International Inc.
Analytical: Mylan Pharmaceuticals

Strength: 5 mg
Outcome: IC

Outcome Decisions: IC - Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76702
Drug Product Name	Oxybutynin Chloride Extended-Release Tablets
Strength	5 mg
Applicant Name	Mylan Pharmaceuticals Inc.
Address	781 Chestnut Ridge Road, Morgantown, WV 26504
Submission Date(s)	June 9, 2004
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	Yes
File Location	V:\firmsAMM\mylan\ltrs&rev\76702a0604

I. Executive Summary

This is a review of a study amendment. Mylan Pharmaceuticals previously submitted acceptable fasting and non-fasting bioequivalence (BE) studies for the 5 mg tablet on March 28, 2003. The application was found incomplete because the dissolution testing was conducted using one medium only (Apparatus 3 [Reciprocating Cylinder] in simulated gastric and intestinal fluids without enzyme). At the request of DBE, the firm submitted an amendment (3/17/2004) containing dissolution profile data in various media. Subsequently, the DBE recommended the following dissolution method and specifications [900 mL, pH 6.8 Phosphate Buffer, Apparatus I (Basket), 100 rpm; 1 hr: NMT (b)(4) 4 h: (b)(4) 10 h: (b)(4) and 24 h: NLT (b)(4)].

In this amendment, the firm did not accept the above FDA-recommended dissolution method citing the following reasons: 1) absence of an acid stage challenge to control the enteric coating of the product, 2) dissolution at L₁ for the 5 mg strength is not achieved, 3) maximum drug release is not attained for the test product, and 4) high variability is observed with the FDA method. The firm now proposes to retain its original dissolution method and specifications [Row 1 (2-hour): pH 1.2 simulated gastric fluid (SGF) w/o enzyme; Rows 2 – 4 (4 – , 8 – and 16 – hour): pH 6.8 simulated intestinal fluid (SIF) w/o enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder); 25 dips per minute; 2 h: (b)(4) 4 h: (b)(4) 8 h: (b)(4) and 16 h: (b)(4)]. The firm has submitted additional dissolution data under varying temperature, humidity and tablet storage conditions using the FDA-recommended method (Phosphate Buffer pH 6.8) along with updated stability data using its own proposed method.

Following the review of the dissolution data submitted in the original application and amendment, the DBE now accepts the firm's proposal to retain its original dissolution method [Row 1 (2-hr): pH 1.2 simulated gastric fluid (SGF) w/o enzyme; Rows 2 – 4 (4 – , 8 – and 16 – hour): pH 6.8 simulated intestinal fluid (SIF) w/o enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder)] for its 5 mg and 10 mg drug products. However, the firm's proposed specifications are not acceptable. The DBE has modified the dissolution specifications to 2 h: 0 – 10%; 4 h: 10 – 30%; 8 h: 40 – 65% and 16 h: NLT 80%. The application is deficient pending the firm's acceptance of the new specifications recommended by the DBE.

Background:

March 28, 2003 - Mylan Pharmaceuticals submitted an original ANDA (76702) containing two BE (fasting and non-fasting) studies for its Oxybutynin ER 5 mg Tablets. The BE studies were found acceptable. The dissolution testing was not conducted in at least three dissolution media as required for modified release drug products. Therefore, the application was found incomplete. A deficiency letter was sent on December 12, 2003, requesting the firm to conduct additional dissolution testing. *The firm had already submitted (January 21, 2003) a separate application (ANDA #76644) for its Oxybutynin ER 10 mg Tablets.* Mylan conducted BE studies on the 5-mg tablets because its formulations for 5-mg and 10-mg tablets are not proportionally similar.

March 17, 2004 – the firm submitted additional data generated from dissolution testing using USP Apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75 and 100 rpm) in 900 mL of various dissolution media (Water, 0.1 N HCl, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer). A significant drug release occurred only in pH 6.8 buffer (paddle or basket) and this was attributed by Mylan to the unique coating and release mechanism of its drug product. Upon reviewing the data, the DBE recommended the following dissolution method and specifications [900 mL, pH 6.8 Phosphate Buffer, Apparatus I (Basket), 100 rpm; 1 hr: NMT (b) (4) 4 h: (b) (4) (b) (4) 10 h: (b) (4) and 24 h: NLT (b) (4) to the firm.

Current Submission (June 9, 2004):

FDA Deficiency Comment:

Please acknowledge that you have accepted the following dissolution method and specifications. The dissolution testing should be conducted in 900 mL of pH 6.8 Phosphate Buffer using USP apparatus I (Basket) at 100 rpm. The test products should meet the following specifications:

1 h: NMT (b) (4)
4 h: (b) (4)
10 h: (b) (4)
24 h: NLT (b) (4)

Firm's Response:

In response to the Agency's request, the firm reviewed the previously submitted drug release results generated using the above FDA recommended dissolution method. The results of the original dissolution data using the FDA recommended method showed that the 5 mg tablet did not meet the L₁ specification criteria for dissolution. Consequently, additional dissolution testing was conducted using the FDA recommended method on different samples, conditions, days and instruments (see Tables I – III). The firm made the following conclusions: 1) the proposed method does not have an acid stage challenge; therefore, no control of the functional enteric coating of Mylan's drug product, 2) Mylan's drug product will not routinely meet the FDA recommended specification for both 5 mg and 10 strengths, 3) the FDA method does not

provide full extent of drug release for the Mylan product, and 4) the FDA method has a high level of variability. Based on these conclusions, the firm felt that the FDA recommended method is not a suitable quality control test for release and stability testing of Mylan's drug product. Instead, the firm proposes to retain the dissolution method [Row 1 (2-hour): pH 1.2 Simulated Gastric Fluid w/o Enzyme; Rows 2 - 4 (4 -, 8 - and 16 - hour): pH 6.8 Simulated Intestinal Fluid w/o Enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder); 25 dips per minute] and specifications [2 h: (b) (4) 4 h: (b) (4) 8 h: (b) (4) and 16 h: (b) (4)] submitted in the original application. It also provided stability data (at 25⁰ C) using its proposed method.

Reviewer's Comments:

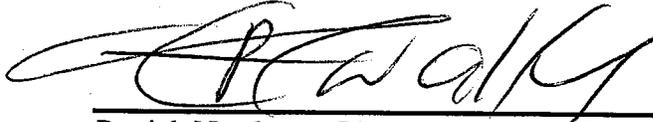
Based on the dissolution data submitted in the original application and this amendment, the firm's proposal to retain its original dissolution method [Row 1 (2-hr): pH 1.2 simulated gastric fluid (SGF) w/o enzyme; Rows 2 - 4 (4 -, 8 - and 16 - hour): pH 6.8 simulated intestinal fluid (SIF) w/o enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder)] for both the 5 mg and 10 mg strengths of its product is now acceptable. However, the firm's proposed specifications are not acceptable. The reviewer recommends the dissolution specifications of 2 h: 0 - 10%; 4 h: 10 - 30%; 8 h: 40 - 65% and 16 h: NLT 80%.

Recommendations

1. The single-dose, fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 5 mg, lot # R1K3865, comparing it to Ditropan® XL Tablets, 5 mg, lot # 0200368 manufactured by Alza Corporation was previously found acceptable to the Division of Bioequivalence. The study demonstrated that under fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 5 mg, were bioequivalent to the reference product, Ditropan® XL Tablets, 5 mg, manufactured by Alza Corporation.
2. The single-dose, non-fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 5 mg, lot # R1K3865, comparing it to Ditropan® XL Tablets, 5 mg, lot # 0200368 manufactured by Alza Corporation was previously found acceptable to the Division of Bioequivalence. The study demonstrated that under non-fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 5 mg, were bioequivalent to the reference product, Ditropan® XL Tablets, 5 mg, manufactured by Alza Corporation.
3. The *in vitro* dissolution testing conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 5 mg, [Row 1 (2-hr): pH 1.2 simulated gastric fluid (SGF) w/o enzyme; Rows 2 - 4 (4 -, 8 - and 16 - hour): pH 6.8 simulated intestinal fluid (SIF) w/o enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder)] is now acceptable. However, the firm's proposed specifications are not acceptable. The Division of Bioequivalence recommends the following dissolution specifications:

However, the firm's proposed specifications are not acceptable. The Division of Bioequivalence recommends the following dissolution specifications:

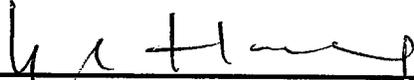
2 hr: 0 - 10%
4 hr: 10 - 30%
8 hr: 40 - 65%
16hr: NLT 80%



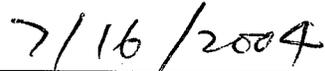
Patrick Nwakama, Pharm.D., Branch III,



Date signed



Yih Chai Huang, Ph.D., Branch III,



Date signed



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

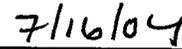


Table I: in vitro Dissolution Testing

FDA Method [pH 6.8 Phosphate buffer, 900 mL, Basket @ 100 rpm] No. Unit Tested: 12

Sampling Times (hour)	Test Product: Oxybutynin Cl Extended Release Tablets Lot Number: R1K3865 Strength: 5 mg		
	MEAN	RANGE	%CV
pH 6.8 Phosphate buffer, 900 mL @ 37⁰C, <u>Basket</u> @ 100 rpm 100 count bottle, stored at warehouse conditions [Date of Assay: 5/19/2004]			
1	6	(b)(4)	12.3
4	21	(b)(4)	17.5
10	50	(b)(4)	11.3
24	94	(b)(4)	4.1
pH 6.8 Phosphate buffer, 900 mL @ 37⁰C, <u>Basket</u> @ 100 rpm 100 count bottle, stored at warehouse conditions [Date of Assay: 5/21/2004]			
1	5	(b)(4)	9.2
4	19	(b)(4)	10.4
10	46	(b)(4)	7.3
24	88	(b)(4)	5.9
pH 6.8 Phosphate buffer, 900 mL @ 37⁰C, <u>Basket</u> @ 100 rpm 100 count bottle; 40⁰C /75% R.H, 3 months [Date of Assay: 5/20/2004]			
1	6	(b)(4)	8.9
4	23	(b)(4)	9.8
10	54	(b)(4)	7.6
24	98	(b)(4)	3.3

Table III (submitted with the **Original** application – March 28, 2003)

Firm's Dissolution Method: <u>Row 1</u> (2-hour): pH 1.2 SGF w/o Enzyme Rows 2 – 4 (4 – , 8 – and 16 – hour): pH 6.8 SIF w/o Enzyme; 250 mL Apparatus 3 (Reciprocating Cylinder); 25 dips per minute Specifications (firm proposed): 2 h: (b) (4) 4 h: (b) (4) 8 h: (b) (4) and 16 h: NLT (b) (4)						
Sampling Time (hours)	Oxybutynin ER Tablets 5 mg Lot No. R1K3865			Ditropan® XL Tablets 5 mg Lot No. 0021413		
	Mean	RSD	Range	Mean	RSD	Range
2	0	188.8	(b) (4)	2	21.7	(b) (4)
4	18	5.6	(b) (4)	11	21.8	(b) (4)
8	51	4.7	(b) (4)	35	12.2	(b) (4)
16	102	2.0	(b) (4)	83	8.1	(b) (4)

Table IV (submitted with the **Original** application (ANDA 76644) – January 21, 2003)

Firm's Dissolution Method: <u>Row 1</u> (2-hour): pH 1.2 SGF w/o Enzyme Rows 2 – 4 (4 – , 8 – and 16 – hour): pH 6.8 SIF w/o Enzyme; 250 mL Apparatus 3 (Reciprocating Cylinder); 25 dips per minute Specifications (firm proposed): 2 h: (b) (4) 4 h: (b) (4) 8 h: (b) (4) and 16 h: NLT 70%						
Sampling Time (hours)	Oxybutynin ER Tablets 10 mg Lot No. R1K0797			Ditropan® XL Tablets 10 mg Lot No. 0112638		
	Mean	% CV	Range	Mean	% CV	Range
2	0	233.6	(b) (4)	1	22.0	(b) (4)
4	17	4.9	(b) (4)	12	15.7	(b) (4)
8	48	2.7	(b) (4)	36	11.9	(b) (4)
16	95	1.7	(b) (4)	81	5.1	(b) (4)

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-702

APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Oxybutynin Chloride ER Tablets, 5 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

1. Your proposed dissolution method (Row 1 (2-hour): pH 1.2 Simulated Gastric Fluid w/o Enzyme; Rows 2 - 4 (4 -, 8 - and 16 - hour): pH 6.8 Simulated Intestinal Fluid w/o Enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder); 25 dips per minute) is now acceptable but the proposed dissolution specifications are not acceptable.
2. Based on the data submitted, the Division of Bioequivalence recommends the following dissolution specifications:

2 hr:	0 - 10%
4 hr:	10 - 30%
8 hr:	40 - 65%
16hr:	NLT 80%

Sincerely yours,

for 

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

CC: ANDA 76702
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P.Nwakama

PE 7/16/2004

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Printed in final on 7/16/2004

Endorsements: (Final with Dates)

HFD-658/ P.Nwakama *PE*
HFD-658/ YC Huang *with 7/16/2004*
HFD-650/ S.Mazzella
HFD-650/ D. Conner *BD 7/16/04*

la

BIOEQUIVALENCE - DEFICIENCIES Submission Date: June 9, 2004

STUDY AMENDMENT (STA) *oic*

Strength: 5 mg
Outcome: IC

Outcome Decisions: IC - Incomplete

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-702 SPONSOR: Mylan Pharmaceuticals, Inc.
 DRUG AND DOSAGE FORM: Oxybutynin Chloride Extended-Release Tablets
 STRENGTH(S): 5 mg
 STUDIES: Fasting and Non-Fasting Studies
 CLINICAL STUDY SITE(S): Kendle International Inc.
 ANALYTICAL SITE(S): Mylan Pharmaceuticals

STUDY SUMMARY: The 90% CI for both in vivo bioequivalence studies are within acceptable limits.
 DISSOLUTION: The firm accepted DBE-recommended dissolution method.

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic <u>Yes</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

Proposed Dissolution Method and Spec from Original Submission Acceptable Yes _____ No X
 (If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Spec acknowledged by firm: Yes X

PROJECT MANAGER: [Signature] DATE: 13AUG04

PRIMARY REVIEWER: PATRICK NWAKAMA BRANCH: III

INITIAL: [Signature] DATE: 8/13/2004

TEAM LEADER: YIH-CHAIN HUANG BRANCH: III

INITIAL: [Signature] DATE: 8/13/2004

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

INITIAL: [Signature] DATE: 8/13/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 076702Orig1s000

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

March 28, 2003

5/13/03
505(j)(2)(A)
OK
Paraphrased
(Reading BC for G.Davis)

(Concur.)
13-MAY-2003
Supriya P. [Signature]

**ELECTRONIC DATA ENCLOSED
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, 5MG

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
- This application consists of a total of 27 volumes and one CD-Rom.
 - Archival Copy - 12 volumes.
 - Review Copy - 13 volumes.
 - Technical Section For Chemistry - 3 volumes.
 - Technical Section For Pharmacokinetics - 10 volumes.
 - Analytical Methods - 2 extra copies; 1 volume each.
 - CD-Rom – eCover Letter, e356h, eTOC, 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, 5mg. Mylan Pharmaceuticals inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

Mylan submitted a separate ANDA (#76-644) on January 21, 2003 for Oxybutynin Chloride Extended-release Tablets, 10mg. The 5mg and 10mg product strengths are subject of separate ANDAs since each ANDA contains Paragraph IV Patent Certification statements and each strength is designated as a Reference Listed Drug requiring separate bioequivalency studies to support their registration and approval.

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.

RECEIVED
MAR 31 2003
OGD / CDER

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Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Gary J. Buehlér
Page 2 of 2

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,

A handwritten signature in black ink, appearing to read "S. Wayne Talton". The signature is written in a cursive style with a long horizontal stroke at the end.

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

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

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

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

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.
- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

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

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.
- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.
- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever

is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

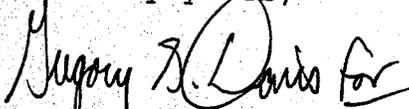
We will correspond with you further after we have had the opportunity to review the application.

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

Should you have questions concerning this application, contact:

Sarah Kim
Project Manager
(301) 827-5848

Sincerely yours,



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

cc: ANDA 76-702
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB ^{6/5} *[Signature]* date 5/13/03
HFD-615/BFritsch, CSO *[Signature]* 5/11/03 date
Word File
V:/FIRMSAM/Mylan/ltrs&rev/76702.ack
FT/
ANDA Acknowledgment Letter!

NAT
RR+CA
on 1355
W. Asher
10/30/03
Bum



MYLAN PHARMACEUTICALS INC

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

September 30, 2003

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

NEW CORRESP

UC

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 5MG
ANDA 76-702
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the above referenced Abbreviated New Drug Application (ANDA), 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), as it pertains to the Paragraph IV patent certification contained in our original application submitted on March 28, 2003 for Oxybutynin Chloride Extended-Release Tablets, 5mg. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

The owner of the patent, and the holder of the application for the listed drug was served with the required notice. Proof of delivery by Registered Mail, Return Receipt evidences receipt by Alza Corporation. A copy of the documentation evidencing Mylan's service and receipt is enclosed. Alza commenced litigation against Mylan on June 26, 2003.

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
Executive Director
Regulatory Affairs

SWT/dn

Enclosures

304 599 2595
OCT 8 1 2003
001-2-00

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\5MG\PATENT-AMENDMENT-092303.DOC

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
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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

December 2, 2003

MINOR AMENDMENT (CMC 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

N/AM

RECEIVED
DEC 03 2003
OGD/CDER

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5MG
ANDA 76-702
RESPONSE TO AGENCY CORRESPONDENCE DATED SEPTEMBER 22, 2003

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the CMC comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated September 22, 2003 (provided in Attachment M). In response to the Agency's comments of September 22nd, Mylan wishes to amend this application as follows:

A. Deficiencies

FDA COMMENT 1: Drug Master File (b)(4) is deficient. The holder of the DMF has been notified of the deficiencies. Please do not submit a MINOR amendment until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.

MYLAN RESPONSE:

(b)(4)

FDA COMMENT 2: Regarding your Drug Substance specification:

MYLAN RESPONSE:

(b)(4)

FDA COMMENT 2b:

MYLAN RESPONSE:

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

(b) (4)

FDA COMMENT 4: Regarding the analytical methods, please provide the LOD data for the process and degradation impurities.

MYLAN RESPONSE: As requested by the Agency, a copy of the method validation report for Limit of Detection for the Related Compounds method (FP-OXYB10-RC-M) has been provided in Attachment K. As described in the original ANDA, the validation reports for Related Compounds are the same as those submitted in Mylan's ANDA 76-644 for Oxybutynin Chloride Extended-release Tablets, 10mg.

FDA COMMENT 5: Please provide the data, or state the page number where the data is found, for the (b) (4) tests. The (b) (4) specifications are listed on page 5312 of your ANDA.

MYLAN RESPONSE: The (b) (4) data was provided in the "Overview of In-Process Testing" and "Overview of Process Validation" documents included in the original ANDA, pages 5207 and 5328, respectively. For the convenience of the reviewer, we have included copies of these referenced pages in Attachment L.

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

FDA COMMENT 1: The cGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

MYLAN RESPONSE: Mylan acknowledges that the firms referenced in the application must be in compliance with cGMPs at the time of approval.

FDA COMMENT 2: Your bioequivalence information (including dissolution data) are pending review by the Division of Bioequivalence (DBE). The final Release and Stability Specifications will be based on the recommendations of DBE.

MYLAN RESPONSE: Mylan acknowledges that our bio-equivalency information is pending review and deficiencies will be communicated separately. Mylan will resolve any issues identified by the Division of Bioequivalence at that time.

Gary J. Buehler
Page 4 of 4

FDA COMMENT 3: Please note that methods validation will be scheduled after testing issues in this letter are resolved.

MYLAN RESPONSE: Mylan acknowledges that methods validation will be scheduled after all issues are resolved. Mylan will provide the information and samples for methods validation upon request. In accordance with the Agency's February 1999 Guidance to Industry, entitled *Organization of an ANDA*, Mylan hereby commits to resolve any issues identified in the methods validation process during review or after approval.

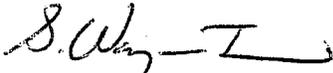
FDA COMMENT 4: A review of the Labels and Labeling is pending. Any deficiencies found will be sent to you under separate cover.

MYLAN RESPONSE: Mylan acknowledges that the labeling portion of our submission is under review and deficiencies will be communicated separately.

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 (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,



S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosure



MYLAN PHARMACEUTICALS INC

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

March 17, 2004

BIOEQUIVALENCE AMENDMENT (CMC 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

BIOEQUIVALENCE AMENDMENT
N/A/B

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5MG
ANDA 76-702
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 23, 2003

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 December 23, 2003 (provided in Attachment C). In response to the Agency's comments of December 23rd, Mylan wishes to amend this application as follows:

FDA COMMENT 1: The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiency has been identified:

You have conducted dissolution testing in one medium only. Please perform dissolution testing using USP Apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75 and 100 rpm) in 900 mL of various dissolution media (e.g. Water, 0.1 N HCl, and buffers at pH 4.5 and 6.8). It may not be necessary to use the higher paddle speeds with Apparatus II if 50 rpm is adequately discriminatory. In addition, please conduct dissolution testing using USP Apparatus VII, Artificial Gastric Fluid w/o Enzyme (37.0 ± 0.5°C), 50 mL, 30 cycles/minute. We recommend sampling times of 1, 2, 4, 10 and 24 hours, or until at least 80% of the drug is dissolved.

MYLAN RESPONSE: As requested, Mylan conducted additional comparative dissolution testing on the 5mg strength of Mylan's Oxybutynin Chloride Extended-release Tablets and Ditropan XL® Tablets.

RECEIVED
MAR 18 2004
OGD/CDER

Department—Fax Numbers	G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\5MG\BIO-AGENCY-LETTER-DATED-122303.doc		
Accounting	(304) 285-6403	Information Systems	(304) 285-6404
Administration	(304) 599-7284	Label Control	(800) 848-0463
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The Agency requested that Mylan perform dissolution testing using USP Apparatus I (Baskets, 100 rpm) and USP Apparatus II (Paddles, 50, 75, and 100 rpm) in 900 mL of various dissolution media (e.g. Water, 0.1N HCl, and buffers at pH 4.5 and 6.8). In response to a similar comment letter received on December 8, 2003 in connection with ANDA 76-702 for the 10mg strength of Oxybutynin Chloride Extended-release Tablets, Mylan performed a comparative dissolution study on the 10mg product by using the recommended media with the highest paddle rotation rate requested (100 ppm). As presented in Attachment A, the only media in which Mylan's 10mg product exhibited drug release was pH 6.8 buffer. This was as expected because Mylan's product uses an enteric coating that does not facilitate drug release at pH values below approximately 5.5. As a result of this study with the 10mg product, Mylan did not conduct dissolution testing with water, 0.1 N HCl, and pH 4.5 buffer on the 5mg product, since the coating for Mylan's 5mg and 10mg products is identical. The other requested apparatus condition (baskets @ 100 rpm and paddles @ 50, 75 and 100 rpm) were performed on the 5mg product using pH 6.8 buffer as the dissolution medium (refer to Attachment B). The Agency also requested that Mylan conduct dissolution testing using Apparatus VII, Artificial Gastric Fluid w/o enzyme ($37.0 \pm 0.5^{\circ}\text{C}$), 50 mL, 30 cycles/minute. As evidenced in the media study discussed above, Mylan's product will not exhibit drug release at the pH requested in this study (approximate pH 1.2); therefore, this testing was not conducted.

In summary, Mylan performed comparative dissolution testing on the 5 mg strength of Mylan's Oxybutynin Chloride Extended-release Tablets and Ditropan XL® Tablets. Due to the coating and release mechanism of Mylan's product; Apparatus I and II, with pH 6.8 buffer, were the only testing conditions investigated. Results from this comparative dissolution study between Mylan's product and Ditropan XL® are presented in Attachment B.

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
Executive Director
Regulatory Affairs

SWT/dn

Enclosure

MYLAN PHARMACEUTICALS INC

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*Central exclus.
to include NDA
exp. 10/15/06 - (net for app)
seeking use for app
S. Wayne Talton
4/27/04*

March 31, 2004

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

NEW CORRESP
XF

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 5MG
ANDA 76-702
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on March 28, 2003.

This current patent amendment (Attachment A) addresses new exclusivity filings by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which have been listed in the FDA's "Orange Book" subsequent to our original submission. The enclosed information is in addition to what has been previously submitted and comprises an update to reflect the newly filed exclusivity 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
Executive Director
Regulatory Affairs

SWT/dn

Enclosures

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APR 01 2004

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Administration	(304) 599-7284
Business Development	(304) 598-5419
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MYLAN PHARMACEUTICALS INC

ORIGINAL

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

June 9, 2004

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

BIOEQUIVALENCE AMENDMENT (CMC INFORMATION ENCLOSED)

ORIG AMENDMENT
N/AB

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5MG
ANDA 76-702
RESPONSE TO AGENCY CORRESPONDENCE DATED APRIL 10, 2004

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 April 10, 2004 (provided in Attachment A). In response to the Agency's comments of April 10th, Mylan wishes to amend this application as follows:

FDA COMMENT 1: The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiency has been identified:

Please acknowledge that you have accepted the following dissolution method and specifications.

The dissolution testing should be conducted in 900 mL of pH 6.8 Phosphate Buffer using USP apparatus I (Basket) at 100 rpm. The test products should meet the following specifications:

1 hr:	NMT	(b) (4)
4 hrs:		(b) (4)
10 hrs:		
24 hrs:	NLT	(b) (4)

MYLAN RESPONSE: Mylan received Minor comment letters from the Division of Bioequivalence on March 19, 2004 and April 10, 2004 for the 10mg (ANDA 76-644) and 5mg (ANDA 76-702) tablet strengths of Oxybutynin Chloride Extended-release Tablets, respectively. A copy of the April 10, 2004 letter is provided in Attachment A. Mylan was requested to update the drug release test and specification for both tablet strengths to the following:

Medium: pH 6.8 phosphate buffer, 900 mL.
Apparatus 1: 100 rpm.
Times: 1, 4, 10, and 24 hours.
Limits: 1 hour: NMT (b) (4)
 4 hours: (b) (4)
 10 hours: (b) (4)
 24 hours: NLT (b) (4)

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JUN 10 2004
CDER

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Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
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Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
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In response to the Agency's request, Mylan reviewed the previously submitted drug release results which were generated using the FDA recommended method. The data show that the originally submitted results for the FDA recommended method do not meet L₁ criteria for the 5mg tablet strength (refer to Attachment B). As a result of this observation, a further evaluation of the proposed method was conducted. The 5mg and 10mg tablet strengths were tested using the proposed method on different samples, conditions, days and instruments. The following conclusions were made.

1. The proposed method does not have an acid stage challenge; therefore, no control of Mylan's functional enteric coating is provided.
2. Mylan's product, which is bioequivalent to Ditropan XL®, will not routinely meet the FDA recommended specification for both the 5mg and 10mg strengths.
3. The proposed method does not provide full extent of drug release for the Mylan product.
4. The proposed method has a high level of variability (Refer to Attachments B, C and D).

Based on these conclusions, the FDA recommended method is not considered to be a suitable quality control test for release and stability testing of Mylan's Oxybutynin Chloride Extended-release Tablets 5mg and 10mg. Mylan recommends that we retain the drug release test and specifications originally submitted in Mylan's ANDAs as described below.

Medium: Row 1: pH 1.2 Simulated Gastric Fluid, without enzymes; 250 mL.
Rows 2-4: pH 6.8 Simulated Intestinal Fluid, without enzymes; 250 mL.

Apparatus 3: 25 dips per minute.

Times: 2, 4, 8, and 16 hours

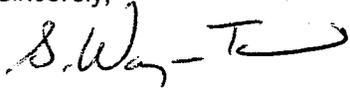
Limits: 2 hours: (b) (4)
4 hours: (b) (4)
8 hours: (b) (4)
16 hours: NLT (b) (4)

Based on the cumulative data, the Mylan ANDA method produces reproducible results, provides an acid challenge test, and achieves a full drug release of the product. Updated room temperature stability data through 18 months using the ANDA method for drug release for Oxybutynin Chloride Extended-release Tablets, 5mg (Lot R1K3865) is provided in Attachment E.

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, appearing to read "S. Wayne Talton". The signature is written in a cursive style with a long horizontal stroke at the end.

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosure

Desk Copy: Sarah Park, Project Manager

MYLAN PHARMACEUTICALS INC

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

July 27, 2004

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

**BIOEQUIVALENCE AMENDMENT
(CMC INFORMATION ENCLOSED)
ORG AMENDMENT**

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5MG
ANDA 76-702
RESPONSE TO AGENCY CORRESPONDENCE DATED JULY 20, 2004

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 July 20, 2004 (provided in Attachment C). In response to the Agency's comments of July 20th, Mylan wishes to amend this application as follows:

FDA COMMENT 1: The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

1. Your proposed dissolution method (Row 1 (2-hour): pH 1.2 Simulated Gastric Fluid w/o Enzyme; Rows 2-4 (4-, 8- and 16-hour): pH 6.8 Simulated Intestinal Fluid w/o Enzyme; 250mL; Apparatus 3 (Reciprocating Cylinder); 25 dips per minute) is now acceptable but the proposed dissolution specifications are not acceptable.
2. Based on the data submitted, the Division of Bioequivalence recommends the following dissolution specifications:

2 hr: 0-10%
4 hr: 10-30%
8 hr: 40-65%
16 hr: NLT 80%

MYLAN RESPONSE: As requested, the recommended dissolution specifications for Oxybutynin Chloride Extended-release Tablets, 5mg have been incorporated into Mylan's stability and quality control programs. Revised finished product specifications and post-approval stability protocol are provided in Attachments A and B, respectively. Please note that a Gratuitous Chemistry Amendment is also being submitted concurrently with this Bioequivalence Amendment under separate cover.

RECEIVED

JUL 29 2004

CD/CDR

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Department—Fax Numbers
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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

July 27, 2004

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

GRATUITOUS CHEMISTRY AMENDMENT (CMC INFORMATION ENCLOSED) ORIG AMENDMENT

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5MG
ANDA 76-702

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to comments received from the Division of Bioequivalence in correspondence dated July 20, 2004 (provided in Attachment A). The July 20th comments requested a revision in the dissolution specifications for Oxybutynin Chloride Extended-release Tablets, 5mg.

Please note that the dissolution specifications recommended by the Division of Bioequivalence have been incorporated into Mylan's stability and quality control programs. 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. A Bioequivalence Amendment is being submitted concurrently with this Chemistry Amendment under separate cover.

Revised finished product specifications with corresponding Certificate of Analysis and a revised post-approval stability protocol are provided in Attachments B and C, respectively. In addition, Mylan is submitting updated stability data tables for Oxybutynin Chloride Extended-release Tablets, 5mg which reflect the recommended dissolution specifications (refer to Attachment D).

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 (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosure

Desk Copy: Sarah Park, Project Manager

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JUL 28 2004
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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 20, 2004

MINOR 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

ORIG AMENDMENT

N/A/F

**RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5 mg
ANDA 76-702
(RESPONSE TO AGENCY CORRESPONDENCE DATED AUGUST 13, 2004)**

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 via e-mail on August 13, 2004. In accordance to the Agency's August 13th correspondence, we wish to amend our application by submitting a revised draft outsert. The bottle labels were also updated to revise our storage statement and to incorporate other minor revisions to be consistent with the innovator's container labeling.

In accordance with the Agency's *Guidances Providing Regulatory Submissions in Electronic Format – ANDAs and Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Oxybutynin Chloride Extended-release Tablets, 5 mg 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, a bookmark is provided within the pdf version.

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 web site for any approved labeling changes.

Should you have any questions regarding this supplement, 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

Desk Copy: John Grace, Team Leader (Cover letter only)
Debbie Catterson, Labeling Reviewer (Cover letter only)
Division of Labeling and Program Support

RECEIVED

AUG 23 2004

OGD/CDER

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER5MG\AGENCY-CORRESPONDENCE DATED AUG 13, 2004. OBXY-RX3.LABELING.doc

Department—Fax Numbers

Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 598-5404
Human Resources (304) 598-5406

Information Systems

Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Product Development (304) 285-6411

Purchasing

Quality Assurance (304) 598-5407
Quality Control (304) 598-5409
Regulatory Affairs (304) 285-6407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232



MYLAN PHARMACEUTICALS INC

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

September 24, 2004

TELEPHONE AMENDMENT (ELECTRONIC LABELING INFORMATION ENCLOSED)

NIAF

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, 5 mg
ANDA 76-702**
(RESPONSE TO AGENCY TELEPHONE CALL RECEIVED ON SEPTEMBER
16, 2004)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to our Labeling Amendment submitted on August 20, 2004. Reference is also made to a telephone call received on September 16, 2004 from Ms. Postelle Birch, of your office, in which she requested that Mylan amend our August 20th submission by adding a subsection 'System Components and Performance' to our outsert to describe our Oxybutynin Chloride Extended-release Tablets. The purpose of this amendment is to provide a revised draft outsert incorporating the text pertaining to Mylan's 'System Components and Performance', as requested by the Agency.

In accordance with the Agency's Guidances *Providing Regulatory Submissions in Electronic Format – ANDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Oxybutynin Chloride Extended-release Tablets, 5 mg as described in the electronic Table of Contents. As a review aid, Mylan has also included Microsoft Word version of our proposed draft outsert. To access this Word file, a bookmark is provided within the pdf version.

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 web site 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

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

RECEIVED

SEP 27 2004

OGD/CDER

Department—Fax Numbers	PROJECT ANDA OXYBUTYNIN CHLORIDE ER15MG TEL EPHONE CORRESPONDENCE DATED SEPT 16, 2004. OXYB-RX5 LABELING.doc		
Accounting	(304) 285-6403	Information Systems	(304) 285-6404
Administration	(304) 599-7284	Label Control	(800) 848-0463
Business Development	(304) 598-5419	Legal Services	(304) 598-5408
Corporate Services	(304) 598-5404	Maintenance & Engineering	(304) 598-5411
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445
		Product Development	(304) 285-6411
		Purchasing	(304) 598-5401
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		Regulatory Affairs	(304) 285-6407
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		Sales & Marketing	(304) 598-3232



MYLAN PHARMACEUTICALS INC

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October 13, 2004

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

ORIG AMENDMENT
NAF

**RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5 mg
ANDA 76-702**
(RESPONSE TO AGENCY TELEPHONE CALL RECEIVED ON OCTOBER 12, 2004)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to our draft labeling included in our Telephone Amendment submitted on September 24, 2004. Reference is also made to a telephone call received on October 12, 2004 from Ms. Postelle Birch, of your office, in which she requested that Mylan amend our September 24th submission by modifying the subsection 'System Components and Performance' in our outsert. The purpose of this amendment is to provide a draft outsert with the revised subsection 'System Components and Performance', as requested by the Agency.

In accordance with the Agency's *Guidances Providing Regulatory Submissions in Electronic Format – ANDAs and Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Oxybutynin Chloride Extended-release Tablets, 5 mg as described in the electronic Table of Contents. As a review aid, Mylan has also included Microsoft Word version of our proposed draft outsert. To access this Word file, a bookmark is provided within the pdf version.

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 web site 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

RECEIVED
OCT 14 2004
OGD/CDER

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

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\5MG\TELEPHONE CORRESPONDENCE DATED OCTOBER 12, 2004. OXYB-RX7 LABELING (10-04).doc

Department—Fax Numbers	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
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Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-702 Applicant Mylan Pharmaceuticals, Inc.
Drug Oxycodone Hydrochloride Extended-release Tablets Strength(s) 5 mg

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

- VIEWER:**
- | | | |
|--|---|--|
| | DRAFT Package | FINAL Package |
| 1. Martin Shimer
Chief, Reg. Support Branch | Date <u>16 March 2004</u>
Initials <u>MS</u> | Date <u>1/12/05</u>
Initials <u>RTR</u> |
- Contains GDEA certification: Yes No Determ. of Involvement? Yes No
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = NDA# 20-897
- Patent/Exclusivity Certification: Yes No Date Checked Patently granted
If Para. IV Certification- did applicant Nothing Submitted
Notify patent holder/NDA holder Yes No Written request issued
Was applicant sued w/in 45 days: Yes No Study Submitted
Has case been settled: Yes No Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes No (no data submitted yet)
Type of Letter: Mylan sued J to PDI on the '355 patent. Suit initiated w/in 45 days
Comments: ∴ 30 month stay of approval = 11/28/2005 eligible for TR MS
- | | | |
|--|--|--|
| 2. Project Manager, <u>Sarah Park</u> Team <u>4</u>
Review Support Branch | Date <u>3/15/04</u>
Initials <u>SEP</u> | Date <u>1/1/04</u>
Initials <u>CL</u> |
|--|--|--|
- Original Rec'd date 3/31/2003 ✓
Date Acceptable for Filing 3/31/2003 ✓
Patent Certification (type) IV
Date Patent/Exclus. expires see attached
Citizens' Petition/Legal Case Yes No Date of Sterility Assur. App. NA
(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
Acceptable Bio reviews tabbed Yes No Modified-release dosage form: Yes No
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes No
Pediatric Waiver Request Accepted Rejected Pending NO TA
- Previously reviewed and tentatively approved Date _____
Previously reviewed and CGMP def./NA Minor issued Date _____
Comments:
- | | |
|---|--|
| 3. David Read (PP IVs Only) Pre-MMA Language included <input checked="" type="checkbox"/>
OGD Regulatory Counsel, Post-MMA Language Included <input type="checkbox"/>
Comments: <u>See rebuttals to letter.</u> | Date <u>5/13/04</u>
Initials <u>RTR</u> |
|---|--|
- | | |
|---|---|
| 4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments: <u>eme satisfactory</u> | Date <u>12/21/04</u>
Initials <u>SEP</u> |
|---|---|
- | | |
|--|---|
| 5. Frank Holcombe <u>First Generics Only</u>
Assoc. Dir. For Chemistry
Comments: (First generic drug review) <u>Sarah Park</u> | Date <u>1/11/05</u>
Initials <u>RW</u> |
|--|---|

REVIEWER:

FINAL ACTION

5. Gregg Davis
Deputy Dir., DLPS

Date _____
Initials _____

Extended-release
RD = Diltrogan XL, Tablets, 5mg
Alza Corp.
NDA 20-897 (001)

6. Peter Rickman
Director, DLPS

Date 11/12/05
Initials PR/et/for

Para. IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No

Comments: *Acceptable QAS dated 8/20/03 verified 11/2/04 by O.A.L. objects noted Bioequivalency studies (fasting and non-fasting) found acceptable 12/12/03. Dissolution studies also found acceptable 4/5/04. Bio study test sites have acceptable OSL inspectional histories. Office Overlap endorsed 8/13/04. Labeling found acceptable for tentative approval 10/19/04. Alza's NRE exclusivity has been addressed via labeling consults to PERSTEAM and review division in a "came put" under BPCA. CMC found acceptable 12/7/04. Method validation was not requested. First generic CMC audit has been completed.*

6. Robert L. West
Deputy Director, OGD

Date 11/12/05
Initials RLW/et/for

Para. IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No

Comments: *Nylan made paragraph 4 certifications to the '895, '754, '268, '355, and '115 patents. Nylan was sued within the 45-day period on the '355 patent only. Litigation is ongoing; the 30-month stay of approval expires on 11/28/05.*

This ANDA is recommended for tentative approval.

7. Gary Buehler
Director, OGD

Date 11/10/05
Initials GB/et/for

Comments: *tentative*
First Generic Approval PD or Clinical for BE Special Scientific or Reg. Issue

8. Project Manager, Team Sarah Park
Review Support Branch

Date 11/12/05
Initials SP

Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification: 2:53pm Time notified of approval by phone 2:03pm Time approval letter faxed
FDA Notification:
1/12/05 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
1/12/05 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.



MYLAN PHARMACEUTICALS INC

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

July 19, 2005

PATENT AMENDMENT

*NHI
PIU to '092
Cumbium
7/26/05*

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, 5MG
ANDA 76-702
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on March 28, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. 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

RECEIVED

JUL 19 2005

OGD / CDER

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\5MG\PATENT-AMENDMENT (NEW PATENT LISTING).DOC

Department—Fax Numbers

Accounting	(304) 285-6403
Administration	(304) 599-7284
Business Development	(304) 598-5419
Corporate Services	(304) 598-5404
Human Resources	(304) 598-5406

Information Systems	(304) 285-6404
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Sales & Marketing	(304) 598-3232



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26505-4310 U.S.A. • (304) 599-2595

NAI
Already certified PIV to '092 on
7/19/2005.
C. Bina 8/3/2005

July 20, 2005

PATENT AMENDMENT

XP

NAI
PIV to '092
C. Bina
7/27/05

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, 5MG
ANDA 76-702
(Patent Information Enclosed)

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This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. 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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JUL 20 2005

OGD / CDER

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\5MG\PATENT-AMENDMENT (NEW PATENT LISTING).DOC

Department—Fax Numbers

Accounting	(304) 285-6403
Administration	(304) 599-7284
Business Development	(304) 598-5419
Corporate Services	(304) 598-5404
Human Resources	(304) 598-5406

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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

NAI
Already certified PIV to '092 on
7/19/2005.
C. Bina 8/3/2005

July 21, 2005

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, 5MG
ANDA 76-702
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on March 28, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. 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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JUL 21 2005

OGD/CDER

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\5MG\PATENT-AMENDMENT (NEW PATENT LISTING).DOC

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Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 598-5404
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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

*NMI
Already PIV art #
092 on 7/19
CMLJin*

July 22, 2005

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, 5MG
ANDA 76-702
(Patent Information Enclosed)

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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

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JUL 22 2005

OGD / OPH

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\5MG\PATENT-AMENDMENT (NEW PATENT LISTING).DOC

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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

NAI
Already PIV cert
to 892 on 7/1
Cruz
8/3/05

July 25, 2005

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

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Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

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JUL 25 2005
CES/GER

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\5MG\PATENT-AMENDMENT (NEW PATENT LISTING).DOC

Department—Fax Numbers

Accounting (304) 285-6403
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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

July 26, 2005

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

XP

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 5MG
ANDA 76-702
(Patent Information Enclosed)

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Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

RECEIVED

JUL 26 2005

OGD/CDER

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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

July 27, 2005

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, 5MG
ANDA 76-702
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on March 28, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. 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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JUL 27 2005

OGD / CDER

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\5MG\PATENT-AMENDMENT (NEW PATENT LISTING).DOC

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MYLAN PHARMACEUTICALS INC

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July 28, 2005

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, 5MG
ANDA 76-702
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on March 28, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. 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

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MYLAN PHARMACEUTICALS INC

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N/XP

August 31, 2005

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, 5MG
ANDA 76-702
(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 Patent Amendment submitted on July 19, 2005 for Oxybutynin Chloride Extended-release Tablets, 5mg. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

The owner of the patent and the holder of the application for the listed drug were served with the required notice. Proof of delivery by Registered Mail, Return Receipt evidences receipt by Alza Corporation on July 26, 2005. 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

SWT/dh

Enclosures

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SEP 01 2005

COMM-FDA

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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 16, 2005

MINOR AMENDMENT - REQUEST FOR FINAL ANDA APPROVAL (CHEMISTRY, PATENT INFORMATION AND ELECTRONIC LABELING 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
N/AM

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5MG
ANDA 76-702
(Request for Final ANDA Approval)

RECEIVED

SEP 19 2005

Dear Mr. Buehler:

OCDC/CDER

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which received Tentative Approval on January 12, 2005, and to the patent litigation pertaining to this application which has not yet been resolved. A copy of the January 12, 2005 Tentative Approval letter has been provided in Attachment A for your reference. As the applicable receipt date of the paragraph IV patent certification notice by the patent owner and NDA holder was May 28, 2003, the 30-month period from the date of said receipt will expire on November 28, 2005. In accordance with the conditions outlined in the January 12, 2005 tentative approval letter and pursuant to 21 CFR 314.107(b)(3)(i)(A), Mylan hereby requests that final approval of ANDA 76-702 be granted upon expiration of the 30-month period. This request for final approval is based on the following application history:

- 1) ANDA 76-702 was submitted to the Agency on March 28, 2003 and considered acceptable for filing on March 31, 2003, as acknowledged in the Agency's letter dated May 13, 2003.
- 2) Mylan's Amendment dated September 30, 2003 provided documentation of receipt of the paragraph IV patent certification notice to the patent and NDA holders as required under section 505(j)(2)(B)(i) of the FD&C Act.
- 3) Expiration of the 30-month period provided for in section 505(j)(2)(B)(i) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i) of the Act will occur on November 28, 2005.

With respect to U.S. Patent 6,919,092 which was recently listed in FDA's "Orange Book", reference is made to our certification contained in our Patent Amendment submitted on July 19, 2005. Reference is also made to our Patent Amendment submitted on August 31, 2005 which provided Documentation of Receipt of Notice. Mylan has not received any notice that legal action was taken within the 45-day statutory period as identified in 21 CFR 314.95(f). Provided in Attachment B is a Patent Amendment from our Legal Department which provides specifics regarding U.S. Patent 6,919,092.

As the patent litigation is currently ongoing with respect to our original patent certification statement and no court decision has yet been rendered, Mylan hereby requests that final approval of ANDA 76-702 be granted on the 30-month provision provided for in 505(j)(5)(B)(ii) of the Act.

G:\Project\ANDA\OXYBUTYNIN CHLORIDE ER\5MG\Request for final approval.doc

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As required by the January 12, 2005 Tentative Approval letter, this amendment also provides notification of the following changes to the conditions outlined in the chemistry, manufacturing and controls (CMC) of this application since the receipt date of Tentative Approval. The proposed production Master Batch Record for Oxybutynin Chloride Extended-release Tablets, 5mg has been revised to allow for the use of an alternate imprinter, a (b) (4) imprinter manufactured by (b) (4) for imprinting the finished drug product (refer to page 37 of the revised batch record provided in Attachment C).

The currently registered production batch record provides for the use of (b) (4) or (b) (4) imprinters. Per the FDA's Guidance for Industry *SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms, Manufacturing Equipment Addendum* (January 1999), the (b) (4) imprinters are within the same class/subclass; therefore, the addition of the (b) (4) printer is considered a minor change. The processing parameters sheets used during manufacturing (b) (4) have also been revised to include minor changes which are fully described on the cover sheets preceding the revised processing parameters sheets provided in Attachment D.

Our drug substance specifications have also been revised in accordance with the current USP and the compendial Assay and Related Compounds procedures have been adopted. The revised specifications, and compendial Assay and Related Compounds procedures with their associated method validation reports are provided in Attachments E, F and G, respectively. In addition, updated room temperature stability data through 24 months for Oxybutynin Chloride Extended-release Tablets, 5mg Lot R1K3865, is provided in Attachment H.

With respect to labeling, our Final Printed Outsert labeling (code OXBT:R1; Revised September 2005) and Final Printed Bottle Labels are provided herein. Mylan's previous draft outsert (OXYB:RX7) was submitted on October 13, 2004. A side-by-side comparison of Mylan's final printed outsert (code OXBT:R1; Revised September 2005) to the previously submitted draft outsert is provided. For the reviewer's convenience, a copy of the Reference Listed Drug (RLD) labeling from the FDA Web Post (Approved June 30, 2004) is also included. Please refer to the enclosed labeling Electronic Table of Contents provided in Attachment I for details.

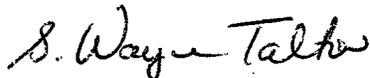
In accordance with the Agency's *Guidances Providing Regulatory Submissions in Electronic Format – ANDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Oxybutynin Chloride Extended-release Tablets as described in the electronic Table of Contents provided in Attachment I. As a review aid, Mylan has also included Microsoft Word version of the proposed final printed labeling. To access these Word files, a bookmark is provided within the pdf version.

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.

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 by telephone at (304) 599-2595, ext. 6551 or by facsimile at (304) 285-6407.

Sincerely,

A handwritten signature in cursive script that reads "S. Wayne Talton".

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

ORIG AMENDMENT

MYLAN PHARMACEUTICALS INC

N/A

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

September 21, 2005

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

GRATUITOUS CHEMISTRY AMENDMENT (CMC INFORMATION ENCLOSED)

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5MG
ANDA 76-702

Dear Mr. Buehler:

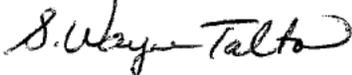
Reference is made to the Abbreviated New Drug Application (ANDA) identified above which received Tentative Approval on January 12, 2005 and our Minor Amendment - Request for Final Approval submitted on September 16, 2005. Reference is also made to a telephone call received on September 19, 2005 from Dr. Mike Darj, of your Office, regarding our pending ANDA for Oxybutynin Chloride Extended-release Tablets, 10mg (ANDA 76-644). For ANDA 76-644, Dr. Dari recommended that we submit revised drug substance specifications to (b) (4) to be consistent with those recently submitted by our supplier.

As requested by Dr. Darj, our drug substance specifications were revised to (b) (4) to be consistent with our supplier. The purpose of this gratuitous chemistry amendment is to also register these revised drug substance specifications to ANDA 76-702. The revised drug substance specifications and revised (b) (4) procedure (b) (4) are provided in Attachments A and B, respectively.

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

Enclosures

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SEP 23 2005

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MYLAN PHARMACEUTICALS INC

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September 29, 2005

GENERAL CORRESPONDENCE (PATENT INFORMATION ENCLOSED – NOTIFICATION OF DISTRICT COURT DECISION)

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

AP

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5MG
ANDA 76-702
(General Correspondence – Notification of District Court Decision)

Dear Mr. Buehler:

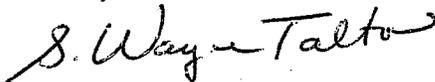
Reference is made to the Abbreviated New Drug Application (ANDA) identified above which was granted Tentative Approval on January 12, 2005 and to our Minor Amendment - Request for Final Approval submitted on September 16, 2005. Reference is also made to our Patent Amendment submitted on September 30, 2003 in which we notified the Agency that Alza Corporation had commenced litigation against Mylan on June 26, 2003 with regard to the Paragraph IV certification submitted to this application pertaining to U.S. Patent No. 6,124,355.

In our September 16th amendment, we acknowledged that the patent litigation pertaining to this application had not yet been resolved. The purpose of this correspondence is to provide a copy of the September 27, 2005 decision from the U.S. District Court for the Northern District of West Virginia (Civil Action No. 1:03CV61). A copy of the district court decision is provided in Attachment A. As noted on page 57 of the attached decision, the court has concluded that Mylan's Oxybutynin Chloride Extended-release Tablets, 5mg does not infringe U.S. Patent No. 6,124,355 and the patent is invalid.

Based on this favorable court decision, there are no legal barriers which would preclude the Agency's ability to render final approval of this application. A similar correspondence, including a copy of the enclosed court decision, is also being submitted to Mylan's pending ANDA 76-644 for Oxybutynin Chloride Extended-release Tablets, 10mg.

This correspondence is submitted in duplicate. Should you require additional information or have any questions regarding this correspondence, 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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SEP 30 2005

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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

October 27, 2005

ORIG AMENDMENT

NIAM

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

TELEPHONE AMENDMENT (CMC INFORMATION ENCLOSED)

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5MG
ANDA 76-702
(Response to Agency Telephone Call Received October 24, 2005)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which was granted Tentative Approval on January 12, 2005, our Minor Amendment - Request for Final Approval submitted on September 16, 2005, and our Gratuitous Chemistry Amendment submitted on September 21, 2005. Reference is also made to a telephone call received on October 24, 2005 from Dr. Mike Darj, of your Office, in which he recommended that we submit revised drug substance specifications to (b) (4)

As requested by Dr. Darj, our drug substance specifications have been revised to (b) (4) to be consistent with our supplier. The revised drug substance specifications and revised (b) (4) procedure (b) (4) are provided in Attachments A and B, respectively.

With respect to the release mechanism of our formulation, the following description is included in our product labeling under the subsection entitled "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.

A hard copy of our prescribing information is provided in Attachment C for the reviewer's reference.

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.

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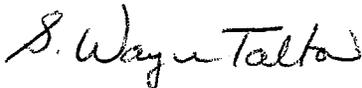
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Gary J. Buehler
Page 2 of 2

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

Enclosures

Desk Copy: Dr. Mike Darj, Review Chemist
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

August 17, 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

YP

**TELEPHONE AMENDMENT
(PATENT INFORMATION ENCLOSED)**

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5MG
ANDA 76-702
(Response to Agency Telephone Call Received August 17, 2006)

*Appeal still
Pending in Fed.
Court.
CA# 06-1019
J. Bina
9/5/06*

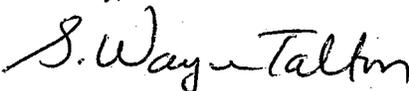
Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which was granted Tentative Approval on January 12, 2005. Reference is also made to a telephone call received on August 17, 2006 from Mr. Robert West, Deputy Director, of your Office, in which he requested a summary of the litigation history regarding this application.

On May 2, 2003, Alza Corporation filed a complaint against Mylan Labs and Mylan Pharms in the Northern District of West Virginia alleging that Mylan's filing of an ANDA for Oxybutynin Chloride Extended-Release Tablets, 10mg (ANDA 76-644) constituted an act of infringement under 35 U.S.C. 271 of United States Patent No. 6,124,355. On June 26, 2003, Alza filed suit in the same court alleging that Mylan's filing of an ANDA for Oxybutynin Chloride Extended-Release Tablets, 5mg (ANDA 76-702) constituted an act of infringement under 35 U.S.C. 271 under the same patent. The two cases were consolidated and assigned to Judge Irene M. Keeley under the case no. 1:03CV61. The district court on September 27, 2005 ruled in favor of Mylan in holding that both Mylan's products did not infringe the asserted claims. On October 11, 2005, Alza appealed the district court decision and oral arguments took place before the Federal Circuit on June 6, 2006 (Case No. 06-1019). A decision by the Federal Circuit is pending.

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

Enclosures

Desk Copy: Mr. Robert West, Deputy Director
Office of Generic Drugs

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AUG 18 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 21, 2006

GENERAL CORRESPONDENCE

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

MC

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 5MG
ANDA 76-702
(Response to Agency Telephone Call Received September 20, 2006)

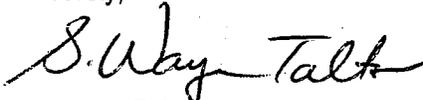
Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which received Tentative Approval on January 12, 2005. Reference is also made to a telephone call received on September 20, 2006 from Mr. Robert West, of your Office, regarding the issuance of a 'mandate' following the final decision of the U.S. Court of Appeals for the Federal Circuit (Case No. 06-1019).

Provided in Attachment A is correspondence from our Legal Department regarding the issuance of the 'mandate' and its potential impact on the triggering of Mylan's 180 days of marketing exclusivity as a first generic.

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

cc: Mr. Robert West, Deputy Director (via facsimile)

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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, desethoxybutynin. 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, desethoxybutynin, 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, desethoxybutynin. 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, Naronha-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
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/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

OGD APPROVAL RCUTING SUMMARY

ANDA # 76-702 Applicant Mylan Pharmaceuticals, Inc.
Drug Oxybutynin Chloride Extended Release Tabs Strength(s) 5mg

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER: DRAFT Package FINAL Package

1. Martin Shimer
Chief, Reg. Support Branch
Date 11/10/05 Date 8/11/06
Initials MS Initials MS

Contains GDEA certification: Yes No Determ. of Involvement? Yes No
(required if sub after 6/1/92) Pediatric Exclusivity System

Patent/Exclusivity Certification: Yes No Date Checked Previous/agent
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: Mylan
Comments: Mylan was not sued. 12/27/04. 1/20/05. 1/21/05. 1/22/05. 1/23/05. 1/24/05. 1/25/05. 1/26/05. 1/27/05. 1/28/05. 1/29/05. 1/30/05. 1/31/05. 2/1/05. 2/2/05. 2/3/05. 2/4/05. 2/5/05. 2/6/05. 2/7/05. 2/8/05. 2/9/05. 2/10/05. 2/11/05. 2/12/05. 2/13/05. 2/14/05. 2/15/05. 2/16/05. 2/17/05. 2/18/05. 2/19/05. 2/20/05. 2/21/05. 2/22/05. 2/23/05. 2/24/05. 2/25/05. 2/26/05. 2/27/05. 2/28/05. 2/29/05. 2/30/05. 3/1/05. 3/2/05. 3/3/05. 3/4/05. 3/5/05. 3/6/05. 3/7/05. 3/8/05. 3/9/05. 3/10/05. 3/11/05. 3/12/05. 3/13/05. 3/14/05. 3/15/05. 3/16/05. 3/17/05. 3/18/05. 3/19/05. 3/20/05. 3/21/05. 3/22/05. 3/23/05. 3/24/05. 3/25/05. 3/26/05. 3/27/05. 3/28/05. 3/29/05. 3/30/05. 3/31/05. 4/1/05. 4/2/05. 4/3/05. 4/4/05. 4/5/05. 4/6/05. 4/7/05. 4/8/05. 4/9/05. 4/10/05. 4/11/05. 4/12/05. 4/13/05. 4/14/05. 4/15/05. 4/16/05. 4/17/05. 4/18/05. 4/19/05. 4/20/05. 4/21/05. 4/22/05. 4/23/05. 4/24/05. 4/25/05. 4/26/05. 4/27/05. 4/28/05. 4/29/05. 4/30/05. 5/1/05. 5/2/05. 5/3/05. 5/4/05. 5/5/05. 5/6/05. 5/7/05. 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2. Project Manager, Jeffery Matheny Team 4 Date 11/21/05 Date 11/21/05
Review Support Branch Initials JM Initials JM

Original Rec'd date 3/31/2003 EER Status Pending Acceptable OAI
Date Acceptable for Filing 3/31/03 Date of EER Status 8/20/2003

Patent Certification (type) See attached IV Date of Office Bio Review 12/12/03, 8/13/04
Date Patent/Exclus. expires See attached Date of Labeling Approv. Sum 10/14/04 12/12/04

Citizens' Petition/Legal Case Yes No Labeling Acceptable Email Rec'd Yes No
(If YES, attach email from PM to CP coord) Labeling Acceptable Email filed Yes No

First Generic Yes No Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes No
MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed Yes No Modified-release dosage form: Yes No
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes

Pediatric Waiver Request Accepted Rejected Pending
Previously reviewed and tentatively approved Date Jan. 12, 2005
Previously reviewed and CGMP def. /NA Minor issued Date _____

Comments:

3. David Read (PP IVs Only) Pre-MMA Language included Date 12/5/05
OGD Regulatory Counsel, Post-MMA Language Included Initials DR

OK, no changes.

4. Div. Dir./Deputy Dir. Date 2/14/06
Chemistry Div. I II OR III Initials DR
Comments:

once satisfactory.

5. Frank Holcombe First Generics Only
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

Date _____
Initials _____

This was completed at the time of the tentative approval issued to Hylan on 11/2/05.

6. Vacant Deputy Dir., DLPS

RD Diltropan XL Extended Release Tablets, 5mg
Alza Corp.
NDA 20-897
(001)

Date _____
Initials _____

7. Peter Rickman
Director, DLPS

Para. IV Patent Cert: Yes No ; Pending Legal Action: Yes No Petition: Yes No

Date 8/17/06
Initials [Signature]

Comments: Acceptable EES dated 8/25/06 verified 8/16/06. No OAT alerts

noted. This ANDA was tentatively approved on 11/2/05 pending the action of ongoing litigation or the expiration of the 30-month period. Refer to the administrative sign-off form completed at that time. On 9/16/05, Hylan proposed several minor CMC updates and requested final approval of the ANDA on 11/2/05 upon expiration of the 30-month period. Additional minor CMC changes were proposed on 9/16/05 and 10/27/05. FH found acceptable for approval 11/2/05 based on 11/2/05. A CMC finding was not requested.

8. Robert L. West
Deputy Director, OGD

Para. IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No

Date _____
Initials _____

Comments: Hylan made paragraph 4 certifications to the 1895, 1759, 1268, 1355, 115 and 1092 patents. Hylan was sued for infringement only on the 1355 patent. The 30-month period associated with this litigation expired on 11/2/05. Hylan has informed the agency that the District Court ruled in Hylan's favor regarding the 1355 patent (11/2/05) concluding that Hylan did not violate this patent. Hylan is eligible for 180-day exclusivity with respect to all listed patents (shared with ZIRMAX on the 1092 patent).

9. Gary Buehler
Director, OGD

Comments: This ANDA is recommended for approval.

Date _____
Initials _____

First Generic Approval PD or Clinical for BE Special Scientific or Reg. Issue

10. Project Manager, Team 12
Review Support Branch Sarah Park-Lanoue

Date 11/13/06
Initials [Signature]

Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

9:50 AM 11/13/06 Time notified of approval by phone 11/13/06 Time approval letter faxed 10:04 AM

FDA Notification:

11/13/06 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

11/14/06 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Approval Letter Faxed to Orange Book Staff @ 301-827-7337: Date/Time:

EES Verified 11/9/06/RWJ