CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-873

Name: Paroxetine Hydrochloride Extended-release Tablets, 12.5 mg (base) and 25 mg (base)

Sponsor: Mylan Pharmaceuticals, Inc.

Approval Date: June 29, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-873

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Tentative Approval Letter	**X**
Labeling	**X**
Labeling Reviews	**X**
Medical Reviews	
Chemistry Reviews	**X**
Bioequivalence Reviews	**X**
Statistical Reviews	
Microbiology Reviews	
Administrative & Correspondence Documents	**X**

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APPLICATION NUMBER:

ANDA 77-873

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-873

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 September 9, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Paroxetine Hydrochloride Extended-release Tablets, 12.5 mg (base) and 25 mg (base).

Reference is also made to the tentative approval letter issued by this office on May 30, 2007, and to your amendments dated February 15, 2006; and June 11, June 20, and June 27, 2007.

We have completed the review of this ANDA and have concluded that adequate information has been provided to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Paroxetine Hydrochloride Extended-release Tablets, 12.5 mg (base) and 25 mg (base), to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Paxil CR Extended-release Tablets, 12.5 mg (base) and 25 mg (base), respectively, of GlaxoSmithKline (GSK). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The “interim” dissolution specifications are as follows:

> For the acid stage, dissolution testing should be conducted for 2 hours in 750 mL of 0.1N HCl. For the buffer stage, dissolution testing should be conducted for 12 hours in 0.05M tris buffer (pH 7.5). Temperature for both stages

should be 37°C using USP apparatus I (basket) at 100 rpm. Both strengths of the test product should meet the following "interim" specifications:

	Time (hours)	Percent Dissolved
Acid Stage	2	NMT (b) (4)
Buffer Stage	2	(b) (4)
	4	
	12	NLT (b) (4)

The "interim" dissolution tests 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 proposed to the "interim" specifications, of if the final specifications are tighter than the "interim" specifications. In all other instances, these data should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, GSK's Paxil CR Extended-release Tablets, 12.5 mg (base) and 25 mg (base), is subject to periods of patent protection. The following patents and expiration dates (with pediatric exclusivity added) are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
4,721,723 (the '723 patent)	June 29, 2007
5,422,123 (the '123 patent)	December 6, 2012
5,789,449 (the '449 patent)	July 6, 2009
5,872,132 (the '132 patent)	November 19, 2015
5,900,423 (the '423 patent)	November 19, 2015
6,121,291 (the '291 patent)	September 17, 2017
6,133,289 (the '289 patent)	November 19, 2015
6,548,084 (the '084 patent)	January 19, 2017
7,229,640 (the '640 patent)	July 19, 2016

With respect to the '123, '132, '423, '291, '289, and '084 patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Paroxetine Hydrochloride Extended-release Tablets 12.5 mg (base) and 25 mg (base), 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. You have notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Mylan within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

With respect to the ‘640 patent, your ANDA contains a paragraph IV certification stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Paroxetine Hydrochloride Extended-release Tablets 12.5 mg (base) and 25 mg (base), under this ANDA. You have notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act. The agency recognizes that, under the Act (as amended in 2003 by the Medicare Prescription Drug, Improvement and Modernization Act) no 30-month of approval stay can arise from this certification and, therefore, the ‘640 patent does not present a barrier to approval of this ANDA at this time.

With respect to the '449 patent, your ANDA contains a statement under section 505(j)(2)(A)(viii) of the Act indicating that this is a method of use patent, and that it does not claim any indication for which you are seeking approval under your ANDA.

With respect to the ‘723 patent, your ANDA contains a paragraph III certification under section 505(j)(2)(A)(vii)(III) of the Act stating that Mylan will not market Paroxetine Hydrochloride Extended-release tablets, 12.5 mg (base) and 25 mg (base), prior to the expiration of this patent. The agency recognizes that the pediatric exclusivity period attaching to the ‘723 patent expired on June 29, 2007.

With respect to 180-day generic drug exclusivity, the agency has concluded that Mylan was the first applicant to submit a substantially complete ANDA with a paragraph IV certification for Paroxetine Hydrochloride Extended-release Tablets 12.5 mg

(base) and 25 mg (base). Therefore, with this approval, Mylan is eligible for 180 days of generic drug exclusivity for Paroxetine Hydrochloride Extended-release Tablets 12.5 mg (base) and 25 mg (base). This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this 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.

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

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

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

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

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Robert L. West
6/29/2007 09:55:16 AM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-873

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-873

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

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 9, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Paroxetine Hydrochloride Extended-release tablets, 12.5 mg and 25 mg.

Reference is also made to your amendments dated November 8, 2005; March 10, April 13, June 9, and August 1, 2006; and February 16, 2007.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Paxil CR, 12.5 mg and 25 mg, of GlaxoSmithKline, is subject to periods of patent protection. The following unexpired patents and expiration dates (with pediatric exclusivity added) are currently listed in the agency's

publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the “Orange Book”):

U.S. Patent Number	Expiration Date
4,721,723 (the '723 patent)	June 29, 2007
5,422,123 (the '123 patent)	December 6, 2012
5,789,499 (the '499 patent)	July 6, 2009
5,872,132 (the '132 patent)	November 19, 2015
5,900,423 (the '423 patent)	November 19, 2015
6,121,291 (the '291 patent)	September 17, 2017
6,133,289 (the '289 patent)	November 19, 2015
6,548,084 (the '084 patent)	January 19, 2017

With respect to the '123, '132, '423, '291, '289, and '084 patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Paroxetine Hydrochloride Extended-release tablets 12.5 and 25 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Mylan Pharmaceuticals, Inc. (Mylan) for infringement of one or more of the patents that were the subjects of the paragraph IV certifications. You have notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Mylan within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

With respect to the '499 patent, your ANDA contains a statement under section 505(j)(2)(A)(viii) of the Act indicating that this is a method of use patent that does not claim any indication for which you are seeking approval under your ANDA.

With respect to the ‘723 patent, your ANDA contains a paragraph III certification under section 505(j)(2)(A)(vii)(III) of the Act stating that Mylan will not market Paroxetine Hydrochloride Extended-release tablets, 12.5 and 25 mg, prior to the expiration of this patent. Therefore, final approval of your ANDA may not be made effective pursuant to section 505(j)(5)(B)(ii) of the Act until the ‘723 patent has expired, currently June 29, 2007 (with pediatric exclusivity added).

To reactivate your ANDA 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. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

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

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

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505 of the Act, and will not be listed in the “Orange Book.” Should you believe that there are grounds for issuing the final approval letter prior to June 29, 2007, you should amend your ANDA accordingly.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Thomas Hinchliffe, Project Manager, at 301-827-5848.

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Robert L. West
5/30/2007 08:50:55 AM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-873

LABELING

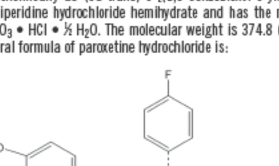
PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS 12.5 mg and 25 mg

℞ only

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of paroxetine or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Paroxetine is not approved for use in pediatric patients.

DESCRIPTION: Paroxetine hydrochloride extended-release tablets are an orally administered psychotropic drug with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic, or other available antidepressant or antipanic agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (3S-trans)-3-[(1,3-benzodioxol-5-yloxy)methyl)]4-(4-fluorophenyl)-piperidine hydrochloride hemihydrate and has the molecular formula of $C_{19}H_{20}FNO_3$ • HCl • ½ H_2O. The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



Paroxetine hydrochloride (hemihydrate) is an odorless, white to almost white crystalline powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

Each enteric film-coated, extended-release tablet contains paroxetine hydrochloride hemihydrate equivalent to 12.5 mg or 25 mg paroxetine. Inactive ingredients consist of colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer type C, microcrystalline cellulose, polydextrose, polyethylene glycol, polysorbate 80, sodium hydroxide, talc, titanium dioxide, triacetin and triethyl citrate. In addition, the 25 mg product contains the following coloring agents: D&C Red No. 30 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake.

In addition, paroxetine hydrochloride extended-release tablets may also contain imprinting ink consisting of either black pigment and natural resin or black iron oxide and propylene glycol.

Paroxetine hydrochloride complies with *USP Chromatographic Purity Test 1.*

PRXT:R2mc

CLINICAL PHARMACOLOGY: Pharmacodynamics: The efficacy of paroxetine in the treatment of major depressive disorder, panic disorder, and social anxiety disorder is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic, $alpha_1$-, $alpha_2$-, beta-adrenergic-, dopamine (D_2)-, $5\text{-}HT_1$-, $5\text{-}HT_2$-, and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic, and $alpha_1$-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics: Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. The elimination half-life is approximately 15 to 20 hours after a single-dose of paroxetine hydrochloride extended-release tablets. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

Absorption and Distribution: Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male and female subjects (n = 23) received single oral doses of paroxetine hydrochloride extended-release tablets at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg), paroxetine C_{max} and $AUC_{0\text{-}inf}$ increased disproportionately with dose (as seen also with immediate-release formulations). Mean C_{max} and $AUC_{0\text{-}inf}$ values at these doses were 2, 5.5, 9, and 12.5 ng/mL, and 121, 261, 338, and 540 ng•hr./mL, respectively. T_{max} was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations. The bioavailability of 25 mg paroxetine hydrochloride extended-release tablets is not affected by food.

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Metabolism and Excretion: The mean elimination half-life of paroxetine was 15 to 20 hours throughout a range of single doses of paroxetine hydrochloride extended-release tablets (12.5 mg, 25 mg, 37.5 mg, and 50 mg). During repeated administration of paroxetine hydrochloride extended-release tablets (25 mg once daily), steady-state was reached within 2 weeks (i.e., comparable to immediate-release formulations). In a repeat dose study in which normal male and female subjects (n = 23) received paroxetine hydrochloride extended-release tablets (25 mg daily), mean steady-state C_{max}, C_{min}, and $AUC_{0\text{-}24}$ values were 30 ng/mL, 20 ng/mL, and 550 ng•hr./mL, respectively.

Based on studies using immediate-release formulations, steady-state drug exposure based on $AUC_{0\text{-}24}$ was several-fold greater than would have been predicted from single-dose data. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of the immediate-release formulation of 20 mg to 40 mg daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10 day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10 day post-dosing period.

Other Clinical Pharmacology Information: *Specific Populations:* *Renal and Liver Disease:* Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min. was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min. and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients: In a multiple-dose study in the elderly at daily doses of 20 mg, 30 mg, and 40 mg of the immediate-release formulation, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions: *In vitro* drug interaction studies reveal that paroxetine inhibits CYP2D6. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone, and atomoxetine (see PRECAUTIONS: Drug Interactions).

Clinical Trials: *Major Depressive Disorder:* The efficacy of paroxetine hydrochloride extended-release tablets as a treatment for major depressive disorder has been established in two 12 week, flexible dose, placebo-controlled studies of patients with DSM-IV Major Depressive Disorder. One study included patients in the age range 18 to 65 years, and a second study included elderly patients, ranging in age from 60 to 88. In both studies, paroxetine hydrochloride extended-release tablets were shown to be significantly more effective than placebo in treating major depressive disorder as measured by the following: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)–Severity of Illness score.

A study of outpatients with major depressive disorder who had responded to immediate-release paroxetine tablets (HDRS total score < 8) during an initial 8 week open treatment phase and were then randomized to continuation on immediate-release paroxetine tablets or placebo for one year demonstrated a significantly lower relapse rate for patients taking immediate-release paroxetine tablets (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Panic Disorder: The effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of panic disorder was evaluated in three 10 week, multicenter, flexible dose studies (Studies 1, 2, and 3) comparing paroxetine extended-release tablets (12.5 to 75 mg daily) to placebo in adult outpatients who had panic disorder (DSM-IV), with or without agoraphobia. These trials were assessed on the basis of their outcomes on 3 variables: (1) the proportions of patients free of full panic attacks at endpoint; (2) change from baseline to endpoint in the median number of full panic attacks; and (3) change from baseline to endpoint in the median Clinical Global Impression Severity score. For Studies 1 and 2, paroxetine hydrochloride extended-release tablets were consistently superior to placebo on 2 of these 3 variables. Study 3 failed to consistently demonstrate a significant difference between paroxetine hydrochloride extended-release tablets and placebo on any of these variables.

For all three studies, the mean dose of paroxetine hydrochloride extended-release tablets for completers at endpoint was approximately 50 mg/day. Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

Long-term maintenance effects of the immediate-release formulation of paroxetine in panic disorder were demonstrated in an extension study. Patients who were responders during a 10 week double-blind phase with immediate-release paroxetine and during a 3 month double-blind extension phase were randomized to either immediate-release paroxetine or placebo in a 3 month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Social Anxiety Disorder: The efficacy of paroxetine hydrochloride extended-release tablets as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of social anxiety disorder was demonstrated in a 12 week, multicenter, double-blind, flexible dose, placebo-controlled study of adult outpatients with a primary diagnosis of social anxiety disorder (DSM-IV). In the study, the effectiveness of paroxetine hydrochloride extended-release tablets (12.5 to 37.5 mg daily) compared to placebo was evaluated on the basis of (1) change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score and (2) the proportion of responders who scored 1 or 2 (very much improved or much improved) on the Clinical Global Impression (CGI) Global Improvement score.

Paroxetine hydrochloride extended-release tablets demonstrated statistically significant superiority over placebo on both the LSAS total score and the CGI Improvement responder criterion. For patients who completed the trial, 64% of patients treated with paroxetine hydrochloride extended-release tablets compared to 34.7% of patients treated with placebo were CGI Improvement responders.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of gender. Subgroup analyses of studies utilizing the immediate-release formulation of paroxetine generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

INDICATIONS AND USAGE: Major Depressive Disorder: Paroxetine hydrochloride extended-release tablets are indicated for the treatment of major depressive disorder.

The efficacy of paroxetine hydrochloride extended-release tablets in the treatment of a major depressive episode was established in two 12 week controlled trials of outpatients whose diagnoses corresponded to the DSM-IV category of major depressive disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least 5 of the following 9 symptoms during the same 2 week period: Depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation.

The antidepressant action of paroxetine in hospitalized depressed patients has not been adequately studied.

Paroxetine hydrochloride extended-release tablets have not been systematically evaluated beyond 12 weeks in controlled clinical trials; however, the effectiveness of immediate-release paroxetine hydrochloride in maintaining a response in major depressive disorder for up to one year has been demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY: Clinical Trials). The physician who elects to use paroxetine hydrochloride extended-release tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Panic Disorder: Paroxetine hydrochloride extended-release tablets are indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of paroxetine hydrochloride extended-release tablets was established in two 10 week trials in panic disorder patients whose diagnoses corresponded to the DSM-IV category of panic disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3 month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, the physician who prescribes paroxetine hydrochloride extended-release tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Social Anxiety Disorder: Paroxetine hydrochloride extended-release tablets are indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of paroxetine hydrochloride extended-release tablets as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the efficacy of paroxetine hydrochloride extended-release tablets was established in a 12 week trial, in adult outpatients with social anxiety disorder (DSM-IV). Paroxetine hydrochloride extended-release tablets have not been studied in children or adolescents with social phobia (see CLINICAL PHARMACOLOGY: Clinical Trials).

The effectiveness of paroxetine hydrochloride extended-release tablets in long-term treatment of social anxiety disorder, i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well controlled trials. Therefore, the physician who elects to prescribe paroxetine hydrochloride extended-release tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS: Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Paroxetine hydrochloride extended-release tablets are contraindicated in patients with a hypersensitivity to paroxetine or to any of the inactive ingredients in paroxetine hydrochloride extended-release tablets.

WARNINGS: Clinical Worsening and Suicide Risk: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality Per 1,000 Patients Treated
	Drug-Related Increases
< 18	14 additional cases
18 to 24	5 additional cases
	Drug-Related Decreases
25 to 64	1 fewer case
≥ 65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION: Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets, for a description of the risks of discontinuation of paroxetine).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for paroxetine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that paroxetine is not approved for use in treating bipolar depression.

Potential for Interaction With Monoamine Oxidase Inhibitors: In patients receiving another serotonin reuptake inhibitor drug in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine hydrochloride, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that paroxetine hydrochloride extended-release tablets not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 2 weeks should be allowed after stopping paroxetine hydrochloride extended-release tablets before starting an MAOI.

Serotonin Syndrome: The development of a potentially life threatening serotonin syndrome may occur with the use of paroxetine hydrochloride extended-release tablets, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of paroxetine hydrochloride extended-release tablets with MAOIs intended to treat depression is contraindicated (see CONTRAINDICATIONS and WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors). If concomitant use of paroxetine hydrochloride extended-release tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see PRECAUTIONS: Drug Interactions).

The concomitant use of paroxetine hydrochloride extended-release tablets with serotonin precursors (such as tryptophan) is not recommended (see PRECAUTIONS: Drug Interactions).

Potential Interaction with Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as Torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose related.

An *in vivo* study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

Usage in Pregnancy: *Teratogenic Effects:* Epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs). In general, septal defects range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS: General: *Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets*). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

A study based on Swedish national registry data evaluated infants of 6,896 women exposed to antidepressants in early pregnancy (5,123 women exposed to SSRIs; including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry population (OR 1.8; 95% confidence interval 1.1 to 2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was 2% vs. 1% in the entire registry population. Among the same paroxetine exposed infants, an examination of the data showed no increase in the overall risk for congenital malformations.

A separate retrospective cohort study using U.S. United Healthcare data evaluated 5,956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8 to 2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study also suggested an increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

Animal Findings: Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD on a mg/m² basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on a mg/m² basis. The no effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

Nonteratogenic Effects: Neonates exposed to paroxetine hydrochloride extended-release tablets and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately 6-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no collaborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

There have also been post-marketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

PRECAUTIONS: General: *Activation of Mania/Hypomania:* During premarketing testing of immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately 1% of paroxetine-treated unipolar patients compared to 1.1% of active control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active control groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety disorder, or PMDD treated with paroxetine hydrochloride extended-release tablets in controlled clinical studies, there were no reports of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder, paroxetine hydrochloride extended-release tablets should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing of immediate-release paroxetine hydrochloride, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Among 1,627 patients who received paroxetine hydrochloride extended-release tablets in controlled clinical trials in major depressive disorder, panic disorder, social anxiety disorder, or PMDD, one patient (0.1%) experienced a seizure. Paroxetine hydrochloride extended-release tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets: Adverse events while discontinuing therapy with paroxetine hydrochloride extended-release tablets were not systematically evaluated in most clinical trials; however, in recent placebo-controlled clinical trials utilizing daily doses of paroxetine hydrochloride extended-release tablets up to 37.5 mg/day, spontaneously reported adverse events while discontinuing therapy with paroxetine hydrochloride extended-release tablets were evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose by 12.5 mg/day to a dose of 25 mg/day for one week before treatment was stopped. For patients receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in dose. With this regimen in those studies, the following adverse events were reported for paroxetine hydrochloride extended-release tablets, at an incidence of 2% or greater for paroxetine hydrochloride extended-release tablets and were at least twice that reported for placebo: Dizziness, nausea, nervousness, and additional symptoms described by the investigator as associated with tapering or discontinuing paroxetine hydrochloride extended-release tablets (e.g., emotional lability, headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events were reported as serious in 0.3% of patients who discontinued therapy with paroxetine hydrochloride extended-release tablets.

During marketing of paroxetine hydrochloride extended-release tablets and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, (particularly when abrupt), including the following: Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations and tinnitus), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with paroxetine hydrochloride extended-release tablets. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

See also PRECAUTIONS: Pediatric Use, for adverse events reported upon discontinuation of treatment with paroxetine in pediatric patients.

Akathisia: The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

Hyponatremia: Several cases of hyponatremia have been reported with immediate-release paroxetine hydrochloride. The hyponatremia appeared to be reversible when paroxetine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Abnormal Bleeding: Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a non-steroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see PRECAUTIONS: Drug Interactions). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of paroxetine with NSAIDs, aspirin, or other drugs that affect coagulation.

Use in Patients with Concomitant Illness: Clinical experience with immediate-release paroxetine hydrochloride in patients with certain concomitant systemic illness is limited. Caution is advisable in using paroxetine hydrochloride extended-release tablets in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with paroxetine hydrochloride. A few cases of acute angle closure glaucoma associated with therapy with immediate-release paroxetine have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when paroxetine hydrochloride extended-release tablets are prescribed for patients with narrow angle glaucoma.

Paroxetine hydrochloride extended-release tablet or the immediate-release formulation has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during premarket testing. Evaluation of electrocardiograms of 682 patients who received immediate-release paroxetine hydrochloride in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine hydrochloride does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance < 30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients: Paroxetine hydrochloride extended-release tablets should not be chewed or crushed, and should be swallowed whole.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with paroxetine and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness and Suicidal Thoughts or Actions" is available for paroxetine. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking paroxetine.

Clinical Worsening and Suicide Risk: Patients, their families and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day to day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Drugs That Interfere with Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Interference with Cognitive and Motor Performance: Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies immediate-release paroxetine hydrochloride has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with paroxetine hydrochloride extended-release tablets does not affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with use of paroxetine hydrochloride extended-release tablets in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medications: Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over the counter drugs, since there is a potential for interactions.

Alcohol: Although immediate-release paroxetine hydrochloride has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking paroxetine hydrochloride extended-release tablets.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy (see WARNINGS: Usage in Pregnancy: *Teratogenic* and *Nonteratogenic Effects*).

Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant (see PRECAUTIONS: Nursing Mothers).

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: *Tryptophan:* As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking immediate-release paroxetine. Consequently, concomitant use of paroxetine hydrochloride extended-release tablets with tryptophan is not recommended (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors: *Serotonin Syndrome*).

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Pimozide: In a controlled study of healthy volunteers, after immediate-release paroxetine hydrochloride was titrated to 60 mg daily, coadministration of a single-dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and paroxetine hydrochloride extended-release tablets are contraindicated (see CONTRAINDICATIONS).

Serotonergic Drugs: Based on the mechanism of action of paroxetine hydrochloride and the potential for serotonin syndrome, caution is advised when paroxetine hydrochloride extended-release tablets are coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible nonselective MAOI) lithium, tramadol, or St. John's Wort (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors: *Serotonin Syndrome*). The concomitant use of paroxetine extended-release tablets with other SSRI's, SNRIs or tryptophan is not recommended (see PRECAUTIONS: Drug Interactions: *Tryptophan*).

Thioridazine: See CONTRAINDICATIONS and WARNINGS.

Warfarin: Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of paroxetine hydrochloride extended-release tablets and warfarin should be undertaken with caution (see PRECAUTIONS: Information for Patients: *Drugs That Interfere with Hemostasis*).

Triptans: There have been rare post-marketing reports of serotonin syndrome with the use of an SSRI and a triptan. If concomitant use of paroxetine hydrochloride extended-release tablets with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors: *Serotonin Syndrome*).

Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug metabolizing enzymes.

Cimetidine: Cimetidine inhibits many cytochrome P450 (oxidative) enzymes. In a study where immediate-release paroxetine (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of paroxetine hydrochloride extended-release tablets after the starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital: Phenobarbital induces many cytochrome P_{450} (oxidative) enzymes. When a single oral 30 mg dose of immediate-release paroxetine was administered at phenobarbital steady-state (100 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustment with paroxetine hydrochloride extended-release tablets are considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin: When a single oral 30 mg dose of immediate-release paroxetine was administered at phenytoin steady-state (300 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to immediate-release paroxetine administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady-state (30 mg once daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when paroxetine hydrochloride extended-release tablets are coadministered with phenytoin; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS: Post-marketing Reports).

Drugs Metabolized by CYP2D6: Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs, and many tricyclics), are metabolized by the cytochrome P_{450} isozyme CYP2D6. Like other agents that are metabolized by CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (> 90%), this CYP2D6 isozyme is saturated early during paroxetine dosing. In one study, daily dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) C_{max}, AUC, and $T_{1/2}$ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been evaluated. In one study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady-state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady-state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when given with paroxetine.

Concomitant use of paroxetine hydrochloride extended-release tablets with other drugs metabolized by cytochrome CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either paroxetine hydrochloride extended-release tablets or the other drug.

Therefore, coadministration of paroxetine hydrochloride extended-release tablets with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be coadministered (see CONTRAINDICATIONS and WARNINGS).

At steady-state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes that, unlike CYP2D6, show no evidence of saturation (see PRECAUTIONS: Drug Interactions: *Tricyclic Antidepressants*).

Drugs Metabolized by Cytochrome CYP3A4: An *in vivo* interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's *in vitro* K_i and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCAs): Caution is indicated in the coadministration of TCAs with paroxetine hydrochloride extended-release tablets, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with paroxetine hydrochloride extended-release tablets (see PRECAUTIONS: Drug Interactions: *Drugs Metabolized by Cytochrome CYP2D6*).

Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, administration of paroxetine hydrochloride extended-release tablets to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Drugs That Interfere with Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with paroxetine.

Alcohol: Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking paroxetine hydrochloride extended-release tablets.

Lithium: A multiple-dose study with immediate-release paroxetine hydrochloride has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when immediate-release paroxetine hydrochloride is coadministered with lithium.

Digoxin: The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady-state. Mean digoxin AUC at steady-state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine hydrochloride extended-release tablets and digoxin should be undertaken with caution.

Diazepam: Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine: Daily oral dosing of immediate-release paroxetine (30 mg once daily) increased steady-state $AUC_{0\text{-}24}$, C_{max}, and C_{min} values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady-state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers: In a study where propranolol (80 mg twice daily) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with immediate-release paroxetine (30 mg once daily) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS: Post-marketing Reports).

Theophylline: Reports of elevated theophylline levels associated with immediate-release paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Fosamprenavir/Ritonavir: Coadministration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of ECT and paroxetine hydrochloride extended-release tablets.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* Two year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 2 (mouse) and 3 (rat) times the maximum recommended human dose (MRHD) on an mg/m² basis. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose related increase in the number of tumors in mice, there was no drug related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis: Paroxetine produced no genotoxic effects in a battery of five *in vitro* and two *in vivo* assays that included the following: Bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility: A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is approximately twice the MRHD on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m² basis).

Pregnancy: *Pregnancy Category D:* See WARNINGS: Usage in Pregnancy: *Teratogenic Effects:*.

Labor and Delivery: The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when paroxetine hydrochloride extended-release tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with paroxetine hydrochloride and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of paroxetine hydrochloride extended-release tablets in a child or adolescent must balance the potential risks with the clinical need.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with immediate-release paroxetine hydrochloride and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with immediate-release paroxetine hydrochloride in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received immediate-release paroxetine hydrochloride and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see DOSAGE AND ADMINISTRATION: Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets).

Geriatric Use: In worldwide premarketing clinical trials with immediate-release

paroxetine hydrochloride, 17% of paroxetine-treated patients (approximately 700) were 65 years or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

In a controlled study focusing specifically on elderly patients with major depressive disorder, paroxetine hydrochloride extended-release tablets were demonstrated to be safe and effective in the treatment of elderly patients (> 60 years) with major depressive disorder. (See CLINICAL PHARMACOLOGY: Clinical Trials and ADVERSE REACTIONS: Table 3.)

ADVERSE REACTIONS: The information included under the "Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Paroxetine Hydrochloride Extended-Release Tablets" subsection of ADVERSE REACTIONS is based on data from eleven placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, three studies were done in patients with panic disorder and one study was conducted in patients with social anxiety disorder. Two of the studies in major depressive disorder, which enrolled patients in the age range 18 to 65 years, are pooled. Information from a third study of major depressive disorder, which focused on elderly patients (60 to 88 years), is presented separately as is the information from the panic disorder studies. Information on additional adverse events associated with paroxetine hydrochloride extended-release tablet and the immediate-release formulation of paroxetine hydrochloride is included in a separate subsection (see Other Events Observed During the Clinical Development of Paroxetine).

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With Paroxetine Hydrochloride Extended-Release Tablets: ***Adverse Events Associated With Discontinuation of Treatment:*** *Major Depressive Disorder:* Ten percent (21/212) of patients treated with paroxetine hydrochloride extended-release tablets discontinued treatment due to an adverse event in a pool of two studies of patients with major depressive disorder. The most common events (≥ 1%) associated with discontinuation and considered to be drug-related (i.e., those events associated with dropout at a rate approximately twice or greater for paroxetine hydrochloride extended-release tablets compared to placebo) included the following:

	Paroxetine Hydrochloride Extended-Release Tablets (n = 212)	Placebo (n = 211)
Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0.0%
Somnolence	1.4%	0.0%

In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of patients treated with paroxetine hydrochloride extended-release tablets discontinued due to an adverse event. Events meeting the above criteria included the following:

	Paroxetine Hydrochloride Extended-Release Tablets (n = 104)	Placebo (n = 109)
Nausea	2.9%	0.0%
Headache	1.9%	0.9%
Depression	1.9%	0.0%
LFT's abnormal	1.9%	0.0%

Panic Disorder: Eleven percent (50/444) of patients treated with paroxetine hydrochloride extended-release tablets in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	Paroxetine Hydrochloride Extended-Release Tablets (n = 444)	Placebo (n = 445)
Nausea	2.9%	0.4%
Insomnia	1.8%	0.0%
Headache	1.4%	0.2%
Asthenia	1.1%	0.0%

Social Anxiety Disorder: Three percent (5/186) of patients treated with paroxetine hydrochloride extended-release tablets in the social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

	Paroxetine Hydrochloride Extended-Release Tablets (n = 186)	Placebo (n = 184)
Nausea	2.2%	0.5%
Headache	1.6%	0.5%
Diarrhea	1.1%	0.5%

Commonly Observed Adverse Events: ***Major Depressive Disorder:*** The most commonly observed adverse events associated with the use of paroxetine hydrochloride extended-release tablets in a pool of two trials (incidence of 5% or greater and incidence for paroxetine hydrochloride extended-release tablets at least twice that for placebo, derived from Table 2) were: Abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning.

Using the same criteria, the adverse events associated with the use of paroxetine hydrochloride extended-release tablets in a study of elderly patients with major depressive disorder were: Abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

Panic Disorder: In the pool of panic disorder studies, the adverse events meeting these criteria were: Abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Social Anxiety Disorder: In the social anxiety disorder study, the adverse events meeting these criteria were: Nausea, asthenia, abnormal ejaculation, sweating, somnolence, impotence, insomnia, and libido decreased.

Incidence in Controlled Clinical Trials: Table 2 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with paroxetine hydrochloride extended-release tablets, aged 18 to 65, who participated in two short-term (12 week) placebo-controlled trials in major depressive disorder in which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 3 enumerates adverse events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated with paroxetine hydrochloride extended-release tablets who participated in a short-term (12 week) placebo-controlled trial in major depressive disorder in which patients were dosed in a range of 12.5 mg to 50 mg/day. Table 4 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72 years) treated with paroxetine hydrochloride extended-release tablets who participated in short-term (10 week) placebo-controlled trials in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 5 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated with paroxetine hydrochloride extended-release tablets who participated in a short-term (12 week), double-blind, placebo-controlled trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 2. Treatment Emergent Adverse Events Occurring in ≥ 1% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Pool of Two Studies in Major Depressive Disorder[1,2]

Body System/Adverse Event	% Reporting Event: Paroxetine Hydrochloride Extended-Release Tablets (n = 212)	% Reporting Event: Placebo (n = 211)
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection[3]	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma[4]	5%	1%
Pain[5]	3%	1%
Allergic Reaction[6]	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation[7]	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%

continued

Table 2. Treatment Emergent Adverse Events Occurring in ≥ 1% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Pool of Two Studies in Major Depressive Disorder[1,2]

Body System/Adverse Event	% Reporting Event: Paroxetine Hydrochloride Extended-Release Tablets (n = 212)	% Reporting Event: Placebo (n = 211)
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision[8]	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation[9,10]	26%	1%
Female Genital Disorder[9,11]	10%	< 1%
Impotence[9]	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder[9]	2%	< 1%
Vaginitis[9]	2%	0%

1. Adverse events for which the paroxetine hydrochloride extended-release tablets reporting incidence was less than or equal to the placebo incidence are not included. These events are: Abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.
2. < 1% means greater than zero and less than 1%.
3. Mostly flu.
4. A wide variety of injuries with no obvious pattern.
5. Pain in a variety of locations with no obvious pattern.
6. Most frequently seasonal allergic symptoms.
7. Usually flushing.
8. Mostly blurred vision.
9. Based on the number of males or females.
10. Mostly anorgasmia or delayed ejaculation.
11. Mostly anorgasmia or delayed orgasm.

Table 3. Treatment Emergent Adverse Events Occurring in ≥ 5% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Study of Elderly Patients with Major Depressive Disorder[1,2]

Body System/Adverse Event	% Reporting Event: Paroxetine Hydrochloride Extended-Release Tablets (n = 104)	% Reporting Event: Placebo (n = 109)
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	< 1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	< 1%
Urogenital System		
Abnormal Ejaculation[3,4]	17%	3%
Impotence[3]	9%	3%

1. Adverse events for which the paroxetine hydrochloride extended-release tablets reporting incidence was less than or equal to the placebo incidence are not included. These events are nausea and respiratory disorder.
2. < 1% means greater than zero and less than 1%.
3. Based on the number of males.
4. Mostly anorgasmia or delayed ejaculation.

Table 4. Treatment Emergent Adverse Events Occurring in ≥ 1% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Pool of Three Panic Disorder Studies[1,2]

Body System/Adverse Event	% Reporting Event: Paroxetine Hydrochloride Extended-Release Tablets (n = 444)	% Reporting Event: Placebo (n = 445)
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma[3]	5%	4%
Cardiovascular System		
Vasodilation[4]	3%	2%
Digestive System		
Nausea	23%	17%
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		
Insomnia	20%	11%
Somnolence	20%	9%
Libido Decreased	9%	4%
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia[5]	2%	< 1%
Myoclonus	2%	< 1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision[6]	3%	< 1%
Urogenital System		
Abnormal Ejaculation[7,8]	27%	3%
Impotence[7]	10%	1%
Female Genital Disorders[9,10]	7%	1%
Urinary Frequency	2%	< 1%
Urination Impaired	2%	< 1%
Vaginitis[9]	1%	< 1%

1. Adverse events for which the reporting rate for paroxetine hydrochloride extended-release tablets was less than or equal to the placebo rate are not included. These events are: Abnormal dreams, allergic reaction, back pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression, dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection, menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis, tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.
2. < 1% means greater than zero and less than 1%.
3. Various physical injuries.
4. Mostly flushing.
5. Mostly muscle tightness or stiffness.
6. Mostly blurred vision.
7. Based on the number of male patients.
8. Mostly anorgasmia or delayed ejaculation.
9. Based on the number of female patients.
10. Mostly anorgasmia or difficulty achieving orgasm.

Table 5. Treatment Emergent Adverse Effects Occurring in ≥ 1% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Social Anxiety Disorder Study[1,2]

Body System/Adverse Event	% Reporting Event: Paroxetine Hydrochloride Extended-Release Tablets (n = 186)	% Reporting Event: Placebo (n = 184)
Body as a Whole		
Headache	23%	17%
Asthenia	18%	7%
Abdominal Pain	5%	4%
Back Pain	4%	1%
Trauma[3]	3%	< 1%
Allergic Reaction[4]	2%	< 1%
Chest Pain	1%	< 1%
Cardiovascular System		
Hypertension	2%	0%
Migraine	2%	1%
Tachycardia	2%	1%
Digestive System		
Nausea	22%	6%
Diarrhea	9%	8%
Constipation	5%	2%
Dry Mouth	3%	2%
Dyspepsia	2%	< 1%
Decreased Appetite	1%	< 1%
Tooth Disorder	1%	0%
Metabolic/Nutritional Disorders		
Weight Gain	3%	1%
Weight Loss	1%	0%
Nervous System		
Insomnia	9%	4%
Somnolence	9%	4%
Libido Decreased	8%	1%
Dizziness	7%	4%
Tremor	4%	2%
Anxiety	2%	1%
Concentration Impaired	2%	0%
Depression	2%	1%
Myoclonus	1%	< 1%
Paresthesia	1%	< 1%
Respiratory System		
Yawn	2%	0%
Skin and Appendages		
Sweating	14%	3%
Eczema	1%	0%
Special Senses		
Abnormal Vision[5]	2%	0%
Abnormality of Accommodation	2%	0%
Urogenital System		
Abnormal Ejaculation[6,7]	15%	1%
Impotence[6]	9%	0%
Female Genital Disorders[8,9]	3%	0%

1. Adverse events for which the reporting rate for paroxetine hydrochloride extended-release tablets was less than or equal to the placebo rate are not included. These events are: Dysmenorrhea, flatulence, gastroenteritis, hypertonia, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.
2. < 1% means greater than zero and less than 1%.
3. Various physical injuries.
4. Most frequently seasonal allergic symptoms.
5. Mostly blurred vision.
6. Based on the number of male patients.
7. Mostly anorgasmia or delayed ejaculation.
8. Based on the number of female patients.
9. Mostly anorgasmia or difficulty achieving orgasm.

A comparison of adverse event rates in a fixed dose study comparing immediate-release paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with the use of immediate-release paroxetine.

Male and Female Sexual Dysfunction with SSRIs: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain; however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

The percentage of patients reporting symptoms of sexual dysfunction in the pool of two placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of three placebo-controlled trials in patients with panic disorder, and in the placebo-controlled trial in patients with social anxiety disorder, are as follows:

	Major Depressive Disorder		Panic Disorder		Social Anxiety Disorder	
	Paroxetine HCl Extended-Release Tablets	Placebo	Paroxetine HCl Extended-Release Tablets	Placebo	Paroxetine HCl Extended-Release Tablets	Placebo
n (males)	**78**	**78**	**162**	**194**	**88**	**97**
Decreased Libido	10%	5%	9%	6%	13%	1%
Ejaculatory Disturbance	26%	1%	27%	3%	15%	1%
Impotence	5%	3%	10%	1%	9%	0%
n (females)	**134**	**133**	**282**	**251**	**98**	**87**
Decreased Libido	4%	2%	8%	2%	4%	1%
Orgasmic Disturbance	10%	<1%	7%	1%	3%	0%

There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with paroxetine hydrochloride extended-release tablet or the immediate-release formulation, had minimal weight loss (about 1 pound). No significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature) were observed in patients treated with paroxetine hydrochloride extended-release tablets, or immediate-release paroxetine hydrochloride, in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In a pool of two placebo-controlled clinical trials, patients treated with paroxetine hydrochloride extended-release tablets or placebo exhibited abnormal values on liver function tests at comparable rates. In particular, the extended-release paroxetine versus placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with paroxetine hydrochloride extended-release tablets and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern.

Two of the patients treated with paroxetine hydrochloride extended-release tablets dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of three studies of patients with panic disorder, 4 of 444 patients treated with paroxetine hydrochloride extended-release tablets and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all four patients decreased substantially after discontinuation of paroxetine hydrochloride extended-release tablets. The clinical significance of these findings is unknown.

In placebo-controlled clinical trials with the immediate-release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients.

Hallucinations: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9,089 patients receiving drug and in 4 of 3,187 patients receiving placebo.

Other Events Observed During the Clinical Development of Paroxetine: The following adverse events were reported during the clinical development of paroxetine hydrochloride extended-release tablet and/or the clinical development of the immediate-release formulation of paroxetine.

Adverse events for which frequencies are provided below occurred in clinical trials with the extended-release formulation of paroxetine. During its premarketing assessment in major depressive disorder, panic disorder and social anxiety disorder, multiple doses of paroxetine hydrochloride extended-release tablets were administered to 1,627 patients in phase three double-blind, controlled, outpatient studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a COSTART based dictionary. The frequencies presented, therefore, represent the proportion of the 1,627 patients exposed to paroxetine hydrochloride extended-release tablets who experienced an event of the type cited on at least one occasion while receiving paroxetine hydrochloride extended-release tablets. All reported events are included except those already listed in Tables one through four and those events where a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was deleted or, when possible, replaced with a more informative term. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase two and three studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to immediate-release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed dose and titration studies. Only those events not previously listed for extended-release paroxetine are included. The extent to which these events may be associated with paroxetine hydrochloride extended-release tablets is unknown.

Events are listed alphabetically within the respective body system. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: Infrequent were chills, face edema, fever, flu syndrome, malaise; rare were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed were adrenergic syndrome, neck rigidity, sepsis.

Cardiovascular System: Infrequent were angina pectoris, bradycardia, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

Digestive System: Infrequent were bruxism, dysphagia, eructation, gastritis, gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal, melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis, glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue edema.

Endocrine System: Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus, hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

Hemic and Lymphatic System: Infrequent were anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: Infrequent were generalized edema, hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, nonprotein nitrogen (NPN) increased.

Musculoskeletal System: Infrequent were arthritis, bursitis, tendonitis; rare were myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis, tenosynovitis, tetany.

Nervous System: Frequent were depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

Respiratory System: Frequent were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

Skin and Appendages: Frequent were rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

Urogenital System: Frequent were dysmenorrhea*; infrequent were albuminuria, amenorrhea*, breast pain*, cystitis, dysuria, prostatitis*, urinary retention; rare were breast enlargement*, breast neoplasm*, female lactation, hematuria, kidney calculus, metrorrhagia*, nephritis, nocturia, pregnancy and puerperal disorders*, salpingitis, urinary incontinence, uterine fibroids enlarged*; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

*Based on the number of men and women as appropriate.

Post-Marketing Reports: Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome like events, serotonin syndrome; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including Torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: Paroxetine hydrochloride is not a controlled substance.

Physical and Psychologic Dependence: Paroxetine hydrochloride extended-release tablets have not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of paroxetine hydrochloride extended-release tablets (e.g., development of tolerance, incrementations of dose, drug seeking behavior).

OVERDOSAGE: Human Experience: Since the introduction of immediate-release paroxetine hydrochloride in the United States, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 nonfatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including Torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdosage Management: Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for paroxetine are known.

A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS: Drug Interactions: *Drugs Metabolized by Cytochrome CPY2D6*).

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION: Major Depressive Disorder: ***Usual Initial Dosage:*** Paroxetine hydrochloride extended-release tablets should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials demonstrating the effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 25 mg dose may benefit from dose increases, in 12.5 mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least one week.

Patients should be cautioned that paroxetine hydrochloride extended-release tablets should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with paroxetine hydrochloride extended-release tablets should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has shown that efficacy is maintained for periods of up to one year with doses that averaged about 30 mg, which corresponds to a 37.5 mg dose of paroxetine hydrochloride extended-release tablets, based on relative bioavailability considerations (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Panic Disorder: ***Usual Initial Dosage:*** Paroxetine hydrochloride extended-release tablets should be administered as a single daily dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should occur in 12.5 mg/day increments and at intervals of at least one week. Patients were dosed in a range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of paroxetine hydrochloride extended-release tablets. The maximum dosage should not exceed 75 mg/day.

Patients should be cautioned that paroxetine hydrochloride extended-release tablets should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3 month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo. Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Social Anxiety Disorder: ***Usual Initial Dosage:*** Paroxetine hydrochloride extended-release tablets should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial demonstrating the effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of social anxiety disorder. If the dose is increased, this should occur at intervals of at least one week, in increments of 12.5 mg/day, up to a maximum of 37.5 mg/day.

Patients should be cautioned that paroxetine hydrochloride extended-release tablets should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with paroxetine hydrochloride extended-release tablets should remain on it. Although the efficacy of paroxetine hydrochloride extended-release tablets beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Special Populations*: Treatment of Pregnant Women During the Third Trimester:* Neonates exposed to paroxetine hydrochloride extended-release tablets and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Dosage for Elderly or Debilitated Patients, and Patients with Severe Renal or Hepatic Impairment: The recommended initial dose of paroxetine hydrochloride extended-release tablets is 12.5 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 50 mg/day.

Switching Patients to or From a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with paroxetine hydrochloride extended-release tablets. Similarly, at least 14 days should be allowed after stopping paroxetine hydrochloride extended-release tablets before starting an MAOI.

Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets: Symptoms associated with discontinuation of immediate-release paroxetine hydrochloride or paroxetine hydrochloride extended-release tablets have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine hydrochloride extended-release tablets are being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED: Paroxetine Hydrochloride Extended-release Tablets are available as 12.5 mg and 25 mg tablets.

The 12.5 mg tablet is a white film-coated, round, unscored tablet with **M** over **P3** imprinted in black ink on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-2003-93
bottles of 30 tablets

NDC 0378-2003-01
bottles of 100 tablets

NDC 0378-2003-05
bottles of 500 tablets

The 25 mg tablet is a lavender film-coated, round, unscored tablet with **M** over **P4** imprinted in black ink on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-2004-93
bottles of 30 tablets

NDC 0378-2004-01
bottles of 100 tablets

NDC 0378-2004-05
bottles of 500 tablets

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

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

PHARMACIST: Dispense a Medication Guide with each prescription.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED MAY 2007
PRXT:R2mc

Medication Guide

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults when the medicine is first started.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is first started or when the dose is changed.
    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

• thoughts about suicide or dying • attempts to commit suicide • new or worse depression • new or worse anxiety • feeling very agitated or restless • panic attacks • trouble sleeping (insomnia)	• new or worse irritability • acting aggressive, being angry, or violent • acting on dangerous impulses • an extreme increase in activity and talking (mania) • other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Revised 5/2007

Medication Guide

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- panic attacks
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This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Revised 5/2007

12.5 mg*

*Each extended-release tablet contains paroxetine hydrochloride equivalent to 12.5 mg of paroxetine.

MYLAN®

NDC 0378-2003-93

ATTENTION: Dispense with Medication Guide

PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS

12.5 mg*

30 TABLETS

℞ only

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.]

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM2003H

12.5 mg*

*Each extended- elease tablet contains paroxetine hydrochloride equivalent to 12 5 mg of paroxetine.

MYLAN®

NDC 0378-2003-01

ATTENTION: Dispense with Medication Guide

PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS

12.5 mg*

100 TABLETS

℞ only

Dispense in a ight, light-resistant container as defined in the USP using a child- esistant closu e.

RM2003A

Keep container tightly closed.

Keep this and all medication out of he each of child en.

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

Usual Dosage: See accompanying p escribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

12.5 mg*

*Each extended-release tablet contains paroxetine hydrochloride equivalent to 12.5 mg of paroxetine.

MYLAN®

NDC 0378-2003-05

ATTENTION: Dispense with Medication Guide

PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS

12.5 mg*

500 TABLETS

℞ only

Dispense in a light, 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.]

Usual Dosage: See accompanying prescribing information.

This container is not intended for dispensing for household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM2003B

25 mg*

*Each extended-release tablet contains paroxetine hydrochloride equivalent to 25 mg of paroxetine.

MYLAN®

NDC 0378-2004-93

ATTENTION: Dispense with Medication Guide

PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS

25 mg*

30 TABLETS

℞ only

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.]

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM2004H

25 mg*

*Each extended-release tablet contains paroxetine hydrochloride equivalent to 25 mg of paroxetine.

MYLAN®

NDC 0378-2004-01

ATTENTION: Dispense with Medication Guide

PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS

25 mg*

100 TABLETS

℞ only

Dispense in a tight, light-resistant container as defined in he USP using a child-resistant closu e.

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.]

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM2004A

25 mg*

*Each extended-release tablet contains paroxetine hydrochloride equivalent to 25 mg of paroxetine.

MYLAN®

NDC 0378-2004-05

ATTENTION: Dispense with Medication Guide

PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS

25 mg*

500 TABLETS

℞ only

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

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.]

Usual Dosage: See accompanying prescribing information.

This container is not intended for dispensing fo household use.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM2004B

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-873

LABELING REVIEWS

A-6.1

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

ANDA Number: 77-873 Date of Submissions: November 8, 2005 and March 10, 2006

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Paroxetine Hydrochloride Extended-Release Tablets, 12.5 mg and 25 mg

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Labeling Deficiencies:

1. CONTAINER - 30s, 100s, 500s

   a. Please ensure that you differentiate your product strengths by using boxing, contrasting colors, and/or some other means.

   b. Delete, "USP" from your statement on the side panel.

2. INSERT

   a. GENERAL

      (1) You have filed paragraph III certifications to the following patents, 4,721,723, 4,839,177 and 5,789,449, expiring December 13, 2005, June 29, 2007 and July 6, 2009, respectively. The patent '449' will expire after the expiration of the I-405 and D-91 exclusivities. However, you have carved out information relating to the two above exclusivities. Please revise and/or cllarify.

      (2) Change "paroxetine hydrochloride extended-release" to paroxetine hydrochloride extended-release tablets" throughout the insert.

   b. DESCRIPTION

      (1) Second and third paragraphs, delete reference to "USP".

      (2) Please indicate lactose type.

      (3) Label your product to indicate with which impurity tests the article complies as stated in the USP 29, monograph for paroxetine hydrochloride. Include this statement as the last paragraph in this section.

3. MEDICATION GUIDE

      (1) Please indicate how many patient medication guides will accompany each container size and how they will be presented.

      (2) Ensure that the medication guide that will be dispensed to the patients complies with 21 CFR 208.20.

Please revise your container labels and insert labeling, as instructed above. The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2alG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

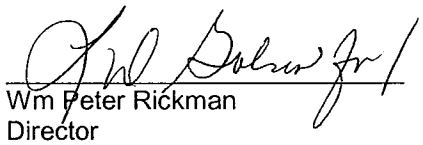
Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be

submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

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

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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



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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling?
Container Labels:

Professional Package Insert Labeling:

BASIS OF APPROVAL:

Patents/exclusivities:

Patent Data – NDA 20-936

No	Expiration	Use Code	Use	File	Labeling Impact
4721723	June 29, 2007			III	None
4839177	December 13, 2006			III	None
5422123	December 6, 2012			IV	None
5789449	July 6, 2009	U-286	Depression	III	None
5872132	November 19, 2015			IV	None
5900423	November 19, 2015			IV	None
6121291	September 17, 2017	U-286	Depression	IV	None
6133289	May 19, 2015	U-286	Depression	IV	None
6548084	January 19, 2017			IV	None

Exclusivity Data - NDA 20-936

Code/sup	Expiration	Use Code	Description		Labeling Impact
I-405	August 29, 2006		TREATMENT OF PREMENSTRUAL DYSPHORIC DISORDER (PMDD) USING AN INTERMITTENT DOSING REGIMEN		Carved out (See comment to firm)
D-91	January 27, 2007		ALTERNATE INTERMITTENT DOSING REGIMEN		Carved out (See comment to firm)

Mylan will not market product until after the expiration of the two above exclusivities.

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Paxil CR®
NDA Number: 20-936
NDA Drug Name: Paxil CR ® (paroxetine hydrochloride) Extended-ReleaseTablets
NDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #: (S-021), approved 3-9-06
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

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 29		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? NO.		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	
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	
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?		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.		X	
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?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
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	
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?		?	
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:

The USP 29 monograph for paroxetine hydrochloride states the following; "Label it to indicate whether it is the anhydrous or the hemihydrate form. Label it to indicate with which impurity tests the article complies."

Which impurity test should Mylan include in their labeling?

FOR THE RECORD:

1. This review was based on the labeling for Paxil® CR(NDA 20-936/S-021) SmithKline Beecham; approved 3/9/06.

2. Patents/exclusivities:

Patent Data – NDA 20-936

No	Expiration	Use Code	Use	File	Labeling Impact
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4839177	December 13, 2006			III	None
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6133289	May 19, 2015	U-286	Depression	IV	**None**
6548084	January 19, 2017			IV	**None**

Exclusivity Data - NDA 20-936

Code/sup	Expiration	Use Code	Description		Labeling Impact
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D-91	January 27, 2007		ALTERNATE INTERMITTENT DOSING REGIMEN		Carved out (See comment to the firm)

Mylan will not market product until after the expiration of the two above exclusivities. I will ask Mylan to include information relating to the above exclusivities which expire before the patent "449, (7/6/09) in which Mylan filed a P-III.

3. Mylan Pharmaceuticals Inc.is the manufacturer (p 9807, V. 1.19).

4. The inactives are listed accurately in the DESCRIPTION section (p 9578 V 1.19 and p. 185 Vol 3.1).

5. Storage/dispensing:

NDA: Store at or below 25°C (77°F). Dispense in a tight, light-resistant container.

ANDA: Store at 20 - 25 °C (68-77°F) [see USP Controlled Room Temperature]". Dispense in a tight, light-resistant container.

USP: Not USP, however the active ingredient is USP and recommends to label to indicate whether the anhydrous or the hemihydrate. Label it to indicate with which impurity tests the article complies. (See comment to the firm)

6. The innovator's 12.5 mg and 25 mg tablets are not scored.
The ANDA has the same scoring configurations.

7. Product line

NDA: 30s
ANDA: 30s, 100s and 500s (all strengths)

8. Packaging [p 6191- 6218, Vol 1.19]

30s and 100s Tablets 75 cc	Bottles Beige, round, HDPE
38 mm (used for 30s, 100s and 500s)	Caps Clear, Polypropylene, CRC Innerseal
500 Tablets 150 cc	Bottles Beige, round, HDPE

10 . The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). (Vol 1.20, p.10118 and V.3.1 pg. 324)

12. Medication Guide

I have asked the firm to describe their plan for distributing the medication guides.

Date of Review: 6-21-06 **Date of Submissions:** 11/8/05 and 3/10/06

Primary Reviewer: Michelle Dillahunt **Date:** 6/27/06

Team Leader: Lillie Golson **Date:** 6/27/06

cc:

ANDA: 77-873
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSAM\MYLAN\LTRS&REV\77873 na1 labeling.doc
Review

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

ANDA Number: 77-873 Date of Submission: August 1, 2006

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Paroxetine Hydrochloride Extended-Release Tablets, 12.5 mg and 25 mg

---

Labeling Deficiencies:

1. CONTAINER - 30s, 100s, 500s

   a. Side panel, revise as follows; "Each extended-release tablet contains paroxetine hydrochloride equivalent to xx mg of paroxetine."

   b. Delete the statement, "[redacted (b) (4)]."

2. INSERT/MEDICATION GUIDE

   a. Clinical Pharmacology, Clinical Trials, Social Anxiety Disorder, delete last paragraph, "[redacted (b) (4)] [redacted (b) (4)]…"

   b. WARNINGS

   (i) Add the following to appear after the subsection; Potential for Interaction With Monoamine Oxidase Inhibitors;

   Serotonin Syndrome

   The development of a potentially life-threatening serotonin syndrome may occur with use of paroxetine hydrochloride extended-release tablets, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

   The concomitant use of paroxetine hydrochloride extended–release tablets with MAOIs intended to treat depression is contraindicated (see CONTRAINDICATIONS and WARNINGS—Potential for Interaction With Monoamine Oxidase Inhibitors). If concomitant use of paroxetine hydrochloride extended-release tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see PRECAUTIONS—Drug Interactions).

   The concomitant use of paroxetine hydrochloride extended-release tablets with serotonin precursors (such as tryptophan) is not recommended (see PRECAUTIONS—Drug Interactions).

   Potential Interaction With Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes–type arrhythmias, and sudden death. This effect appears to be dose related.

   An in vivo study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

   (ii) Nonteratogenic Effects, add the following as the second, third and fourth paragraphs;

   Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants

exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.
There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.
When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

c. PRECAUTIONS

(i). Delete (b) (4) subsection.

(ii). Information for Patients, add the following as the first paragraph;
"Paroxetine hydrochloride extended-release tablets should not be chewed or crushed, and should be swallowed whole."

(iii). Clinical Worsening and Suicide Risk, delete last paragraph, " (b) (4) (b) (4) "

(iv) Serotonergic Drugs, revise subsection as follows; "Based on the mechanism of action of paroxetine hydrochloride and the potential for serotonin syndrome, caution is advised when paroxetine hydrochloride extended-release tablets is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see WARNINGS—Serotonin Syndrome). The concomitant use of paroxtine extended release tablets with other SSRIs, SNRIs or tryptophan is not recommended (see PRECAUTIONS—Drug Interactions, Tryptophan).

(v) Triptans, revise subsection as follows; " There have been rare postmarketing reports of serotonin syndrome with the use of an SSRI and a triptan. If concomitant use of paroxetine hydrochloride extended-release tablets with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS—Serotonin Syndrome)"

d. ADVERSE REACTIONS, Other Events Observed During the Clinical Development of Paroxetine, second paragraph, second sentence, revise as follows; "…panic disorder and social anxiety disorder, multiple doses of paroxtetine hydrochloride extended-release tablets…"

e. MEDICATION GUIDE

Please provide a sample sheet electronically in final printed format of your (b) (4) medication guides.

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

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

-http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling and your last submission with all differences annotated and explained.

NOTES/QUESTIONS TO THE CHEMIST:

The USP 29 monograph for paroxetine hydrochloride states the following; "Label it to indicate whether it is the anhydrous or the hemihydrate form. Label it to indicate with which impurity tests the article complies."

Which impurity test should Mylan include in their labeling?
Hi Michelle,
They used Test 1.

Barbara

From: Dillahunt, Michelle
Sent: Tuesday, June 27, 2006 12:45 PM
To: Scott, Barbara
Cc: Ya, Naiqi; Golson, Lillie D
Subject: RE: ANDA 77-873 (Paroxetine Hydrochloride Extended-Release Tablets-Mylan)

I don't think we need to get together for a discussion. Do you know which test Mylan used?

Thanks,
Michelle

From: Scott, Barbara
Sent: Monday, June 26, 2006 10:36 AM
To: Dillahunt, Michelle
Cc: Ya, Naiqi
Subject: RE: ANDA 77-873 (Paroxetine Hydrochloride Extended-Release Tablets-Mylan)

Hi Michelle,

After speaking with my Team Leader, we feel that the USP probably just wants 'Test 1 or Test 2' specified on the labeling from the Chrom. Purity test. This would give some indication of the synthetic route that was used and the related impurities for it. Please let us know if you would like to get together for further discussion.

Thanks,
Barbara

FOR THE RECORD:

1. This review was based on the labeling for Paxil® CR (NDA 20-936/S-023, 030, 031) SmithKline Beecham; approved 8/22/06.

2. Patents/exclusivities:

Patent Data – NDA 20-936

No	Expiration	Use Code	Use	File	Labeling Impact
4721723	June 29, 2007			**III**	None
5422123	December 6, 2012			**IV**	None
5789449	July 6, 2009	U-788	METHOD OF TREATING PSYCHIATRIC SYMPTOMS ASSOCIATED WITH PREMENSTRUAL DISORDERS USING PAROXETINE	**MOU**	None
5872132	November 19, 2015			**IV**	None
5900423	November 19, 2015			**IV**	None
6121291	September 17, 2017	U-286	Depression	**IV**	None
6133289	May 19, 2015	U-286	Depression	**IV**	None

6548084	January 19, 2017			**IV**	None

Exclusivity Data - NDA 20-936

Code/sup	Expiration	Use Code	Description		Labeling Impact
I-405	August 29, 2006		TREATMENT OF PREMENSTRUAL DYSPHORIC DISORDER (PMDD) USING AN INTERMITTENT DOSING REGIMEN		Carved out
D-91	January 27, 2007		ALTERNATE INTERMITTENT DOSING REGIMEN		Carved out

See email from Martin Shimer dated 1/26/07:
Please note that the use code associated with the '449 patent covering the Paxil CR NDA 20-936 has been changed. This change will now allow OGD to accept and review Mylan's labeling with their Section viii statement to the '449.

Thanks,

Marty

3. It was decided not to include the water of hydration of the product, paroxetine hydrochloride hemihydrate on the container labels for the immediate release product. This can also be applied to the extended-release product. (See email below from Lillie Golson form 9/22/06)

   I spoke with Peter and Cec this morning. He presented to the division directions and OC that we try not to label our products with the waters of hydration unless specifically stated in the monograph for the dosage form. He said they all seemed agreeable to the idea, but he has not received final word yet. With that in mind, because the monograph for the tablet does not include this labeling statement regarding the water, the firms should not include in their labeling per Peter.

4. Mylan Pharmaceuticals Inc.is the manufacturer (p 9807, V. 1.19).

5. The inactives are listed accurately in the DESCRIPTION section (p 9578 V 1.19 and p. 185 Vol 3.1).

6. Storage/dispensing:

   NDA: Store at or below 25^{o}C (77^{o}F). Dispense in a tight, light-resistant container.

   ANDA: Store at 20 - 25 ^{o}C (68-77^{o}F) [see USP Controlled Room Temperature]". Dispense in a tight, light-resistant container.

   USP: Not USP, however the active ingredient is USP and recommends to label to indicate whether the anhydrous or the hemihydrate. Label it to indicate with which impurity tests the article complies. (See comment to the firm)

7. The innovator's 12.5 mg and 25 mg tablets are not scored.
   The ANDA has the same scoring configurations.

8. Product line

   NDA: 30s
   ANDA: 30s, 100s and 500s (all strengths)

9. Packaging [p 6191- 6218, Vol 1.19]

30s and 100s Tablets 75 cc	Bottles Beige, round, HDPE
38 mm (used for 30s,	Caps

100s and 500s)	Clear, Polypropylene, CRC Innerseal
500 Tablets 150 cc	Bottles Beige, round, HDPE

10 . The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). (Vol 1.20, p.10118 and V.3.1 pg. 324)

11. Medication Guide

Mylan's final printed outsert will contain one complete copy of the Medication Guide at the end of the prescribing information. Additional copies will be available for distribution to patients as (b) (4)

Appropriate instructions have also been included for the pharmacist in the 'How Supplied" section of the outsert and on the center panel of Mylan's container labels to instruct the pharmacist to provide a Medication Guide to the patient.

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

/s/

Michelle Dillahunt
2/5/2007 01:01:48 PM
MEDICAL OFFICER

Lillie Golson
2/5/2007 06:52:23 PM
MEDICAL OFFICER

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

ANDA Number: 77-873 Date of Submission: February 16, 2007

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Paroxetine Hydrochloride Extended-Release Tablets, 12.5 mg and 25 mg

---

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No, electronic

1. CONTAINER - 30s, 100s, 500s

   Satisfactory in FPL as of the February 16, 2007 amendment.

2. INSERT/MEDICATION GUIDE

   Satisfactory in FPL as of the February 16, 2007 amendment.

3. MEDICATION GUIDE

   Satisfactory in FPL as of the February 16, 2007 amendment.

Revisions needed pre-approval. None

BASIS OF APPROVAL:

Patents/exclusivities:

Patent Data – NDA 20-936

No	Expiration	Use Code	Use	File	Labeling Impact
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6548084	January 19, 2017			**IV**	None

Exclusivity Data - NDA 20-936

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There are no unexpired exclusivities in the Orange Book Database for this drug product.		

See email from Martin Shimer dated 1/26/07:
Please note that the use code associated with the '449 patent covering the Paxil CR NDA 20-936 has been changed. This change will now allow OGD to accept and review Mylan's labeling with their Section viii statement to the '449.

Thanks,
Marty

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Paxil CR®
NDA Number: 20-936
NDA Drug Name: Paxil CR ® (paroxetine hydrochloride) Extended-ReleaseTablets
NDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #. (S-023, 030, 031), approved 8-22-06
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

NOTES/QUESTIONS TO THE CHEMIST:

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FOR THE RECORD:

1. This review was based on the labeling for Paxil® CR(NDA 20-936/S-023, 030, 031) SmithKline Beecham; approved 8/22/06.

2. It was decided not to include the water of hydration of the product, paroxetine hydrochloride hemihydrate on the container labels for the immediate release product. This can also be applied to the extended-release product. (See email below from Lillie Golson form 9/22/06)

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3. Mylan Pharmaceuticals Inc.is the manufacturer (p 9807, V. 1.19).

4. The inactives are listed accurately in the DESCRIPTION section (p 9578 V 1.19 and p. 185 Vol 3.1).

5. Storage/dispensing:

NDA: Store at or below 25°C (77°F). Dispense in a tight, light-resistant container.

ANDA: Store at 20 - 25 °C (68-77°F) [see USP Controlled Room Temperature]". Dispense in a tight, light-resistant container.

USP: Not USP, however the active ingredient is USP and recommends to label to indicate whether the anhydrous or the hemihydrate. Label it to indicate with which impurity tests the article complies. (See comment to the firm)

6. The innovator's 12.5 mg and 25 mg tablets are not scored.
The ANDA has the same scoring configurations.

7. Product line

NDA: 30s
ANDA: 30s, 100s and 500s (all strengths)

8. Packaging [p 6191- 6218, Vol 1.19]

30s and 100s Tablets 75 cc	Bottles Beige, round, HDPE
38 mm (used for 30s, 100s and 500s)	Caps Clear, Polypropylene, CRC Innerseal
500 Tablets 150 cc	Bottles Beige, round, HDPE

9. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). (Vol 1.20, p.10118 and V.3.1 pg. 324)

10. Medication Guide

Mylan's final printed outsert will contain one complete copy of the Medication Guide at the end of the prescribing information. Additional copies will be available for distribution to patients as (b) (4)

Appropriate instructions have also been included for the pharmacist in the 'How Supplied" section of the outsert and on the center panel of Mylan's container labels to instruct the pharmacist to provide a Medication Guide to the patient.

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

/s/

Michelle Dillahunt
3/8/2007 10:38:43 AM
MEDICAL OFFICER

Lillie Golson
3/8/2007 01:31:34 PM
MEDICAL OFFICER

APPROVAL SUMMARY
(Supersedes the approval summary dated 2/16/07)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-873 Date of Submission: May 14 and May 18, 2007

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Paroxetine Hydrochloride Extended-Release Tablets, 12.5 mg and 25 mg

---

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No, electronic

1. CONTAINER - 30s, 100s, 500s

   Satisfactory in FPL as of the February 16, 2007 amendment.

2. INSERT/MEDICATION GUIDE

   Satisfactory in FPL as of the May 14, 2007 amendment.

3. MEDICATION GUIDE

   Satisfactory in FPL as of the May 14, 2007 amendment.

Revisions needed pre-approval.
INSERT
1. BOXED WARNINGS, last paragraph, add the following as the last sentence, (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

2. PRECAUTIONS

   a. General; Activation of Mania/Hypomania, third sentence, revise as follows; "…social disorder treated…

   b. Seizures, second sentence, delete "or PMDD".

BASIS OF APPROVAL:

Patents/exclusivities:

Patent Data – NDA 20-936

No	Expiration	Use Code	Use	File	Labeling Impact
4721723	June 29, 2007			**III**	None
5422123	December 6, 2012			**IV**	None
5789449	July 6, 2009	U-788	METHOD OF TREATING PSYCHIATRIC SYMPTOMS ASSOCIATED WITH PREMENSTRUAL DISORDERS USING PAROXETINE	**MOU**	None
5872132	November 19, 2015			**IV**	None
5900423	November 19, 2015			**IV**	None
6121291	September 17, 2017	U-286	Depression	**IV**	None
6133289	May 19, 2015	U-286	Depression	**IV**	None
6548084	January 19, 2017			**IV**	None

Exclusivity Data - NDA 20-936

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There are no unexpired exclusivities in the Orange Book Database for this drug product.		

See email from Martin Shimer dated 1/26/07:

Please note that the use code associated with the '449 patent covering the Paxil CR NDA 20-936 has been changed. This change will now allow OGD to accept and review Mylan's labeling with their Section viii statement to the '449.

Thanks,
Marty

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Paxil CR®
NDA Number: 20-936
NDA Drug Name: Paxil CR ® (paroxetine hydrochloride) Extended-ReleaseTablets
NDA Firm: SmithKline Beecham
Date of Approval of NDA Insert and supplement #. (S-023, 030, 031), approved 8-22-06
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

NOTES/QUESTIONS TO THE CHEMIST:

The USP 29 monograph for paroxetine hydrochloride states the following; "Label it to indicate whether it is the anhydrous or the hemihydrate form. Label it to indicate with which impurity tests the article complies."

Which impurity test should Mylan include in their labeling?
Hi Michelle,
They used Test 1.

Barbara

From: Dillahunt, Michelle
Sent: Tuesday, June 27, 2006 12:45 PM
To: Scott, Barbara
Cc: Ya, Naiqi; Golson, Lillie D
Subject: RE: ANDA 77-873 (Paroxetine Hydrochloride Extended-Release Tablets-Mylan)

I don't think we need to get together for a discussion. Do you know which test Mylan used?

Thanks,
Michelle

From: Scott, Barbara
Sent: Monday, June 26, 2006 10:36 AM
To: Dillahunt, Michelle
Cc: Ya, Naiqi
Subject: RE: ANDA 77-873 (Paroxetine Hydrochloride Extended-Release Tablets-Mylan)

Hi Michelle,

After speaking with my Team Leader, we feel that the USP probably just wants 'Test 1 or Test 2' specified on the labeling from the Chrom. Purity test. This would give some indication of the synthetic route that was used and the related impurities for it. Please let us know if you would like to get together for further discussion.

Thanks,
Barbara

FOR THE RECORD:

1. This review was based on the labeling for Paxil® CR(NDA 20-936/S-023, 030, 031) SmithKline Beecham; approved 8/22/06. Mylan has added the revised suicidal warnings that were made available on FDA's website on May 2, 2007. The template can be found on the following link,
   http://www.fda.gov/cder/drug/antidepressants/default.htm

2. It was decided not to include the water of hydration of the product, paroxetine hydrochloride hemihydrate on the container labels for the immediate release product. This can also be applied to the extended-release product. (See email below from Lillie Golson form 9/22/06)

   I spoke with Peter and Cec this morning. He presented to the division directions and OC that we try not to label our products with the waters of hydration unless specifically stated in the monograph for the dosage form. He said they all seemed agreeable to the idea, but he has not received final word yet. With that in mind, because the monograph for the tablet does not include this labeling statement regarding the water, the firms should not include in their labeling per Peter.

3. Mylan Pharmaceuticals Inc.is the manufacturer (p 9807, V. 1.19).

4. The inactives are listed accurately in the DESCRIPTION section (p 9578 V 1.19 and p. 185 Vol

3.1).

5. Storage/dispensing:

NDA: Store at or below 25°C (77°F). Dispense in a tight, light-resistant container.

ANDA: Store at 20 - 25 °C (68-77°F) [see USP Controlled Room Temperature]". Dispense in a tight, light-resistant container.

USP: Not USP, however the active ingredient is USP and recommends to label to indicate whether the anhydrous or the hemihydrate. Label it to indicate with which impurity tests the article complies. (See comment to the firm)

6. The innovator's 12.5 mg and 25 mg tablets are not scored.
The ANDA has the same scoring configurations.

7. Product line

NDA: 30s
ANDA: 30s, 100s and 500s (all strengths)

8. Packaging [p 6191- 6218, Vol 1.19]

30s and 100s Tablets 75 cc	Bottles Beige, round, HDPE
38 mm (used for 30s, 100s and 500s)	Caps Clear, Polypropylene,CRC Innerseal
500 Tablets 150 cc	Bottles Beige, round, HDPE

9. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). (Vol 1.20, p.10118 and V.3.1 pg. 324)

10. Medication Guide

Mylan's final printed outsert will contain one complete copy of the Medication Guide at the end of the prescribing information.

Mylan currently has a contract with (b) (4) for the distribution of medication guides. The contract (b) (4). The contract is (b) (4).

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

/s/

Michelle Dillahunt
5/24/2007 10:26:42 AM
LABELING REVIEWER

Lillie Golson
5/24/2007 12:06:51 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-873

CHEMISTRY REVIEWS

ANDA 77-873

Paroxetine Hydrochloride Extended Release Tablets, 12.5 and 25 mg

Mylan Pharmaceuticals, Inc.

Barbara O. Scott

OGD/DC2

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-873

2. REVIEW #: 1a

3. REVIEW DATE: March 1, 2006 Revision Date: April 28, 2006; May 12, 2006; June 12, 2006; April 30, 2007 (N. Ya)

4. REVIEWER: Barbara O. Scott

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
none	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Application	September 9, 2005
Major Amendment (New Strength)	November 7, 2005
Major Amendment	April 13, 2006
Major Amendment	June 9, 2006
Gratuitous Amendment (change imprinting ink)	March 16, 2007
T-con Amendment (see Appendix B for comments)	April 24, 2007
T-con Amendment (see Appendix B for comments)	May 3, 2007

7. NAME & ADDRESS OF APPLICANT:

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attn: S. Wayne Talton
Phone: 304.599.2595
FAX: 304.285.6407

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION:

The basis for Mylan's proposed ANDA for Paroxetine Hydrochloride Extended-Release Tablets is the approved reference listed drug, Paxil CR® the subject of ANDA 20-936 held by Glaxo Smith Kline (GSK).

To the best of Mylan's knowledge the following patents are invalid, unenforceable or will not be infringed by the manufacture, sale, use, offer for sale, or importation of Paroxetine Hydrochloride Extended-Release Tablets, the subject of this application:

Patent Number	Expiration Date
US 5,422,123 PED	Dec. 6, 2012
US 5,872,132 PED	Nov. 19, 2015
US 5,900,423 PED	Nov. 19, 2015
US 6,133,289 PED	Nov. 19, 2015
US 6,548,084 PED	Jan. 19, 2017
US 6,121,291 PED	Sep. 17, 2017

There are three patents that claim the listed product, Paxil CR®:

Patent #	Expiration Date
US 4,839,177	June 13, 2006/PED Exclusivity Dec. 13, 2006
US 4,721,723	Dec. 29, 2006/PED Exclusivity June 29, 2007
US 5,789,449	Jan. 6, 2009/PED Exclusivity July 6, 2009 Use Code U-286 is associated with this patent

The following exclusivities are:

Exclusivity	Dates
New Indication (I-358) for Panic Disorder	Expired: Feb. 12, 2005; Associated PED expired Aug. 21, 2005
New Indication (I-405) for Premenstrual Dysophoric Disorder	Expires: Aug. 28, 2006
New Dosing Schedule (D-91) for Alternate Intermittant Dosing Regimen	Expires: Jan. 27, 2007

Mylan will provide notice to each patent owner subject to Paragraph IV and also to the holder of the approved application for the listed drug claimed by said patents. Mylan seeks to market its Paroxetine Hydrochloride Extended Release Tablets, 12.5 mg and 25

mg, upon FDA approval, following the expiration of U.S. Patent Numbers: 4,721,723; 5,789,449; 4,839,177 and their associated PED exclusivities; the expiration of exclusivities D-91 and I-405; and prior to the expiration of U.S. Patent Numbers: 5,422,123;5,872,132; 5,900,423; 6,133,289; 6,121,291; and 6,548,084.

10. PHARMACOL. CATEGORY:

The drug product is indicated for the treatment of major depressive disorder, panic disorder, social anxiety disorder and premenstrual dysphoric disorder.

11. DOSAGE FORM:

Extended Release Tablet

12. STRENGTH/POTENCY:

12.5 mg and 25 mg (TDI = 75 mg/day)

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

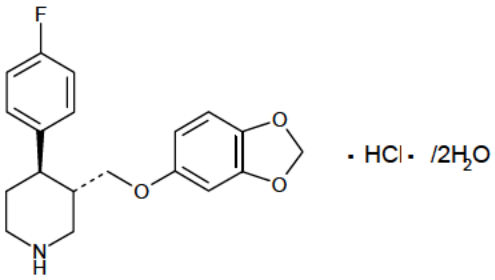
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

USAN	Paroxetine Hydrochloride Hemihydrate
Ingredient Dictionary name	Paroxetine
Trade name	Paroxetine
Chemical name	(3S-trans) 3-[1,3-benzodioxyl-5-yloxy)methyl]-4-(4-flurophenyl)-piperidine hydrochloride, hemihydrate (-)-(3S,4R)-4-(p-fluorophenyl)-3-([(3,4-methylenedioxy)phenoxy]methyl)piperidine Hydrochloride, hemihydrate (3S,4R) -3-[1,3-benzodioxol -5-yloxy)methyl]-4-(4-fluorophenyl)piperidine hydrochloride hemihydrate
CAS number	110429-35-1
Molecular Weight	374.83 g/mole



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	May 12, 2006	B. Scott
	III			4	N/A		LOA p. 10097
	III			4	N/A		LOA p. 10099
	III			4	N/A		LOA p. 10101
	III			4	N/A		LOA p. 10104
	III			4	N/A		LOA p. 10106
	III			4	N/A		LOA p. 10108
	III			4	N/A		LOA p. 10110

[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)
DMF Letters of Authorization and Technical data are provided on pp. 10068-10112, vol. 1.19

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Assigned for inspection (b) (4) Mylan 1/2/2006	Acceptable 1/30/07	
Methods Validation	N/A as per OGD policy		
Labeling	Acceptable	3/8/07	MDillahunt
Bioequivalence	Acceptable	7/21/2006	
EA	Exclusion		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 77-873

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application 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(s) and Drug Substance(s)

The drug substance is a compendial item but the drug product in the extended release form is not. There is a monograph for Paroxetine Hydrochloride Tablets.

The proposed drug product is Paroxetine Hydrochloride Extended Release Tablets, 12.5 mg and 25 mg. The active ingredient is Paroxetine Hydrochloride Hemihydrate, USP. The inactive ingredients are: Lactose, NF; Microcystalline Cellulose, NF; Hypromellose, USP; Hydroxypropyl Cellulose, NF; Magnesium Stearate, NF; Colloidal Silicon Dioxide, NF; D&C Red #30 Lake (b) (4) Methacrylic Acid Copolymer, NF; Talc, USP; Triethyl Citrate, NF; Polysorbate 80, NF; Sodium Hydroxide, NF; (b) (4) (b) (4) (25 mg), (b) (4) (12.5 mg), Fine Black Pharmaceutical Ink; (b) (4) Black (b) (4) imprinting ink; (b) (4).

The RLD is not scored.

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

The drug product is indicated for the treatment of major depressive disorder, panic disorder, social anxiety disorder and premenstrual dysphoric disorder.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is approvable.

Following this page, 25 pages withheld in full - (b)(4)

Appendix B

Deficiencies FAXED to Mylan March 10, 2006:

The deficiencies presented below represent MINOR deficiencies and the current review cycle will remain open. You should respond to these deficiencies with a telephone amendment within ten days. If you have questions regarding these deficiencies please contact the Project Manager, Tom Hinchliffe, at 301-827-5771. Please submit documentation by fax to the attention of the Project Manager at 301-443-3839. Please also submit official hard copies of any faxed documentation to the Document Room.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.
10.
11.

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

1. Please provide all stability data collected to date for both strengths.

2. The DMF by (b) (4) (DMF # (b) (4) has been reviewed and is inadequate. Please do not respond to these deficiencies until (b) (4) has contacted you that they have resolved all outstanding issues.

3. Please remove all annotations from the ANDA that refer to (b) (4) we will not consider it until a formal amendment is received.

Deficiency FAXED to Mylan May 31, 2006:

The deficiencies presented below represent MINOR deficiencies and the current review cycle will remain open. You should respond to these deficiencies with a telephone amendment within ten days. If you have questions regarding these deficiencies please contact the Project Manager, Tom Hinchliffe, at 301-827-5771. Please submit documentation by fax to the attention of the Project Manager at 301-443-3839. Please also submit official hard copies of any faxed documentation to the Document Room.

1. Please include (b) (4) .

Comments Communicated to Mylan by phone on April 12, 2007:

1. (b) (4) in accordance with the current USP monograph.

2. With respect to (b) (4), please explain why (b) (4)

3. Please add (b) (4)

Comment Communicated to Mylan by phone on April 30, 2007:

1. With respect to your (b) (4)

cc: ANDA 77-873
DIV FILE
Field Copy

Endorsements
HFD-640/B. Scott/3/9/07
HFD-640/N. Ya/
HFD-640/T. Hinchliffe/3/8/07

F/T by:rad

V:\FIRMSAM\Mylan\LTRS&REV\77873CR01a.DOC

TYPE OF LETTER: approval

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

/s/

Thomas Hinchliffe
5/30/2007 08:30:45 AM
CSO
for BScott on extended leave

Naiqi Ya
5/30/2007 09:33:26 AM
CHEMIST

Final Approval Following a Tentative Approval
Abbreviated New Drug Application Regulatory Assessment

---

1. ANDA # 77-873

2. NAME AND ADDRESS OF APPLICANT

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

3. LEGAL BASIS FOR SUBMISSION

With respect to the '123, '132, '423, '291, '289, and '084 patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Paroxetine Hydrochloride Extended-release tablets 12.5 and 25 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Mylan Pharmaceuticals, Inc. (Mylan) for infringement of one or more of the patents that were the subjects of the paragraph IV certifications. You have notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Mylan within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

With respect to the '499 patent, your ANDA contains a statement under section 505(j)(2)(A)(viii) of the Act indicating that this is a method of use patent that does not claim any indication for which you are seeking approval under your ANDA.

With respect to the ‘723 patent, your ANDA contains a paragraph III certification under section 505(j)(2)(A)(vii)(III) of the Act stating that Mylan will not market Paroxetine Hydrochloride Extended-release tablets, 12.5 and 25 mg, prior to the expiration of this patent. The agency recognizes that the ‘723 patent has expired as of June 29, 2007.

4. PROPRIETARY NAME – NA

5. NONPROPRIETARY NAME

Paroxetine Hydrochloride Extended-Release Tablets

6. CURRENT SUBMISSIONS AND OTHER DATES:

June 11, 2007

7. PHARMACOLOGICAL CATEGORY

The drug product is indicated for the treatment of major depressive disorder, panic disorder, social anxiety disorder and premenstrual dysphoric disorder.

8. Rx or OTC - RX

9. SAMPLES AND RESULTS -NA

10. LABELING STATUS - Acceptable - 3/8/07

11. BIOEQUIVALENCY STATUS - Acceptable 7/21/2006

12. MICROBIOLOGY STATUS - NA

13. ESTABLISHMENT INSPECTION

Acceptable - 1/30/2007

14. CONCLUSIONS AND RECOMMENDATIONS

CMC Approvable Per acceptable CMC review by Barbara Scott dated 5/30/07 in DFS.

No changes to CMC have occurred.

PROJECT MANAGER: Thomas Hinchliffe DATE COMPLETED: 6/19/07

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

/s/

Thomas Hinchliffe
6/29/2007 09:40:52 AM
CSO

Naiqi Ya
6/29/2007 09:42:22 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-873

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-873
Drug Product Name	Paroxetine HCl ER tablet
Strength	25 mg and 12.5 mg
Applicant Name	Mylan Pharmaceuticals Inc.
Submission Date(s)	9 Sep 2005; Amendment for an additional strength (12.5 mg) - 8 Nov 05
First Generic	Y
Reviewer	J. Lee
File Location	**V:\firmsam\mylan\ltrs&rev\77873D905.doc**
Clinical Site	PRACS Institute; East Grand Forks, MN
Analytical Site	Mylan; Morgantown, WVa.

EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The FDA method consist of 2 stages viz. 2 hours of acid stage (750 ml of 0.1 N HCl using paddle at 150 rpm) followed by 12 hours of buffer stage (1000 ml of 0.05M tris buffer pH 7.5 using paddle at 150 rpm). Mylan's dissolution data with the FDA method gave "erratic" results in the second stage because of floating tablet particles due to high paddle speed (150 rpm). Mylan conducted a series of dissolution testing with paddle at 50 and 75 rpm as well as basket at 100 rpm and determined that basket at 100 rpm is better than paddle at any speed. Mylan's used the following dissolution method.

Acid stage (2hrs) in 750 ml of 0.1 N HCl with basket at 100 rpm at 37^0 C followed by Buffer stage (12 hrs) in 0.05M tris buffer pH 7.5 with basket at 100 rpm at 37^0 C.
Based on the dissolution data Mylan proposed following dissolution specifications.
The DBE agrees with the Mylan's method but recommends alternative specifications.

		Firm's proposal	DBE proposal
Acid stage	2 hrs	NMT (b) (4)	NMT (b) (4)
Buffer Stage	2hrs		
	4hrs		
	12hrs	NLT	NLT

Mylan needs to acknowledge the dissolution testing method and specifications.

Mylan also submitted dissolution data in four different media. The dissolution data are acceptable.

The firm has submitted all the CTD tables.

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

RLD METHOD

Step 1

Medium	0.1N HCl for 2 hrs
Volume	750 ml
Temperature	37°C
Apparatus	II
Rotational Speed	150 rpm
Specification	NMT (b) (4) in 2 hrs

Step 2

Medium	pH 7.5 Tris buffer containing 50 mmol Tris
Volume	1000 ml
Temperature	37°C
Apparatus	II
Rotational Speed	150 rpm
Specification	1 hr: NMT (b) (4); 2 hrs: (b) (4); 4 hrs: (b) (4) (b) (4) 6 hrs: NLT (b) (4) dissolved

Source of Method: DBE Dissolution Data Base

Table 1. Summary of In Vitro Dissolution Data

Using sponsor's proposed method

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)						Study Report Location
					Acid Stage	Buffer Stage					
					2 hours	1 hour	2 hours	4 hours	8 hours	12 hours	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R1N1802	12.5mg tablet	Apparatus: 1 (basket) Speed: 100 rpm Medium: Acid Stage - 0.1N Hydrochloric Acid Buffer Stage – 0.05M Tris Buffer, pH 7.5 ± 0.05 Volume: Acid Stage – 750mL Buffer Stage – 1000mL Temperature: 37°C ± 0.5°C	12	1% RSD 31.6%	7% RSD 13.3%	20% RSD 10.4%	55% RSD 5.9%	95% RSD 2.4%	98% (b) (4) RSD 2.1%	Volume 1, pages 9536-9539
N/A	Paxil CR® Tablets Lot 773F06	12.5mg tablet		12	0% RSD 93.9%	5% RSD 16.1%	16% RSD 12.2%	52% RSD 5.5%	94% RSD 2.2%	99% (b) (4) RSD 2.5%	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R1N0377	25mg tablet	Apparatus: 1 (basket) Speed: 100 rpm Medium: Acid Stage - 0.1N Hydrochloric Acid Buffer Stage – 0.05M Tris Buffer, pH 7.5 ± 0.05 Volume: Acid Stage – 750mL Buffer Stage – 1000mL Temperature: 37°C ± 0.5°C	12	0% RSD 346.4%	7% RSD 7.2%	21% RSD 8.5%	65% RSD 5.9%	93% RSD 2.1%	99% (b) (4) RSD 1.5%	Original ANDA Volume 18, pages 9535-9539
N/A	Paxil CR® Tablets Lot 1274P07	25mg tablet		12	0% (b) (4) RSD 346.4%	5% (b) (4) RSD 17.6%	16% RSD 12.6%	45% RSD 13.3%	90% RSD 6.9%	100% (b) (4) RSD 1.5%	

Using sponsor's proposed method w/4 different media

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range) 1 hour	2 hour	4 hours	Study Report Location
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R1ND377	25mg tablet	Apparatus: 1 (basket) Speed: 100 rpm Medium: Water Volume: 1000mL Temperature: 37°C ± 0.5°C	6	0%	0%	0% (b) (4)	Original ANDA Volume 18, page 9563
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R1ND377	25mg tablet	Apparatus: 1 (basket) Speed: 100 rpm Medium: 0.1N Hydrochloric Acid Volume: 1000mL Temperature: 37°C ± 0.5°C	6	0%	0%	0% (b) (4)	Original ANDA Volume 18, page 9564
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R1ND377	25mg tablet	Apparatus: 1 (basket) Speed: 100 rpm Medium: pH 4.5 acetate Volume: 1000mL Temperature: 37°C ± 0.5°C	6	0%	0%	0% (b) (4)	Original ANDA Volume 18, page 9565

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range) 1 hour	2 hours	4 hours	6 hours	8 hours	12 hours	Study Report Location
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R1ND377	25mg tablet	Apparatus: 1 (basket) Speed: 100 rpm Medium: pH 6.8 phosphate Volume: 1000mL Temperature: 37°C ± 0.5°C	12	5%	12%	33%	55%	77%	96% (b) (4)	Original ANDA Volume 18, pages 9571-9572
N/A	Paxil CR® Tablets Lot 1674F07	25mg tablet		12	4%	12%	39%	68%	84%	97% (b) (4)	

Using FDA-recommended method with paddles @ 50 and 75 rpm and basket @ 100 rpm

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)						Study Report Location
					1 hour	2 hours	4 hours	6 hours	8 hours	12 hours	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot: R1N1808	12.5mg tablet	Apparatus: 2 (paddles) Speed: 50 rpm Medium: pH 6.8 phosphate Volume: 1000mL Temperature: 37°C ± 0.5°C	12	4%	12%	21%	35%	48%	72% (b) (4)	Amendment Volume 1, pages 9567-9568
N/A	Paxil CR® Tablets Lot: Y165F06	12.5mg tablet		12	5%	13%	33%	52%	69%	85% (b) (4)	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot: R1N1808	12.5mg tablet	Apparatus: 2 (paddles) Speed: 75 rpm Medium: pH 6.8 phosphate Volume: 1000mL Temperature: 37°C ± 0.5°C	12	6%	13%	31%	52%	68%	93% (b) (4)	Amendment Volume 1, pages 9567-9568
N/A	Paxil CR® Tablets Lot: Y165F06	12.5mg tablet		12	5%	14%	39%	62%	79%	95% (b) (4)	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot: R1N1808	12.5mg tablet	Apparatus: 1 (basket) Speed: 100 rpm Medium: pH 6.8 phosphate Volume: 1000mL Temperature: 37°C ± 0.5°C	12	6%	14%	35%	60%	84%	95% (b) (4)	Amendment Volume 1, pages 9567-9568
N/A	Paxil CR® Tablets Lot: Y165F06	12.5mg tablet		12	7%	19%	44%	65%	84%	96% (b) (4)	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot: R1N0377	25mg tablet	Apparatus: 2 (paddles) Speed: 50 rpm Medium: pH 6.8 phosphate Volume: 1000mL Temperature: 37°C ± 0.5°C	12	4%	12%	25%	41%	55%	76% (b) (4)	Original ANDA Volume 16, pages 9567-9568
N/A	Paxil CR® Tablets Lot: 1674F07	25mg tablet		12	3%	12%	30%	52%	67%	86% (b) (4)	

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)						Study Report Location
					1 hour	2 hours	4 hours	6 hours	8 hours	12 hours	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R1N0377	25mg tablet	Apparatus: 2 (paddles) Speed: 75 rpm Medium: 0.05M pH 6.8 phosphate Volume: 1000mL Temperature: 37°C ± 0.5°C	12	3%	9%	23%	37%	53%	77% (b) (4)	Original ANDA Volume 16, pages 9569-9570
N/A	Paxil CR® Tablets Lot 1674P07	25mg tablet		12	3%	10%	30%	52%	67%	85% (b) (4)	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R1N0377	25mg tablet	Apparatus: 1 (basket) Speed: 100 rpm Medium: pH 6.8 phosphate Volume: 1000mL Temperature: 37°C ± 0.5°C	12	5%	12%	33%	55%	77%	96% (b) (4)	Original ANDA Volume 16, pages 9571-9572
N/A	Paxil CR® Tablets Lot 1674P07	25mg tablet		12	4%	13%	39%	65%	84%	97% (b) (4)	

Using FDA-recommended method

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)							Study Report Location
					Acid Stage	Buffer Stage						
					2 hours	1 hour	2 hours	4 hours	6 hours	8 hours	12 hours	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R1N1306	12.5mg tablet	Apparatus: 2 (paddles) Speed: 150 rpm Medium: Acid Stage - 0.1N Hydrochloric Acid Buffer Stage – 0.05M Tris Buffer, pH 7.5 Volume: Acid Stage – 750mL Buffer Stage – 1300mL Temperature: 37°C ± 0.5°C	12	0%	12%	35%	66%	87%	93%	93% (b) (4)	Amendment Volume 1, pages 9574-9575
N/A	Paxil CR® Tablets Lot Y165P06	12.5mg tablet		12	0%	7%	22%	60%	87%	94%	95% (b) (4)	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R1N0377	25mg tablet	Apparatus: 2 (paddles) Speed: 150 rpm Medium: Acid Stage - 0.1N Hydrochloric Acid Buffer Stage – 0.05M Tris Buffer, pH 7.5 Volume: Acid Stage – 750mL Buffer Stage – 1300mL Temperature: 37°C ± 0.5°C	12	0%	7%	24%	64%	89%	97%	95% (b) (4)	Original ANDA Volume 16, pages 9574-9575
N/A	Paxil CR® Tablets Lot 1674P07	25mg tablet		12	0%	3%	15%	53%	116%	96%	97% (b) (4)	

*Tablets float under these conditions. This high value can be attributed to the aspiration of large tablet particles into the sampling syringe.

Table 2. SAS Transport Files

Are the SAS files located in the EDR? (Yes/No)	
Fasting BE Study	
Plasma Data	Y
PK data	Y
Fed BE Study	
Plasma Data	Y
PK Data	Y

COMMENTS:

1. The sponsor has conducted dissolution testing using the FDA-recommended method, but has proposed another method for the following reason: "the use of a paddle at the high rate of rotation caused the 'RLD' and the Mylan product to remain suspended in the medium throughout the test. Because the tablets did not sink, particles of the tablets would float and be drawn into the syringe during sampling, causing falsely elevated concentrations of paroxetine in the sample. This phenomenon caused isolated aberrant results (i.e., (b) (4)%) in the drug release profile."

   "Based on these results, Mylan adopted the Agency's recommended dissolution media, but changed the apparatus to baskets at 100 rpm to eliminate tablet floating. This method provides typical dissolution test conditions and serves as a suitable quality control test for the drug release of the finished dosage form. Mylan has established drug release specifications using this proposed method."

2. The sponsor has also conducted dissolution testing with their modified method using 4 other media - water, 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The first 3 media yielded no dissolution. The pH 6.8 buffer yielded adequate, but slower dissolution than the Tris buffer medium.

   Additional dissolution testing [pH 6.8 buffer] was conducted using the paddle at 50 and 75 rpm and the basket at 100 rpm. It appears, based on the submitted data, that the optimal release profile was obtained using the sponsor's proposed method.

DEFICIENCY COMMENTS:

1. The reviewer finds Mylan's proposed dissolution method justified. However, the firm should modify their proposed specifications:

   Medium: 750 ml of 0.1N HCl for 2 hrs [acid stage]
   Specification: NMT (b) (4)% dissolved

   Medium: 1000 ml of 0.05M Tris buffer, pH 7.5 [buffer stage]
   Specification: 2 hrs: (b) (4)%
   4 hrs: %
   12 hrs: NLT (b) (4)%

After reviewing the data for the test products only using Mylan's proposed method, the DBE believes that at 4 hrs, the specification should be (b) (4)%. The DBE can support the other specifications.

The firm should be advised to modify the specification at 4 hrs.

RECOMMENDATIONS:

1. The dissolution testing conducted by Mylan Pharmaceuticals Inc. on its paroxetine HCl ER tablets is acceptable.

2. The dissolution testing should be conducted in 750 ml of 0.1N HCl at 37°C using USP XXIX apparatus I (basket) at 100 rpm [acid stage] and 1000 ml of 0.05M Tris buffer, pH 7.5 at 37°C using USP XXIX apparatus I (basket) at 100 rpm [buffer stage]. The test product should meet the following specifications:

   NMT (b) (4)% dissolved in 2 hrs [acid stage]

   2 hrs: (b) (4)%
   4 hrs: %
   12 hrs: NLT (b) (4)% dissolved [buffer stage]

   The sponsor should acknowledge the dissolution specifications.

E. Lee 1-27-06

Reviewer JLee
Team # II
Division of Bioequivalence
Office of Generic Drugs

1/27/2006

Team Leader SGNerurkar
Team # II
Division of Bioequivalence
Office of Generic Drugs

2/1/06

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

BIOEQUIVALENCE DEFICIENCY

ANDA: 77-873 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Paroxetine HCl ER tablets; 12.5 and 25 mg

The Division of Bioequivalence has completed its review of the dissolution testing portion of your application. The review of the bioequivalence studies and waiver request will be done at a later date.

1. We accept your proposed dissolution method based on your justification as follows:

   Apparatus I (basket) at 100 rpm
   750 ml of 0.1N HCl [acid stage]
   and 1000 ml of 0.05M Tris buffer, pH 7.5 [buffer stage]

   Based on the submitted data on your test products only, we wish to modify your proposed specifications:

   NMT (b) (4) dissolved in 2 hrs [acid stage]

   2 hrs: (b) (4)%
   4 hrs: %
   12 hrs: NLT (b) (4)% dissolved [buffer stage]

   Please acknowledge the above specifications.

2. We acknowledge that you have submitted the study summaries in CTD format.

Sincerely yours,

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

CC: ANDA 77-873
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Reviewer
HFD/650/ Project Manager

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Endorsements:
HFD-650/Reviewer E.S. 1-27-06
HFD-650/Team Leader
HFD-650/D.P. Conner BMS 2/1/06

1/27/06

BIOEQUIVALENCE - INCOMPLETE Submission date: 9 Sep 2005

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

1. DISSOLUTION (Dissolution Data)		Strength:	25 mg
	X	**Outcome:**	**IC**
2. DISSOLUTION (Dissolution Data) amendment for additional strength 8 Nov 2005	X	Strength:	12.5 mg
		Outcome:	**IC**

Outcome Decisions: AC or IC – Acceptable or Incomplete

WinBio Comments: IC

The sponsor should acknowledge the recommended dissolution specifications.

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-873
Drug Product Name	Paroxetine Hydrochloride Extended-release Tablets
Strength	25 mg and 12.5 mg
Applicant Name	Mylan Pharmaceuticals, Inc.
Address	Morgantown, WV
Submission Date(s)	Sept. 9, 2005
Amendment Date(s)	Nov. 8, 2005 (addition of 12.5 mg strength) Feb. 15, 2006 (Diss ACK)
Reviewer	Bing V. Li
First Generic	Yes
File Location	V:\firmsam\mylan\ltrs&rev\77873N0905.doc

I. Executive Summary

This submission consisted of two bioequivalence (BE) studies, one under fasting and the other fed conditions and dissolution data on all strengths of the test and reference products. The studies were conducted on the Paroxetine Hydrochloride Extended-release Tablets, 25 mg tablets, comparing them with GlaxoSmithKline's Paxil CR®, 25 mg tablets. The BE studies were conducted as two-way, crossover studies in healthy subjects (n=72 and n=69 for the fasting and fed studies, respectively) given a dose of one tablet in each study. Statistical analyses of the plasma concentration data for paroxetine demonstrate bioequivalence in both studies.

The results for the fasting study are as follows (point estimate, 90% CI): LAUC∞: 0.95, 82.1 - 110.5%; $LAUC_{0-t}$: 0.95, 81.3 - 110.0%; and LC_{max}: 0.99, 84.8-114.5%. The results for the fed study are as follows (point estimate, 90% CI): LAUC∞: 1.03, 92.4 - 114.4%; $LAUC_{0-t}$: 1.07, 95.6 -119.8%; and LC_{max}: 1.09, 95.5 - 123.9%.

The submission also contains comparative dissolution data using FDA recommended dissolution method. The dissolution results met the FDA recommended specifications. The dissolution testing is **acceptable.**

The firm also requested a waiver of *in vivo* bioequivalence study requirements for its Paroxetine Hydrochloride Extended-release Tablets, 12.5 mg. The formulation of 12.5 mg strength is proportionally similar to that of the 25 mg strength. The waiver is granted.

The application is acceptable with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Paroxetine Hydrochloride Extended-release Tablets, 25 mg
Reference Product*	Paxil CR® 25 mg
RLD Manufacturer	GlaxoSmithKline
NDA No.	20-936
RLD Approval Date	Feb 16, 1999
Indication	Treatment of Major depressive disorder, panic disorder, social anxiety disorder and premenstrual dysphoric disorder

* The RLD currently listed in the Orange book is the Paxil CR® 37.5 mg. Since the firm is not seeking the approval for 37.5 mg tablet. The firm used Paxil CR® 25 mg as the RLD for its Paroxetine Hydrochloride Extended-release Tablets, 25 mg.

B. PK/PD Information

Bioavailability*	Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt
Food Effect*	The bioavailability of 25 mg PAXIL CR is not affected by food
Tmax*	6-8 hrs
Metabolism*	Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome P_{450} IID $_6$. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment.
Excretion*	Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period
Half-life*	15 to 20 hours
Relevant OGD or DBE History	**Control 03-833,** Mylan, submitted on Oct. 24, 2003, the DBE recommends the followings:

1. Single dose fasting study on 37.5 mg strength tablets.

2. Single dose fed study on 37.5 mg strength tablets.

3. Measure only parent compound.

4. Two lower strengths (12.5 mg and 25 mg) may be waived based on:

    1). Acceptable BE studies on the 37.5 mg tablets
    2). Formulations are proportionally similar
    3). Acceptable dissolution data

5. The dissolution testing should be conducted in the following media:

    1). Four media (water, and pH 1.2, pH 4.5, and pH 6.8 buffers)
    2). Dissolution testing should also be conducted using the

FDA method.
Step 1: 750 mL of 0.1N HCl for 2 hours
Step 2: 1000 mL, pH 7.5 Tris Buffer containing 50 mmole Tris
USP paddle, 150 rpm

Please note this is not the dissolution method for this application.

DBE has reviewed the following control documents and the recommendations are as same as above.

Control 02-227 and 02-522, [redacted], submitted on April 26, 2002
Control 02-281, [redacted], submitted on May 17, 2002
Control 02-362 and 04-434, [redacted], submitted on June 21, 2002
Control 02-604, [redacted], submitted on Oct. 17, 2002
Control 03-320, [redacted], submitted on April 22, 2003
Control 03-373, [redacted], submitted on May 8, 2003
Control 03-548, [redacted] submitted on July 9, 2003
Control 03-631, [redacted] submitted on Aug. 7, 2003
Control 03-853, [redacted], submitted on Oct. 22, 2003
Control 04-372, [redacted], submitted on April 19, 2004
Control 04-1114, [redacted] submitted on Nov. 29, 2004
Control 05-0003, [redacted] submitted on Jan. 4, 2005
Control 05-0178, [redacted] submitted on Feb 3, 2005
Control 05-1325, [redacted], submitted on Oct. 19, 2005
Control 05-1408, [redacted], submitted on Nov. 17, 2005
Control 06-0311, [redacted], submitted on March 4, 2006

Agency Guidance

Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (March 2003)

Drug Specific Issues (if any)

Paxil CR® is marketed in three tablet strengths as 12.5 mg, 25 mg and 37.5 mg ER tablets. In the past, the Orange Book listed all three strengths as the Reference Listed Drugs, suggesting that biostudies are requested on all three strengths. However, based on the October 2000 Guidance for Industry entitled Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations, only two

bioequivalence studies, a fasting study and a fed study on the 37.5 mg ER Tablet are requested for an ANDA submission.

* From 2002-2006 Thomson PDR.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	yes	2 (one original and one re-dose study)
Single-dose fed	yes	2 (one original and one re-dose study)
Steady-state	no	
In vitro dissolution	yes	2
Waiver requests	yes	1
BCS Waivers	no	
Vasoconstrictor Studies	no	
Clinical Endpoints	no	
Failed Studies	no	
Amendments	no	

D. Pre-Study Bioanalytical Method Validation (from the firm's e-submission of CTD format tables)

	Parent
Analyte	Paroxetine (PARO)
Internal Standard (IS)	(b) (4)
Method Description	Liquid/Liquid Extraction – LC – MS/MS
Limit of Quantitation (ng/mL)	0.05 ng/mL
Average Recovery of Drug (%)	81.85%
Average Recovery of IS (%)	84.14%
Standard Curve Concentrations (ng/mL)	0.05, 0.1, 0.15, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 10.0 ng/mL
QC Concentrations (ng/mL)	0.15 ng/mL, 1.0 ng/mL, 6.0 ng/mL
QC Intraday Precision Range (%)	1.43% to 11.53%
QC Intraday Accuracy Range (%)	-7.67% to 15.36%
QC Interday Precision Range (%)	2.09% to 9.82%
QC Interday Accuracy Range (%)	-4.20 to 7.78%
Bench-Top Stability (hrs)	12 hours @ room temperature
Stock Stability (days)	39 days @ 4°C PARO, 59 days @ 4°C (b) (4), 59 days @ 4°C PARO (b) (4) working solution stability
Processed Stability (hrs)	72 hours @ room temperature
Freeze-Thaw Stability (cycles)	4 cycles
Long-Term Storage Stability (days)	163 days @ -70°C, 96 days @ -15°C
Dilution Integrity	Two-fold
Selectivity	No significant interfering peaks noted in blank plasma samples

Reviewer's Comment:

Acceptable.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	PARO-0509
Study Design	Single dose, randomized, two-period, two-treatment, two sequence, crossover
No. of subjects enrolled	75
No. of subjects completing	73
No. of subjects analyzed	73 (2 dropouts: sub #54 and #75) 72 completed statistical analysis (the firm identified subject #59 as an outlier and was excluded from statistical analysis of the study)
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 40 Female: 32
Test product	Paroxetine Hydrochloride Extended-Release 25 mg Tablet
Reference product	Paxil CR® 25 mg Tablet
Strength tested	25 mg
Dose	1 x 25 mg

Summary of Statistical Analysis, Fasting Bioequivalence Study (including subject # 59)			
Parameter	**Point Estimate**	**90% Confidence Interval**	
		Low	**Upper**
AUC∞	90.70	**76.69**	107.27
AUC0-t	89.89	**75.68**	106.77
Cmax	94.62	80.41	111.35

Reviewer's Comments:

1. Subject #59 was excluded from the statistical analysis. The firm stated that "*subject #59 was found to have a pharmacokinetic response, which was discordant with the remainder of the study population. The ratios of test to reference were 0.05 and 0.02 for Cmax and AUC, respectively. The response of subject #59 was determined to be a within-subject outlier for Cmax and AUC when assessed by the Maximum Normal Residual Test. Subject 59 was re-dosed in an identical manner, along with three randomly chosen subjects previously dosed in the fasting study. In the re-dose study, subject #59 was found to have plasma concentrations in the range of the study group observed in the original study. The results from the re-dosing study support anomalous*

values in the original study for subject #59. As a result, this data justified the exclusion of the aberrant data of subject 59 from the original data set in the fasting study." (vol. 1.1, page 146).

Based on the results of the redosing study, it is reasonable to exclude subject #59 from the statistical analysis.

2. The re-dosing was performed according to the protocol amendment. In the future submission, the firm should make clear in its protocol, prior to the conducting of the bioequivalence study of its methodology of how to treat the PK abnormities.

Table Summary of Original and Re-dose Ratios of Test and Reference for Primary Pharmacokinetic Parameters (Study # PARO-0509A), N=4 (A= Test, B=Reference)

SUMMARY OF ORIGNAL AND REDOSE RATIOS OF TEST TO REFERENCE FOR PRIMARY PHARMACOKINETIC PARAMETERS

STUDY PARO-0509A

	AUCL (ng*hr/mL)	Ratio (A/B)	AUCI (ng*hr/mL)	Ratio (A/B)	CPEAK (ng/mL)	Ratio (A/B)
Subject 24, A	375.3	1.396	376.8	1.393	13.27	1.475
Subject 24, B	268.9		270.4		8.996	
Subject 24, A Re-dose	373.4	0.791	375.0	0.790	11.98	0.787
Subject 24, B Re-dose	471.9		474.4		15.22	
Subject 37, A	142.7	0.831	144.0	0.831	4.592	0.874
Subject 37, B	171.7		173.4		5.252	
Subject 37, A Re-dose	119.0	0.773	120.6	0.772	3.437	0.766
Subject 37, B Re-dose	154.0		156.1		4.489	
Subject 59, A	3.857	0.022	4.507	0.026	0.375	0.050
Subject 59, B	171.5		173.4		7.427	
Subject 59, A Re-dose	8.804	0.674	9.645	0.676	0.713	0.841
Subject 59, B Re-dose	13.07		14.27		0.847	
Subject 66, A	154.1	1.083	156.8	1.083	6.152	1.324
Subject 66, B	142.4		144.8		4.645	
Subject 66, A Re-dose	78.87	0.407	80.54	0.414	3.405	0.432
Subject 66, B Re-dose	193.7		194.5		7.878	
Range of Ratios (A/B) originally observed for all subjects in PARO-0509, excluding Subject 59						
Minimum		0.136		0.142		0.187
Maximum		5.124		5.014		4.453

(Source: Attachment 1A and 1B of original BE Report PARO-0509 and Attachment 1 of this report)

A=Mylan, B= Paxil CR™

Summary of Statistical Analysis Fasting Bioequivalence Study (after excluding subject # 59)			
Parameter	**Point Estimate**	**90% Confidence Interval**	
		Low	**Upper**
AUC∞	0.95	82.08	110.48
AUC0-t	0.95	81.27	110.02
Cmax	0.99	84.82	114.46

Reanalysis of Study Samples, Fasting Bioequivalence Study Additional information in Appendix, Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays***		**Actual number**		**% of total assays***	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0%	0%	0	0	0%	0%
Reason A (Sample Outside Limits of Curve Range (ALQ))	12	29	0.34 %	0.83 %	12	29	0.34 %	0.83 %
Reason B (Abnormal Internal Standard (IS) Response)	3	16	0.09 %	0.46 %	3	15	0.09 %	0.43 %
Reason C (Improper dilution factor)	1	3	0.03 %	0.09 %	1	3	0.03 %	0.09 %
Reason D (Sample Lost During Assay Procedure)	1	5	0.03 %	0.14 %	1	5	0.03 %	0.14 %
Reason E (Interfering Peaks with IS or Analyte in Blanks)	1	0	0.03 %	0%	1	0	0.03 %	0%
Reason F (Sample Outside Limits of Curve Range (BLQ))	0	0	0%	0%	0	0	0%	0%
Total	18	53	0.51 %	1.52 %	18	52	0.51 %	1.49 %

*** Based on total number of samples analyzed: 3377**

Did use of recalculated plasma concentration data change study outcome?
No. There is no PK repeat in the fasting study.

2. Single-dose Fasting Bioequivalence Study (Re-dose study)

Study Summary, Fasting Bioequivalence Study	
Study No.	PARO-0509A
Study Design	Single dose, randomized, two-period, two-treatment, two sequence, crossover
No. of subjects enrolled	4
No. of subjects completing	4
No. of subjects analyzed	4
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male 3 Female 1
Test product	Paroxetine Hydrochloride Extended-Release 25 mg Tablet
Reference product	Paxil CR® 25 mg Tablet
Strength tested	25 mg
Dose	1 x 25 mg

Reanalysis of Study Samples, Fasting Bioequivalence Study Additional information in Appendix, Table 6								
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
There were no repeats performed for this study								

Did use of recalculated plasma concentration data change study outcome? No.

3. Single-dose Fed Bioequivalence Study

Study Summary, Fed Bioequivalence Study	
Study No.	PARO-0510
Study Design	Single dose, randomized, two-period, two-treatment, two sequence, crossover
No. of subjects enrolled	75
No. of subjects completing	73 completed study (2 dropouts: sub #31 and #43)
No. of subjects analyzed	71 (sub #15 and #34 experienced diarrhea and were dropped by PK/DM department prior to sample analysis) 69 included in the statistical analysis of the study (sub #49 has high pre-dose plasma concentration which is greater than 5% and was not included in the statistical analysis. The firm identified subject #24 as an outlier and this subject was excluded)
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 47 Female: 22
Test product	Paroxetine Hydrochloride Extended-Release 25 mg Tablet
Reference product	Paxil CR® 25 mg Tablet
Strength tested	25 mg
Dose	1 x 25 mg

Summary of Statistical Analysis, Fed Bioequivalence Study (including subject #24)			
Parameter	**Point Estimate**	**90% Confidence Interval**	
		Low	**Upper**
AUC∞	1.03	92.36	114.43
AUC0-t	1.11	97.73	**125.50**
Cmax	1.13	97.86	**130.07**

Reviewer's comments:

1. Subjects #15 and #34 experienced diarrhea within 24 hours of dosing (vol 1.14, page 7354). The labeling indicated that the dosing regimen for the Paroxetine HCl ER tablet is once a daily. **The firm did not analyze their blood samples**. The reviewer considers it acceptable.

2. Subject #49 has high pre-dose plasma concentration which is greater than 5%. This subject was not included in the statistical analysis of the study.

3. The firm stated that "*subject #24 was found to have a pharmacokinetic response (Test to Reference ratios of 15.22 and 11.90 for Cmax and AUCt), which was discordant with the remainder of the study population. The response of subject 24 was determined to be a within-subject outlier for Cmax and AUC when assessed by the Maximum Normal Residual Test. Subject 24 was re-dosed in an identical manner, along with three randomly chosen subjects previously dosed in the fed study. In the re-dose study, subject #24 was found to have plasma concentrations within the range of the study group observed in the original study. The results from the re-dosing study support anomalous values in the original study for subject #24. As a result, this data justified the exclusion of the aberrant data of subject 24 from the original data set in the fed study.*" (Vol. 1.10, page 4751).

Based on the results of the redosing study, it is reasonable to exclude subject #24 from the statistical analysis.

4. The re-dosing was performed according to the protocol amendment. In the future submission, the firm should make clear in its protocol, prior to the conducting of the bioequivalence study of its methodology of how to treat the PK abnormities.

Table Summary of Original and Re-dose Ratios of Test and Reference for Primary Pharmacokinetic Parameters (Study # PARO-0510A), N=4 (A= Test, B=Reference)

SUMMARY OF ORIGNAL AND REDOSE RATIOS OF TEST TO REFERENCE FOR PRIMARY PHARMACOKINETIC PARAMETERS

STUDY PARO-0510A

	AUCL (ng*hr/mL)	Ratio (A/B)	AUCI (ng*hr/mL)	Ratio (A/B)	CPEAK (ng/mL)	Ratio (A/B)
Subject 8, A	9.642	0.670	10.33	0.670	0.659	0.878
Subject 8, B	14.389		15.42		0.751	
Subject 8, A Re-dose	23.28	7.016	25.26	5.634	1.494	7.152
Subject 8, B Re-dose	3.318		4.483		0.209	
Subject 24, A	27.17	11.90	28.72	-	1.415	15.22
Subject 24, B	2.284		-		0.093	
Subject 24, A Re-dose	6.012	0.279	7.023	0.313	0.481	0.347
Subject 24, B Re-dose	21.52		22.45		1.386	
Subject 41, A	258.4	0.688	262.4	0.694	9.774	0.858
Subject 41, B	375.7		377.8		11.39	
Subject 41, A Re-dose	285.9	0.898	291.8	0.908	7.500	0.806
Subject 41, B Re-dose	318.3		321.3		9.306	
Subject 52, A	19.83	0.333	22.86	0.373	1.384	0.410
Subject 52, B	59.61		61.25		3.374	
Subject 52, A Re-dose	33.20	1.678	34.36	1.594	1.984	2.668
Subject 52, B Re-dose	19.79		21.56		0.744	
Range of Ratios (A/B) originally observed for all subjects in PARO-0510, excluding Subject 24						
Minimum		0.333		0.344		0.305
Maximum		6.364		3.726		8.136

(Source: Attachment 1A and 1B of original BE Report PARO-0510 and Attachment 1 of this report)

A=Mylan, B=Paxil CR™

Summary of Statistical Analysis, Fed Bioequivalence Study (excluding subject #24)			
Parameter	**Point Estimate**	**90% Confidence Interval**	
		Low	**Upper**
AUC∞	1.03	92.43	114.35
AUC0-t	1.07	95.59	119.84
Cmax	1.09	95.46	123.88

Reanalysis of Study Samples, Fed Bioequivalence Study, Additional information in Appendix, Table 28								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays***		**Actual number**		**% of total assays***	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0%	0%	0	0	0%	0%
Reason A (Sample Outside Limits of Curve Range (ALQ))	27	19	0.75 %	0.53 %	27	19	0.75 %	0.53 %
Reason B (Abnormal Internal Standard (IS) Response)	21	19	0.58 %	0.53 %	21	19	0.58 %	0.53 %
Reason C (Improper dilution factor)	3	3	0.08 %	0.08 %	3	2	0.08 %	0.06 %

Reason D (Sample Lost During Assay Procedure)	0	1	0%	0.03 %	0	1	0%	0.03 %
Reason E (Interfering Peaks with IS or Analyte in Blanks)	4	1	0.11 %	0.03 %	4	1	0.11 %	0.03 %
Reason F (Sample Outside Limits of Curve Range (BLQ))	8	4	0.22 %	0.11 %	8	4	0.22 %	0.11 %
Total	63	47	1.74 %	1.30 %	63	46	1.74 %	1.27 %

*** Based on total number of samples analyzed: 3552**

Did use of recalculated plasma concentration data change study outcome?
No. There is no PK repeat in the fed study.

4. Single-dose Fed Bioequivalence Study (Re-dose study)

Study Summary, Fed Re-dose Bioequivalence Study	
Study No.	PARO-0510A
Study Design	Single dose, randomized, two-period, two-treatment, two sequence, crossover
No. of subjects enrolled	4
No. of subjects completing	4
No. of subjects analyzed	4
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 3 Female: 1
Test product	Paroxetine Hydrochloride Extended-Release 25 mg Tablet
Reference product	Paxil CR® 25 mg Tablet
Strength tested	25 mg
Dose	1 x 25 mg

Reanalysis of Study Samples, Fed Bioequivalence Study, PARO-0510A-Fed Study Re-dose, Additional information in Appendix, Table 28A								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays***		**Actual number**		**% of total assays***	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0%	0%	0	0	0%	0%
Reason B (Abnormal Internal Standard (IS) Response)	0	1	0%	0.51 %	0	1	0%	0.51 %
Total	0	1	0%	0.51 %	0	1	0%	0.51 %

*** Based on total number of samples analyzed: 192**

Did use of recalculated plasma concentration data change study outcome?
No. There is no PK repeat in the fed re-dose study.

Reviewer's Comments on the Clinical Studies:

1. In the original fasting study (PARO-0509), subject #59 had test-to-reference ratios of 0.05 and 0.02 for Cmax and AUC, respectively, indicating that subject #59 had a low response to the **test** product. When subject #59 was re-dosed, this subject had low responses to both test and reference products although the test/reference ratios for Cmax and AUC fell within the ratios of the study group. Contrary to the fasting study, in the original fed study (PARO-0910), subject #24 had test/reference ratios of 15.22 and 11.90 for Cmax and AUCt, respectively, indicating that this subject had a low response to the **reference** product. When subject #24 was re-dosed, this subject had low responses to both test and reference products although the test/reference ratios for Cmax and AUC fell within the ratios of the study group. These results imply that the abnormities of the subject #59 and #24 were not product quality related, rather, it might be drug substance (Paroxetine) related. The variability in subject #24's pharmacokinetic data from these two studies is consistent with the observation that, in other studies submitted to the OGD, paroxetine generally shows high pharmacokinetic variability.

2. High **INTER** subject variations were also observed in both fasting and fed studies. For example, in the original fasting study, for subjects #26 and #31 treated with the reference product B, the AUCi values were 2146 ng.hr/mL and 8.48 ng.hr/mL, and the Cmax values were 29.95 ng/mL and 0.55 ng/mL, respectively. Similarly, in the original fed study, for subjects #28 and #29 treated with the test product A, the AUCi values were 1647 ng.hr/mL and 11.53 ng.hr/mL, and the Cmax values were 28.84 ng/mL and 0.38 ng/mL respectively (refer to Statistical results in the attachment section for details).

F. Formulation

Location in appendix	Section B, Page 50
Are inactive ingredients within IIG limits?	Yes
If yes, list ingredients outside of limits	
If a tablet, is the product scored?	No
If yes, which strengths are scored?	
Is scoring of RLD the same as test?	RLD was not scored
Is the formulation acceptable?	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	Firm		
Medium **Volume (mL)**	Acid stage (2hrs): 750 ml of 0.1 N HCl Buffer stage (12 hrs): 0.05M tris buffer pH 7.5		
USP Apparatus type	I (basket)		
Rotation (rpm)	100 rpm		
Firm's proposed specifications	Acid stage Buffer Stage	2 hrs 2hrs 4hrs 12hrs	NMT (b) (4) NLT
FDA-recommended specifications	Acid stage Buffer Stage	2 hrs 2hrs 4hrs 12hrs	NMT (b) (4) NLT
F2 metric calculated?	Yes		
If no, reason why F2 not calculated			
Is method acceptable?	Yes		
If not then why?			

F2 metric, lower strengths compared to highest strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
12.5 mg	25 mg	85.65	68.62

F2 metric, test compared to reference	
Strength	F2 metric
12.5 mg	74.73
25 mg	62.72

The firm accepted DBE recommended specifications.

H. Waiver Request(s)

Strengths for which waivers are requested	12.5 mg
Regulation cited	Section 21 CFR320.22 (d) (2)
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	No
If not then why?	Pending acceptable BE studies

I. Comments

The following comments should be communicated to the firm for **future submissions**:

1. The firm did not include the T1/2 data in its disc containing PK dataset. The firm should provide this information in the future submissions.

2. In the future, the firm should include its approach for treating subjects with aberrant pharmacokinetic parameters (AUC, Cmax) in its study protocols (i.e., re-dosing study).

3. The firm should provide its methodology of dealing with subjects that may develop experience diarrhea in its study protocols.

J. Recommendations

1. The in vivo bioequivalence study conducted under fasting conditions by Mylan Pharmaceuticals, Inc., on its Paroxetine Hydrochloride Extended-release Tablets, 25 mg, Lot# R1N0377, comparing to Paxil CR® tablets, 25 mg, lot #1874P07, manufactured by GlaxoSmithKline, is **acceptable.**

2. The in vivo bioequivalence study conducted under fed conditions by Mylan Pharmaceuticals, Inc., on its Paroxetine Hydrochloride Extended-release Tablets, 25 mg, Lot# R1N0377, comparing to Paxil CR® tablets, 25 mg, lot #1874P07, manufactured by GlaxoSmithKline, is **acceptable.**

3. The dissolution testing conducted by Mylan Pharmaceuticals, Inc., on its Paroxetine Hydrochloride Extended-release Tablets, 25 mg and 12.5 mg, is **acceptable**.

   The dissolution testing should be conducted using the FDA recommended method and the product should meet the FDA recommended specifications as follows:

Medium and Volume	Acid stage (2hrs): 750 ml of 0.1 N HCl Buffer stage (12 hrs): 0.05M tris buffer pH 7.5		
Temperature	37^0 C		
Apparatus	I (basket)		
Rotational Speed	100 rpm		
FDA-recommended specifications	Acid stage Buffer Stage	2 hrs 2hrs 4hrs 12hrs	NMT (b) (4) NLT

4. The waiver of *in vivo* bioequivalence study requirements for Paroxetine Hydrochloride Extended-release Tablets, 12.5 mg, is granted.

The firm should be informed of the above recommendations.

Bing V. Li, Ph. D. — Date 7/20/06
Reviewer, Branch I
Division of Bioequivalence

Moheb H. Makary — Date 7/21/06
Moheb H. Makary, Ph. D.
Group Leader, Branch I
Division of Bioequivalence

Barbara M. Davit — Date 7/21/06
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

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IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	PARO-0509
Study Title	Single-Dose Fasting In Vivo Bioequivalence Study of Paroxetine Hydrochloride Controlled-Release Tablets (25 mg; Mylan) to Paxil CR® Tablets (25 mg; GSK) in Healthy Volunteers
Clinical Site	PRACS Institute, Ltd.
Principal Investigator	James D. Carlson, Pharm. D.
Study/Dosing Dates	Period I: April 9, 2005 Period II: April 23, 2005
Analytical Site	Mylan Pharmaceuticals Inc. Bioanalytical Department
Analytical Director	(b) (6), Lab Manager
Analysis Dates	May 9, 2005 to August 26, 2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	140 days

* Paroxetine is stable under storage condition of -70°C for 163 days.

Treatment ID	Test	Reference
Test or Reference	A	B
Product Name	Paroxetine Hydrochloride Extended-Release 25 mg Tablet	Paxil CR® 25 mg Tablet
Manufacturer	Mylan	GlaxoSmithKline
Batch/Lot No.	Lot# R1N0377	1874P07
Manufacture Date	3/7/05	NA
Expiration Date	NA	exp: 8/06
Strength	25 mg	
Dosage Form	Tablets	
Batch Size	(b) (4)	NA
Production Batch Size	NA	NA
Potency	97.2%	98.7%
Content Uniformity (mean, %CV)	Ave: 97.3%; RSD = 1.3%	NA
Formulation	See Appendix Section B	NA
Dose Administered	1 x 25 mg	
Route of Administration	Orally with 240 ml water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 1, 2, 7, 8, 10, 11, 13, 14, 19, 21, 22, 24, 25, 27, 31, 32, 34, 35, 37, 38, 41, 42, 46, 48, 50, 51, 52, 55, 57, 59, 61, 63, 68, 70, 71, 72, 74 BA: 3, 4, 5, 6, 9, 12, 15, 16, 17, 18, 20, 23, 26, 28, 29, 30, 33, 36, 39, 40, 43, 44, 45, 47, 49, 53, 54, 56, 58, 60, 62, 64, 65, 66, 67, 69, 70, 73
Blood Sampling Times	Pre-dose (0), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 24, 30, 36, 48, 72, 96 and 120 hrs (23 samples)
Blood Volume Collected/Sample	10 ml
Blood Sample Processing/Storage	Blood samples were collected in sodium heparin vacutainers and cooled in ice bath, then centrifuged at 3000 rpm under 4°C for 10 min under refrigeration. Plasma was extracted, divided in two aliquots and stored in suitably labeled tubes at -70°C ± 15°C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Overnight of at least 10 hours
Length of Confinement	Patients entering the clinical site no later than 4: 00 pm on the day prior to dosing and remain at the clinical site until 24 hours after dosing.
Safety Monitoring	Vital signs measured at 6, 12, 24, 48, 72, 96 and 120 hours post-dose

Comments on Study Design: Acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects

Age		**Weight**		**Age Groups**		**Gender**		**Race**	
				Range	**%**	**Sex**	**%**	**Category**	**%**
				<18	0			Caucasian	97.2%
Mean	24.90	Mean	157	18-40	90%	Male	56%	Afr. Amer.	0
SD	10.05	SD	22.8	41-64	8%	Female	44%	Hispanic	1.4%
Range	18	Range	106	65-75	1%			Asian	1.4%
	69		207	>75	0			Others	0

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
54	Elected to withdraw due to personal reasons	Prior to II	No
75	Difficult phlebotomy	I	No

Table 3 Study Adverse Events (cited from the firm's CTD format table)

Body System/Adverse Event [1]	Fasting Bioequivalence Study PARO-0509		Non-Fasting Bioequivalence Study PARO-0510	
	Test N=73 [2]	Reference N=75 [2]	Test N=74 [2]	Reference N=74 [2]
	n (%) [3]	n (%) [3]	n (%) [3]	n (%) [3]
Gastrointestinal disorders				
Abdominal pain	-	-	-	1 (1.35%)
Abdominal pain upper	-	-	1 (1.35%)	1 (1.35%)
Diarrhoea	-	-	1 (1.35%)	1 (1.35%)
Nausea	-	-	3 (4.05%)	3 (4.05%)
Stomach discomfort	-	-	3 (4.05%)	-
Vomiting	-	-	-	1 (1.35%)
General disorders and administration site conditions				
Vessel puncture site bruise	-	1 (1.33%)	-	-
Infections and infestations				
Otitis media acute	-	-	1 (1.35%)	-
Nervous system disorders				
Dizziness	1 (1.37%)	2 (2.67%)	1 (1.35%)	3 (4.05%)
Headache	4 (5.48%)	1 (1.33%)	6 (8.11%)	5 (6.76%)
Respiratory, thoracic and mediastinal disorders				
Cough	-	-	1 (1.35%)	-
Nasal congestion	1 (1.37%)	-	-	1 (1.35%)
Nasopharyngitis	1 (1.37%)	-	-	-
Pharyngolaryngeal pain	1 (1.37%)	-	-	-
Viral upper respiratory tract infection	1 (1.37%)	-	-	-
Total Subjects Reporting at Least One Adverse Event	7 (9.59%)	4 (5.33%)	9 (12.16%)	11 (14.86%)

[1] MedDRA Version 8.0
[2] N = Number of subjects dosed for each treatment
[3] n = Number of subjects reporting at least one incidence of respective adverse event; (%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Table 4 Protocol Deviations

1. Subjects 07, 32, 33, 35, 39, 57 59, and 60 failed to return for at least one of the ambulatory blood sample collections.
2. Some sampling time deviations.

Comments on Dropouts/Adverse Events/Protocol Deviations: Acceptable.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Parent
QC Conc. (ng/mL)	0.1500, 1.000, 6.000
Between Run Precision (%CV)	3.2 – 8.8
Between Run Accuracy (%)	98.9-102.1
Cal. Standards Conc. (ng/mL)	0.05000, 0.1000, 0.1500, 0.5000, 1.000, 2.000, 4.000, 6.000, 8.000, 10.00
Between Run Precision (%CV)	2.2-5.5
Between Run Accuracy (%)	97.1-104.3
Linearity Range (range of R^2 values)	0.9918-0.9996

Comments on Study Assay Quality Control: Acceptable.

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

Comments on Chromatograms: Acceptable.

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

SOP No.	Date of SOP	SOP Title
D-400-04	04-06-04	Reassay or Reinjection of Clinical Samples
D-401-07	04-06-04	Evaluation and Acceptance Criteria for Analytical Runs
D-416-03	04-06-04	Reassay of Whole Subjects

Table 7 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Acceptable.

d) Pharmacokinetic Results
(After excluding subject #59)

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC∞	ng.hr/mL	201.68	176.01	240.42	179.27	0.84
AUC0-t	ng.hr/mL	183.98	159.27	216.92	168.40	0.85
Cmax	ng/mL	5.61	103.14	6.26	116.67	0.90
T1/2	hr	14.67	61.27	14.00	56.17	1.05
Kel	1/hr	0.06	32.89	0.06	30.12	0.99
Tmax	hr	12.21	37.77	11.76	24.90	1.04

Reviewer's Comment:

The firm did not include the T1/2 data in its disc containing the PK dataset. The firm should include this information in its electronic disc containing the PK dataset in the future.

Table 9 Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI	
	Mean	Mean		Low	Upper
LAUC∞	82.49	86.63	0.95	82.08	110.48
LAUC0-t	77.22	81.66	0.95	81.27	110.02
LCmax	3.42	3.47	0.99	84.82	114.46

Table 10 Additional Study Information

Root mean square error, $LAUC_{0-t}$	0.545145
Root mean square error, $LAUC_{\infty}$	0.539404
Root mean square error, LC_{max}	0.527202
K_{el} and AUC_{∞} determined for how many subjects?	71
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	1 (< 5% Cmax)
-first measurable drug concentration as C_{max}	0
Were the subjects dosed as more than one group?	Yes

Comments on Pharmacokinetic and Statistical Analysis:

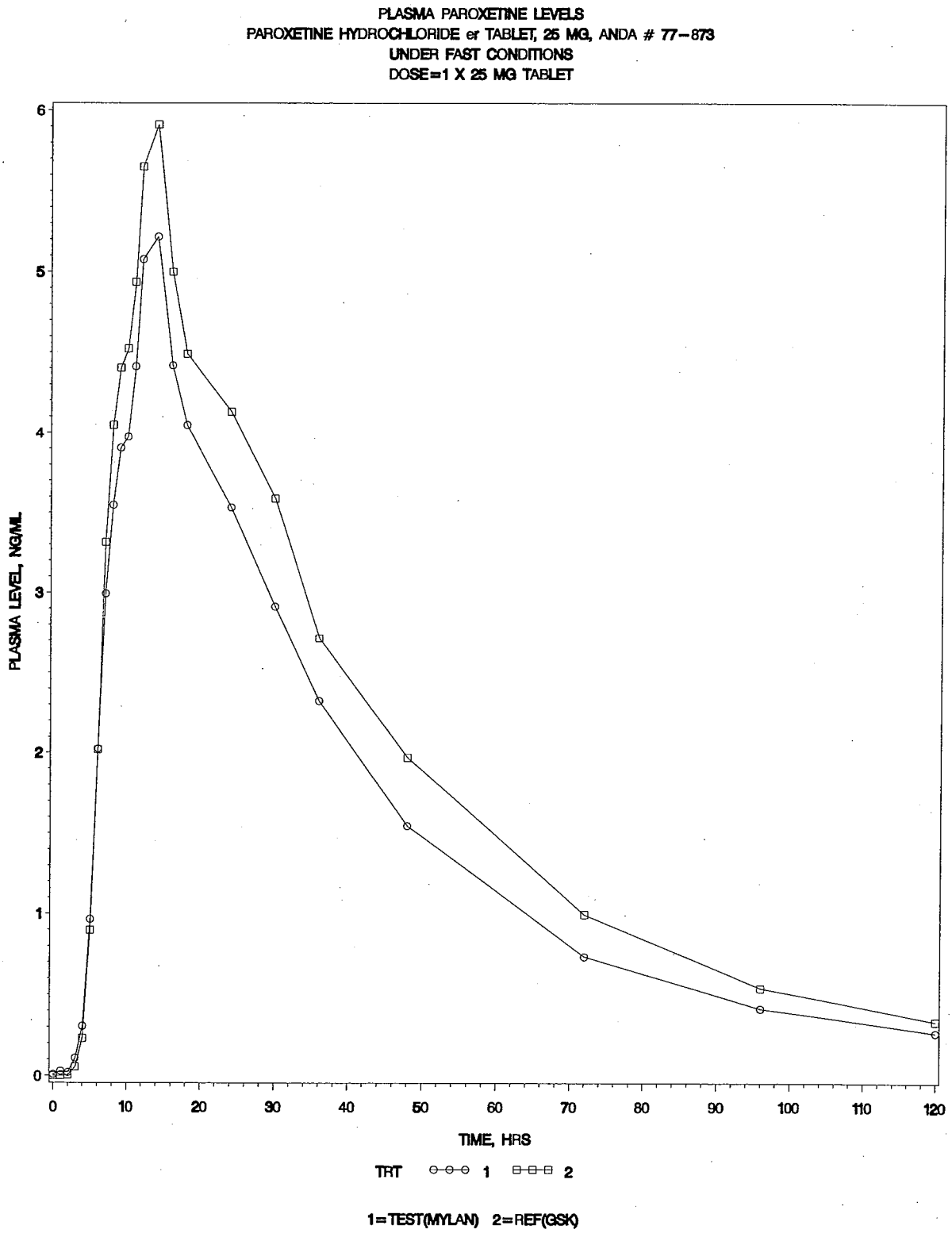
1. The 90% CI for the PK parameters agree well with reviewer's calculations.
2. The 90% confidence intervals for $lnAUC_{0-t}$, $lnAUC_{\infty}$ and lnC_{max} are within the acceptable limits of 80-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: Acceptable.

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Time	Test (n=72)		Reference (n=72)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.01	848.53	0.00	.	.
1	0.03	625.10	0.00	.	.
2	0.02	444.46	0.00	608.94	5.20
3	0.11	179.97	0.05	248.19	1.97
4	0.30	126.88	0.23	178.72	1.33
5	0.97	116.88	0.90	136.08	1.08
6	2.02	112.45	2.02	136.18	1.00
7	2.99	112.92	3.31	135.29	0.90
8	3.55	107.98	4.05	133.63	0.88
9	3.91	109.05	4.40	127.94	0.89
10	3.97	105.77	4.52	122.70	0.88
11	4.41	107.09	4.94	120.36	0.89
12	5.08	107.67	5.65	119.04	0.90
14	5.22	108.92	5.91	120.53	0.88
16	4.42	112.03	5.00	122.77	0.88
18	4.05	116.64	4.49	122.84	0.90
24	3.53	129.43	4.13	135.60	0.86
30	2.91	147.44	3.59	151.86	0.81
36	2.32	165.99	2.72	173.05	0.86
48	1.55	192.71	1.97	202.37	0.78
72	0.74	286.79	1.00	257.74	0.74
96	0.42	312.14	0.54	302.80	0.77
120	0.27	380.97	0.34	354.69	0.79

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



2. Single-dose Fasting Bioequivalence Study (**re-dosing study**)

a) Study Design

Study Information	
Study Number	PARO-0509A
Study Title	Single-Dose Fasting In Vivo Bioequivalence Study of Paroxetine Hydrochloride Controlled-Release Tablets (25 mg; Mylan) to Paxil CR® Tablets (25 mg; GSK) in Healthy Volunteers
Clinical Site	PRACS Institute, Ltd.
Principal Investigator	James D. Carlson, Pharm. D.
Study/Dosing Dates	Period I: July 30, 2005 Period II: August 13, 2005
Analytical Site	Mylan Pharmaceuticals Inc. Bioanalytical Department
Analytical Director	(b) (6) Lab Manager
Analysis Dates	Aug 23, 2005 to August 25, 2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	26 days

* Paroxetine is stable under storage condition of -70°C for 163 days.

Treatment ID	**Test**	**Reference**
Test or Reference	A	B
Product Name	Paroxetine Hydrochloride Extended-Release 25 mg Tablet	Paxil CR® 25 mg Tablet
Manufacturer	Mylan	GlaxoSmithKline
Batch/Lot No.	Lot# R1N0377	1874P07
Manufacture Date	3/7/05	NA
Expiration Date	NA	exp: 8/06
Strength	25 mg	
Dosage Form	Tablets	
Batch Size	(b) (4)	NA
Production Batch Size	NA	NA
Potency	97.2%	98.7%
Content Uniformity (mean, %CV)	Ave: 97.3%; RSD = 1.3%	NA
Formulation	See Appendix Section B	NA
Dose Administered	1 x 25 mg	
Route of Administration	Orally with 240 ml water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 24, 37, 59 BA: 66
Blood Sampling Times	Pre-dose (0), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 24, 30, 36, 48, 72, 96 and 120 hrs (23 samples)
Blood Volume Collected/Sample	10 ml
Blood Sample Processing/Storage	Blood samples were collected in sodium heparin vacutainers and cooled in ice bath, then centrifuged at 3000 rpm under 4°C for 10 min under refrigeration. Plasma was extracted, divided in two aliquots and stored in suitably labeled tubes at -70°C ± 15°C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Overnight of at least 10 hours
Length of Confinement	Patients entering the clinical site no later than 4: 00 pm on the day prior to dosing and remain at the clinical site until 24 hours after dosing.
Safety Monitoring	Vital signs measured at 6, 12, 24, 48, 72, 96 and 120 hours post-dose

Comments on Study Design: Acceptable.

b). Clinical Results

Table 12A Demographics of Study Subjects

Subjects	Age	Weight (lb)	Gender	Race
59	20	179	M	Caucasian
37	20	171	M	Caucasian
24	47	118	F	Caucasian
66	20	152	M	Caucasian

Table 13A Dropout Information

None.

Table 14A Study Adverse Events

Subject #59 had a headache when treated with treatment A.

Table 15A Protocol Deviations

None.

Comments on Dropouts/Adverse Events/Protocol Deviations: Acceptable.

c). Bioanalytical Results

Table 16A Assay Quality Control – Within Study

	Parent
QC Conc. (ng/mL)	0.1500, 1.000, 6.000
Between Run Precision (%CV)	2.22-4.29
Between Run Accuracy (%)	97.97-101.78
Cal. Standards Conc. (ng/mL)	0.05000, 0.1000, 0.1500, 0.5000, 1.000, 2.000, 4.000, 6.000, 8.000, 10.00
Between Run Precision (%CV)	0.55-3.97
Between Run Accuracy (%)	104.40-97.56
Linearity Range (range of R^2 values)	0.9983-0.9992

Comments on Study Assay Quality Control: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Results of Subject #59 were included

Comments on Chromatograms: Acceptable.

Table 17A SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
D-400-04	04-06-04	Reassay or Reinjection of Clinical Samples
D-401-07	04-06-04	Evaluation and Acceptance Criteria for Analytical Runs
D-416-03	04-06-04	Reassay of Whole Subjects

Table 18A Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Acceptable.

d). Pharmacokinetic Results (fast re-dosing)

Table 19A Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11A and Figure 1A

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC∞	ng.hr/mL	146.45	108.66	209.83	91.82	0.70
AUC0-t	ng.hr/mL	145.03	109.59	208.16	92.30	0.70
Cmax	ng/mL	4.88	100.34	7.11	86.13	0.69
Kel	1/hr	0.06	21.97	0.06	16.53	1.02
Tmax	hr	14.50	45.92	12.00	23.57	1.21

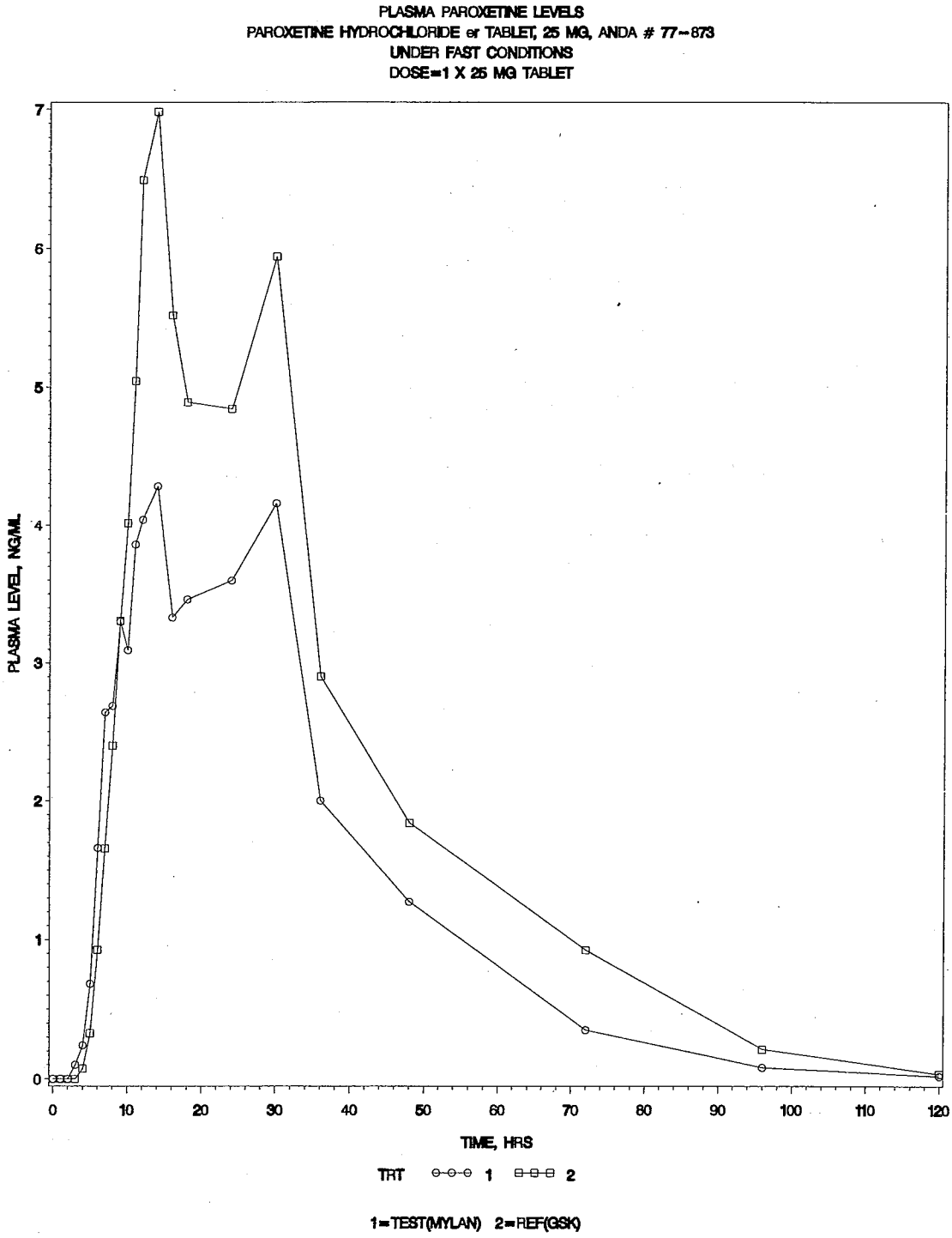
Comments on Pharmacokinetic and Statistical Analysis: Acceptable.

Summary and Conclusions, Single-Dose Fasting Re-dose Bioequivalence Study: Acceptable.

Table 20A Mean Plasma Concentrations, Single-Dose Fasting Re-dose Bioequivalence Study

Time	Test (n=4)		Reference (n=4)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
1	0.00	.	0.00	.	.
2	0.10	200.00	0.00	.	.
3	0.24	179.33	0.07	148.58	3.25
4	0.68	172.24	0.33	103.26	2.09
5	1.66	171.13	0.93	85.10	1.79
6	2.64	168.25	1.66	69.33	1.59
7	2.69	158.87	2.40	65.87	1.12
8	3.30	153.05	3.30	71.36	1.00
9	3.09	147.93	4.01	80.25	0.77
10	3.86	140.93	5.04	79.86	0.77
11	4.04	121.76	6.49	85.88	0.62
12	4.28	104.13	6.98	88.39	0.61
14	3.33	105.18	5.52	93.33	0.60
16	3.46	106.15	4.89	87.65	0.71
18	3.60	96.37	4.84	84.84	0.74
24	4.16	72.38	5.94	57.30	0.70
30	2.00	96.68	2.90	97.28	0.69
36	1.27	107.16	1.84	103.09	0.69
48	0.35	120.36	0.92	114.83	0.38
72	0.08	135.57	0.21	104.70	0.39
96	0.02	200.00	0.04	200.00	0.56
120	0.00	.	0.00	.	.

Figure 1A Mean Plasma Concentrations, Single-Dose Fasting Re-dose Bioequivalence Study



3. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	PARO-0510
Study Title	Single-Dose Food In Vivo Bioequivalence Study of Paroxetine Hydrochloride Controlled-Release Tablets (25 mg; Mylan) to Paxil CR® Tablets (25 mg; GSK) in Healthy Volunteers
Clinical Site	PRACS Institute, Ltd.
Principal Investigator	James D. Carlson, Pharm. D.
Study/Dosing Dates	Period I: April 23, 2005 Period II: May 7, 2005
Analytical Site	Mylan Pharmaceuticals Inc. Bioanalytical Department
Analytical Director	(b) (6) Lab Manager
Analysis Dates	May 18, 2005 to June 30, 2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	68 days

* Paroxetine is stable under storage condition of -70°C for 163 days.

Treatment ID	**Test**	**Reference**
Test or Reference	A	B
Product Name	Paroxetine Hydrochloride Extended-Release 25 mg Tablet	Paxil CR® 25 mg Tablet
Manufacturer	Mylan	GlaxoSmithKline
Batch/Lot No.	Lot# R1N0377	1874P07
Manufacture Date	3/7/05	NA
Expiration Date	NA	exp: 8/06
Strength	25 mg	
Dosage Form	Tablets	
Batch Size	(b) (4)	NA
Production Batch Size	NA	NA
Potency	97.2%	98.7%
Content Uniformity (mean, %CV)	Ave: 97.3%; RSD = 1.3%	NA
Formulation	See Appendix Section B	NA
Dose Administered	1 x 25 mg	
Route of Administration	Orally with 240 ml water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 1, 6, 7, 8, 13, 14, 15, 16, 17, 18, 21, 23, 25, 30, 31, 32, 34, 35, 36, 38, 42, 44, 47, 48, 51, 52, 54, 55, 58, 60, 61, 62, 65, 67, 68, 70, 73, 75 BA: 2, 3, 4, 5, 9, 10, 11, 12, 19, 20, 22, 24, 26, 27, 28, 29, 33, 37, 39, 40, 41, 43, 45, 46, 49, 50, 53, 56, 57, 59, 63, 64, 66, 69, 71, 72, 74
Blood Sampling Times	Pre-dose (0), 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, 30, 36, 48, 72, 96 and 120 hours (24 samples)
Blood Volume Collected/Sample	10 mls
Blood Sample Processing/Storage	Blood samples were collected in sodium heparin vacutainers and cooled in ice bath, then centrifuged at 3000 rpm under 4°C for 10 min under refrigeration. Plasma was extracted, divided in two aliquots and stored in suitably labeled tubes at -70°C ± 15°C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 21**
Length of Fasting before Meal	Overnight of at least 10 hours
Length of Confinement	Patients entering the clinical site no later than 4: 00 pm on the day prior to dosing and remain at the clinical site until 24 hours after dosing.
Safety Monitoring	Vital signs measured at 6, 12, 24, 48, 72, 96 and 120 hours post-dose
Standard FDA Meal Used?	Yes
If no, then meal is listed in table below	

Comments on Study Design: Acceptable.

b) Clinical Results

Table 21 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	97.1
Mean	25.7	Mean	159.2	18-40	87	Male	68	Afr. Amer.	1.4
SD	10.2	SD	25.6	41-64	13	Female	32	Hispanic	1.4
Range	18	Range	107.0	65-75	0			Asian	0
	58		219.0	>75	0			Others	0

Table 22 **Dropout Information**

Subject No	Reason	Replaced?
31	Elected to withdraw during period II due to vomiting, nausea and headache	No
43	Elected to withdraw during prior to period II due to family emergency	No

Table 23 Study Adverse Events (cited from the firm's CTD format table)

Body System/Adverse Event [1]	Fasting Bioequivalence Study PARO-0509		Non-Fasting Bioequivalence Study PARO-0510	
	Test N=73 [2]	Reference N=75 [2]	Test N=74 [2]	Reference N=74 [2]
	n (%) [3]	n (%) [3]	n (%) [3]	n (%) [3]
Gastrointestinal disorders				
Abdominal pain	-	-	-	1 (1.35%)
Abdominal pain upper	-	-	1 (1.35%)	1 (1.35%)
Diarrhoea	-	-	1 (1.35%)	1 (1.35%)
Nausea	-	-	3 (4.05%)	3 (4.05%)
Stomach discomfort	-	-	3 (4.05%)	-
Vomiting	-	-	-	1 (1.35%)
General disorders and administration site conditions				
Vessel puncture site bruise	-	1 (1.33%)	-	-
Infections and infestations				
Otitis media acute	-	-	1 (1.35%)	-
Nervous system disorders				
Dizziness	1 (1.37%)	2 (2.67%)	1 (1.35%)	3 (4.05%)

Headache	4 (5.48%)	1 (1.33%)	6 (8.11%)	5 (6.76%)
Respiratory, thoracic and mediastinal disorders				
Cough	-	-	1 (1.35%)	-
Nasal congestion	1 (1.37%)	-	-	1 (1.35%)
Nasopharyngitis	1 (1.37%)	-	-	-
Pharyngolaryngeal pain	1 (1.37%)	-	-	-
Viral upper respiratory tract infection	1 (1.37%)	-	-	-
Total Subjects Reporting at Least One Adverse Event	7 (9.59%)	4 (5.33%)	9 (12.16%)	11 (14.86%)

Table 24 Protocol Deviations

1. Few subjects failed to return to clinical for at least one of the blood sample collection.
2. One subject took Ibuprofen 14 days before the study and three other subjects took lactated Ringers, toradol, and Acetaminophen during the study.
3. Some sampling time deviations.

Comments on Adverse Events/Protocol Deviations:

1. Subject #31 vomited at 0.33, 7.0 and 7.25 hours after period II dose administration. It was discovered that she has a history of migraines which was not disclosed in the medical history. She elected to withdraw during period II due to vomiting, nausea and headache.
2. Subject #15 and #34 were excluded **prior to the sample analyses** due to the diarrhea. Subject #15 had a diarrhea 3 hours after dosed test product A. Subject #34 had a diarrhea 13 hours after dosed reference product B. The mean Tmax for the test and reference products are 15 hours and 18 hours, respectively. It is possible that the diarrhea had some impact on the absorption of the drug therefore, these subjects were excluded. However, the firm did not state it in its protocol. In the future, the firm should specify such circumstances in the protocol.

c) Bioanalytical Results

Table 25 Assay Quality Control – Within Study

	Parent
QC Conc. (ng/mL)	0.1500, 1.000, 6.000
Between Run Precision* (%CV)	3.72-9.83
Between Run Accuracy* (%)	99.23-101.35
Cal. Standards Conc. (ng/mL)	0.05000, 0.1000, 0.1500, 0.5000, 1.000, 2.000, 4.000, 6.000, 8.000, 10.00
Between Run Precision (%CV)	1.9-5.5
Between Run Accuracy (%)	97.0-103.2
Linearity Range (range of R^2 values)	0.9921-0.9995

* There were some QC outliers during the runs. The values summarized here have excluded the outliers values (Vol. 1.10, p 4966).

Comments on Study Assay Quality Control: Acceptable.

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

Comments on Chromatograms: Acceptable.

Table 26 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
D-400-04	04-06-04	Reassay or Reinjection of Clinical Samples
D-401-07	04-06-04	Evaluation and Acceptance Criteria for Analytical Runs
D-416-03	04-06-04	Reassay of Whole Subjects

Table 27 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Acceptable.

d) Pharmacokinetic Results

Table 28 Arithmetic Mean Pharmacokinetic Parameters (After excluding subject #24)

Mean plasma concentrations are presented in Table 31 and Figure 2

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC∞	ng.hr/mL	224.75	160.17	226.31	168.66	0.99
AUC0-t	ng.hr/mL	204.45	151.56	197.06	160.20	1.04
Cmax	ng/mL	5.81	110.07	5.54	116.46	1.05
Kel	1/hr	0.06	38.55	0.05	33.06	1.03
T1/2	hr	15.65	62.22	17.73	128.2	0.88
Tmax	hr	15.42	40.70	18.49	62.84	0.83

Reviewer's Comment:

The firm did not include the Thalf data in its disc containing the PK dataset. The firm should include this information in its electronic disc containing the PK dataset in the future.

Table 29 Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI	
	Mean	Mean		Low	Upper
LAUC∞	82.36	80.11	1.03	92.43	114.35
LAUC0-t	77.01	71.94	1.07	95.59	119.84
LCmax	3.24	2.98	1.09	95.46	123.88

Table 30 Additional Study Information

Root mean square error, LAUC0-t	0.398060
Root mean square error, LAUC∞	0.357269
Root mean square error, LCmax	0.458739
Kel and AUC∞ determined for how many subjects?	66
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	5 (< 5% Cmax)*
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	no

* Subject #49 has a measurable drug concentration at 0 hr which is above 5% of its Cmax. This subject was excluded from the statistical analysis.

Comments on Pharmacokinetic and Statistical Analysis:

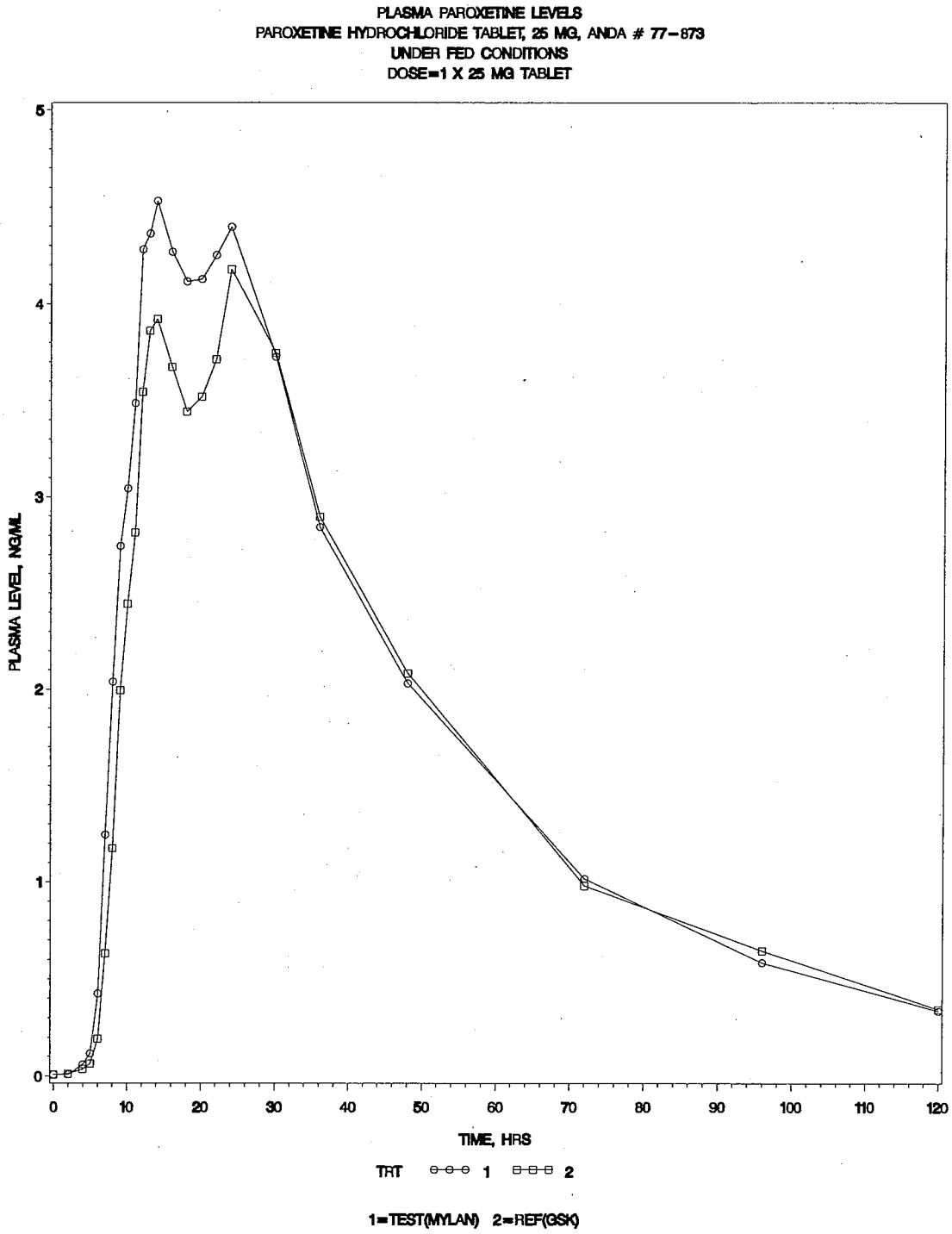
1. The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree well with firm's calculations.
2. The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{\infty}$ and LC_{max} are within the acceptable limits of 80-125%.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:
Acceptable.

Table 31 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Time	Test (n=69)		Reference (n=69)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.01	506.78	0.01	611.37	0.93
2	0.01	485.74	0.01	438.58	0.67
4	0.06	415.60	0.04	351.07	1.64
5	0.12	340.06	0.06	397.63	1.81
6	0.43	203.80	0.19	299.27	2.21
7	1.25	153.52	0.63	207.65	1.97
8	2.04	152.00	1.18	177.16	1.74
9	2.74	156.35	1.99	183.26	1.38
10	3.04	157.77	2.44	177.83	1.25
11	3.49	150.34	2.81	169.91	1.24
12	4.28	136.16	3.54	163.81	1.21
13	4.36	125.98	3.86	157.45	1.13
14	4.53	120.57	3.92	149.42	1.16
16	4.27	116.91	3.67	140.85	1.16
18	4.12	118.02	3.44	140.08	1.20
20	4.13	119.86	3.52	142.03	1.17
22	4.25	120.71	3.71	135.68	1.14
24	4.40	122.96	4.18	131.37	1.05
30	3.73	136.65	3.75	140.69	0.99
36	2.84	151.68	2.90	153.98	0.98
48	2.03	173.23	2.08	176.70	0.98
72	1.02	210.31	0.98	229.95	1.04
96	0.58	247.47	0.65	244.13	0.91
120	0.34	275.17	0.34	306.06	0.98

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



4. Single-dose Fed Bioequivalence Study (re-dosing study)

a) Study Design

Study Information	
Study Number	PARO-0510A
Study Title	Single-Dose Food In Vivo Bioequivalence Study of Paroxetine Hydrochloride Controlled-Release Tablets (25 mg; Mylan) to Paxil CR® Tablets (25 mg; GSK) in Healthy Volunteers
Clinical Site	PRACS Institute, Ltd.
Principal Investigator	James D. Carlson, Pharm. D.
Study/Dosing Dates	Period I: July 16, 2005 Period II: July 30, 2005
Analytical Site	Mylan Pharmaceuticals Inc. Bioanalytical Department
Analytical Director	(b) (6) Lab Manager
Analysis Dates	August 19, 2005 to August 26, 2005
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	41 days

* Paroxetine is stable under storage condition of -70°C for 163 days.

Treatment ID	**Test**	**Reference**
Test or Reference	A	B
Product Name	Paroxetine Hydrochloride Extended-Release 25 mg Tablet	Paxil CR® 25 mg Tablet
Manufacturer	Mylan	GlaxoSmithKline
Batch/Lot No.	Lot# R1N0377	1874P07
Manufacture Date	3/7/05	NA
Expiration Date	NA	exp: 8/06
Strength	25 mg	
Dosage Form	Tablets	
Batch Size	(b) (4)	NA
Production Batch Size	NA	NA
Potency	97.2%	98.7%
Content Uniformity (mean, %CV)	Ave: 97.3%; RSD = 1.3%	NA
Formulation	See Appendix Section B	NA
Dose Administered	1 x 25 mg	
Route of Administration	Orally with 240 ml water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 8, 52 BA: 24, 41
Blood Sampling Times	Pre-dose (0), 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, 30, 36, 48, 72, 96 and 120 hours (24 samples)
Blood Volume Collected/Sample	10 mls
Blood Sample Processing/Storage	Blood samples were collected in sodium heparin vacutainers and cooled in ice bath, then centrifuged at 3000 rpm under 4°C for 10 min under refrigeration. Plasma was extracted, divided in two aliquots and stored in suitably labeled tubes at -70°C ± 15°C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See 34A
Length of Fasting before Meal	Overnight of at least 10 hours
Length of Confinement	Patients entering the clinical site no later than 4: 00 pm on the day prior to dosing and remain at the clinical site until 24 hours after dosing.
Safety Monitoring	Vital signs measured at 6, 12, 24, 48, 72, 96 and 120 hours post-dose
Standard FDA Meal Used?	Yes
If no, then meal is listed in table below	

Comments on Study Design: Acceptable.

b) Clinical Results

Table 32A Demographics of Study Subjects

Subjects	Age	Weight (lb)	Gender	Race
#24	28	182	M	Caucasian
#41	25	139	M	Caucasian
#8	19	188	M	Caucasian
#52	22	163	F	Caucasian

Table 33A Dropout Information

None.

Table 34A Study Adverse Events

Subjects	Events	Test or Reference
#24	Pruritis (all over body itch)	Test
#52	Arthralgia (right knee pain)	Test

Table 35 Protocol Deviations

One sampling time deviation and one concomitant medication (Claritin).

Comments on Adverse Events/Protocol Deviations: Acceptable.

c) Bioanalytical Results

Table 36A Assay Quality Control – Within Study

	Parent
QC Conc. (ng/mL)	0.1500, 1.000, 6.000
Between Run Precision* (%CV)	3.8-2.7
Between Run Accuracy* (%)	98.7-102.1
Cal. Standards Conc. (ng/mL)	0.05000, 0.1000, 0.1500, 0.5000, 1.000, 2.000, 4.000, 6.000, 8.000, 10.00
Between Run Precision (%CV)	0.6-3.8
Between Run Accuracy (%)	92.3-104.9
Linearity Range (range of R^2 values)	0.9952-0.9992

Comments on Study Assay Quality Control: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Results of Subject #24 were included

Comments on Chromatograms: Acceptable.

Table 37A SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
D-400-04	04-06-04	Reassay or Reinjection of Clinical Samples
D-401-07	04-06-04	Evaluation and Acceptance Criteria for Analytical Runs
D-416-03	04-06-04	Reassay of Whole Subjects

Table 38A Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays: Acceptable.

d) Pharmacokinetic Results

Table 39A Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in 44A and 3A

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC∞	ng.hr/mL	89.61	150.96	92.45	165.28	0.97
AUC0-t	ng.hr/mL	87.09	152.71	90.72	167.45	0.96
Cmax	ng/mL	2.86	110.06	2.91	147.38	0.98
Kel	1/hr	0.06	26.93	0.06	26.65	1.01
T1/2	hr	NA	NA	NA	NA	NA
Tmax	hr	14.50	25.50	15.00	42.51	0.97

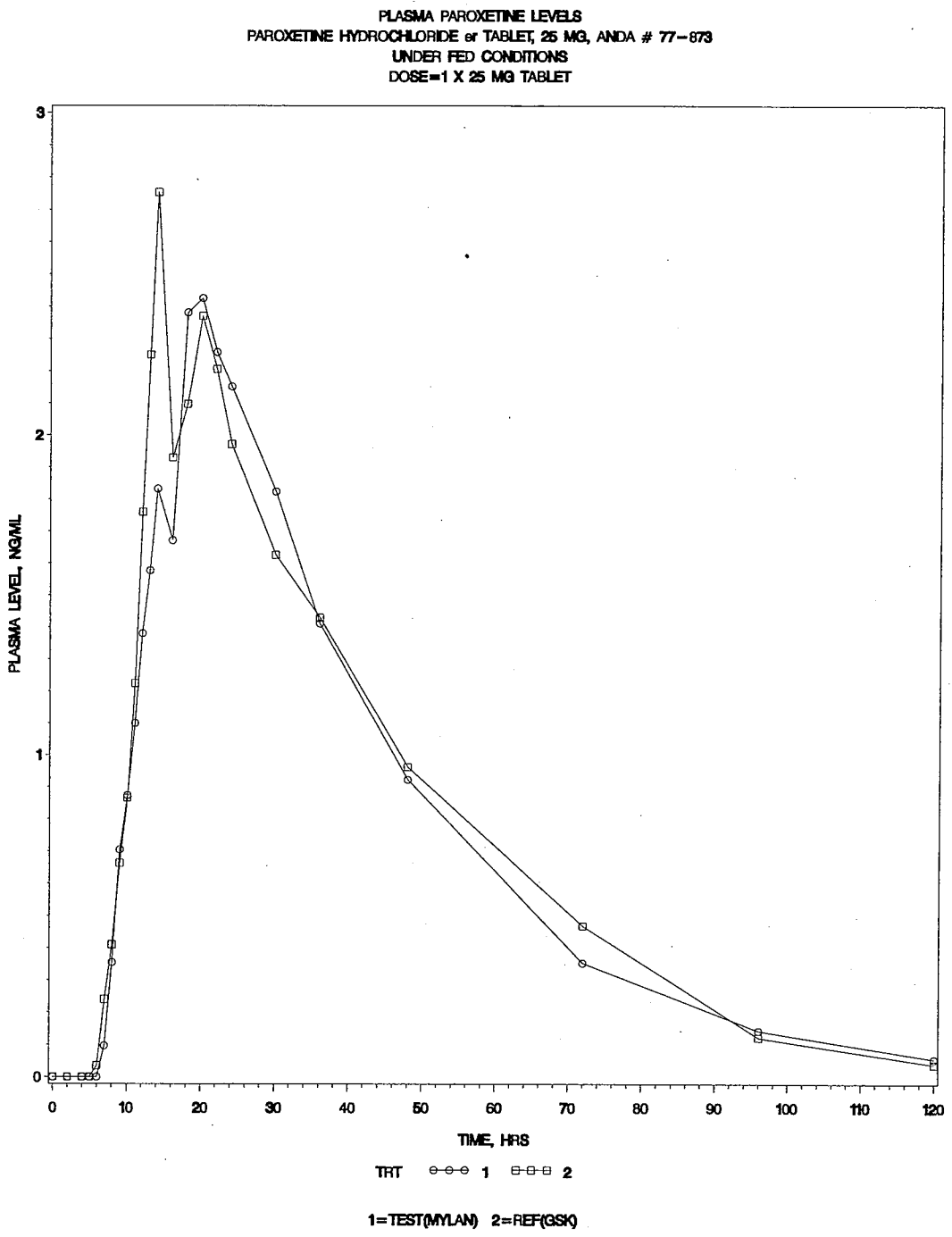
Comments on Pharmacokinetic and Statistical Analysis: Acceptable.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study: Acceptable.

Table 40A Mean Plasma Concentrations, Single-Dose Fed Re-dose Bioequivalence Study

Time	Test (n=4)		Reference (n=4)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
2	0.00	.	0.00	.	.
4	0.00	.	0.00	.	.
5	0.00	.	0.00	.	.
6	0.00	. .	0.03	200.00	0.00
7	0.10	124.61	0.24	151.60	0.40
8	0.35	62.82	0.41	132.18	0.87
9	0.70	48.59	0.66	115.70	1.06
10	0.87	54.59	0.87	121.19	1.01
11	1.10	42.94	1.22	136.02	0.90
12	1.38	45.48	1.76	146.59	0.78
13	1.58	53.69	2.25	153.27	0.70
14	1.83	79.90	2.75	159.35	0.67
16	1.67	119.63	1.93	151.86	0.87
18	2.38	143.88	2.10	154.65	1.14
20	2.43	140.34	2.37	160.10	1.02
22	2.26	141.40	2.21	159.91	1.02
24	2.15	150.69	1.97	154.24	1.09
30	1.82	164.14	1.63	161.79	1.12
36	1.41	166.18	1.43	169.68	0.99
48	0.92	176.78	0.96	181.70	0.96
72	0.35	189.12	0.47	188.83	0.75
96	0.14	200.00	0.12	200.00	1.18
120	0.06	200.00	0.04	200.00	1.43

Figure 3A Mean Plasma Concentrations, Single-Dose Fed Re-dose Bioequivalence Study



B. Formulation Data

Ingredient	Amount (mg)/Tablet		Amount (%) Tablet	
	12.5mg	25mg	12.5mg	25mg
(b) (4)				
Total	220.4	220.4	100	100

[1] Equivalent to 12.5mg of Paroxetine
[2] Equivalent to 25mg of Paroxetine

Reviewer's Comment on Formulation:

1. The inactive ingredients in the formulation are within the acceptable range of the Inactive Ingredient Database for the dosage form (tablet) and route of administration (oral). (V:\firmsam\ MYLAN\LTRS&REV\77873cr1.doc).

2. The formulation of the 12.5 mg strength tablet is proportionally similar to that of the 25 mg strength tablet.

3. The formulation is acceptable

C. Dissolution Data

Dissolution Method:

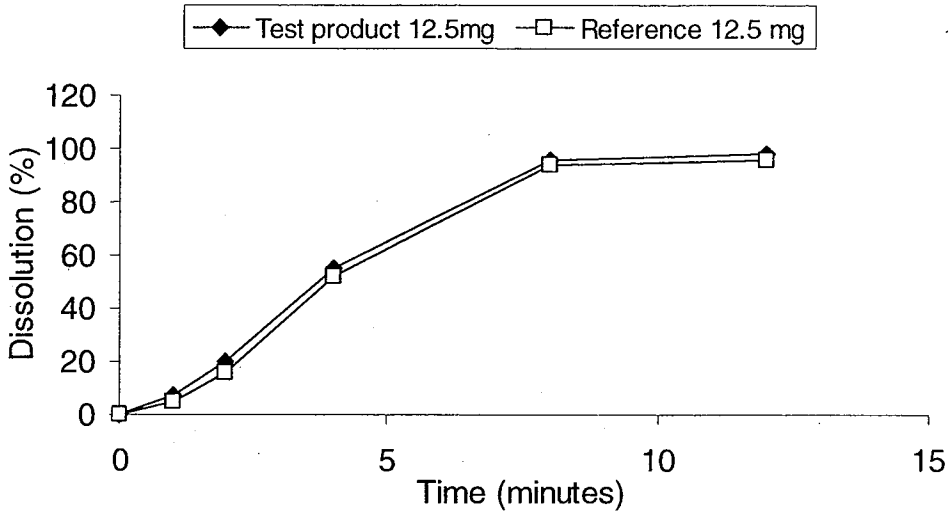
Medium and Volume	Acid stage (2hrs): 750 ml of 0.1 N HCl Buffer stage (12 hrs): 0.05M tris buffer pH 7.5		
Temperature	37^0 C		
Apparatus	I (basket)		
Rotational Speed	100 rpm		
Firm's proposed specifications	Acid stage Buffer Stage	2 hrs 2hrs 4hrs 12hrs	NMT (b) (4) NLT
FDA-recommended specifications	Acid stage Buffer Stage	2 hrs 2hrs 4hrs 12hrs	NMT (b) (4) NLT

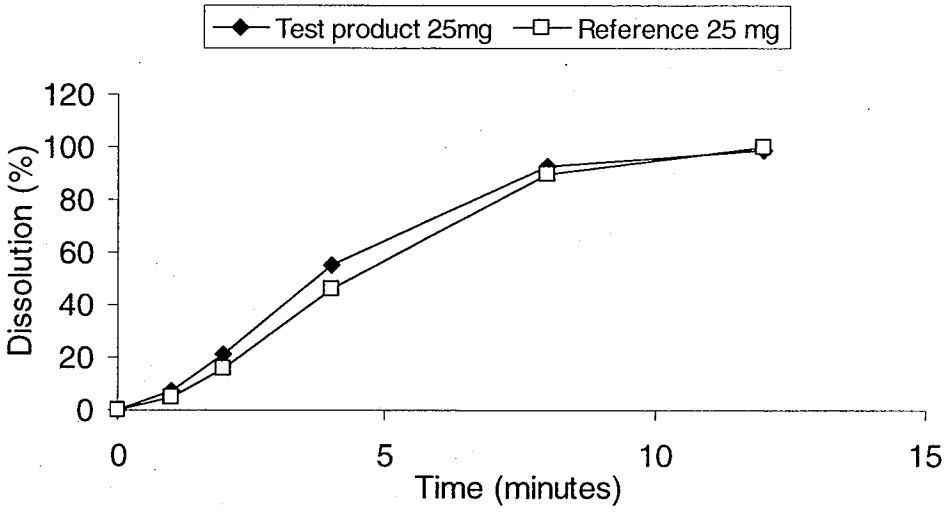
Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean % Dissolved (Range)						Study Report Location
					Acid Stage	Buffer Stage					
					2 hours	1 hour	2 hours	4 hours	8 hours	12 hours	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R3N1608	12.5mg tablet	Apparatus: 1 (basket) Speed: 100 rpm Medium: Acid Stage - 0.1N Hydrochloric Acid Buffer Stage – 0.05M Tris Buffer, pH 7.5 ± 0.05 Volume: Acid Stage – 750mL Buffer Stage – 1000mL Temperature: 37°C ± 0.5°C	12	1% RSD 31.8%	7% RSD 13.3%	20% RSD 10.4%	55% RSD 5.8%	96% RSD 2.4%	98% (b) (4) RSD 2.1%	Volume 1, pages 9536-9539
N/A	Paxil CR® Tablets Lot 773P06	12.5mg tablet		12	0% RSD 93.9%	5% RSD 18.1%	16% RSD 12.2%	52% RSD 6.5%	94% RSD 2.2%	96% (b) (4) RSD 2.8%	
N/A	Paroxetine Hydrochloride Extended-release Tablets Lot R1N0377	25mg tablet	Apparatus: 1 (basket) Speed: 100 rpm Medium: Acid Stage - 0.1N Hydrochloric Acid Buffer Stage – 0.05M Tris Buffer, pH 7.5 ± 0.05 Volume: Acid Stage – 750mL Buffer Stage – 1000mL Temperature: 37°C ± 0.5°C	12	0% (b) (4) RSD 345.4%	7% RSD 7.0%	21% RSD 8.5%	55% RSD 6.8%	93% RSD 3.1%	99% (b) (4) RSD 1.8%	Original ANDA Volume 18, pages 9536-9539
N/A	Paxil CR® Tablets Lot 1874P07	25mg tablet		12	0% (b) (4) RSD 345.4%	5% RSD 17.6%	16% RSD 12.6%	45% RSD 13.3%	90% RSD 6.9%	100% (b) (4) RSD 1.5%	

Reviewer's Comments on Dissolution:

1. The firm submitted its dissolution testing using the firm proposed dissolution method as listed above. The DBE agrees with Mylan's method but recommends alternative specifications (V:\firmsam\mylan\ltrs&rev\77873D905.doc).
2. The firm accepted DBE recommended specifications. The dissolution testing is complete.
3. The firm also submitted its dissolution testing results on three other media and the FDA recommended method. Details please refer to the dissolution review (V:\firmsam\mylan\ltrs&rev\77873D905.doc).

Dissolution Profile:





D. Consult Reviews

V:\firmsam\ MYLAN\LTRS&REV\77873cr1.doc
V:\firmsam\mylan\ltrs&rev\77873D905.doc

E. SAS Output

	Fasting and Fed Studies for Paroxetine Hydrochloride Extended-release Tablets 25 mg					
	Fasted			Fed		
	Including sub. 59	Excluding sub 59	Re-dose study	Including sub. 24	Excluding sub 24	Re-dose study
SAS Program	77873_Fast_Parc xetine_Prog_w59	77873_Fast_Parc xetine_Prog_wo5	77873_Fast redose_Paroxetir	77873_Fed_Paro etine_Prog_w24.	77873_Fed_Paro etine_Prog_wo24	77873_Fed redose_Paroxetir
Statistical Output	77873_Fast_Parc xetine_Stat_w59	77873_Fast_Parc xetine_Stat_wo5	77873_Fast redose_Paroxetir	77873_Fed_Paro etine_Stat_w24.t	77873_Fed_Paro etine_Stat_wo24	77873_Fed redose_Paroxetir
Plasma Concentration Data	77873 conc pk data.xls					

F. Additional Attachments

None.

BIOEQUIVALENCE COMMENTS

ANDA: 77-873 APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Paroxetine Hydrochloride Extended-release Tablets, 25 mg and 12.5 mg

The Division of Bioequivalence has completed its review of your submission (s) acknowledged on the cover sheet and has no further questions at this time.

We acknowledge that you have accepted the following dissolution method and specifications:

The dissolution testing should be conducted using the FDA recommended method and the product should meet the FDA recommended specifications as follows:

Medium and Volume	Acid stage (2hrs): 750 ml of 0.1 N HCl Buffer stage (12 hrs): 0.05M tris buffer pH 7.5
Temperature	37^0 C
Apparatus	I (basket)
Rotational Speed	100 rpm
FDA-recommended specifications	Acid stage: 2 hrs NMT (b)(4) Buffer Stage: 2hrs 4hrs 12hrs NLT

The following comments pertain to your **future submissions**:

1. Please provide the T1/2 information in your disc containing PK dataset.

2. Please provide your approach for treating subjects with aberrant pharmacokinetic parameters (AUC, Cmax), in the study protocols (i.e., re-dosing study).

3. Please provide your methodology of dealing with subjects that may develop diarrhea, in the study protocols.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are

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

Sincerely yours,

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

ANDA 77-873
Paroxetine HCl ER Tablets

CC: ANDA #77-873
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

V:\firmsam\mylan\ltrs&rev\77873N0905.doc
Printed in final

Endorsements: (Final with Dates)
HFD-650/ Reviewer B. Li BL 7/20/06
HFD-650/ Bio Team Leader M. Makary MHM 7/21/06
HFD-650/ D. Conner BMD 7/2/06

BIOEQUIVALENCE - COMMENTS

Submission Date: 09/09/05

1. Fasting Study
Clinical: PRACS Institute, Ltd.
Analytical: Mylan Pharmaceuticals Inc.

Strength: 25 mg
Outcome: AC

2. Fasting Study (re-dose)
Clinical: PRACS Institute, Ltd.
Analytical: Mylan Pharmaceuticals Inc.

Strength: 25 mg
Outcome: AC

3. Fed Study
Clinical: PRACS Institute, Ltd.
Analytical: Mylan Pharmaceuticals Inc.

Strength: 25 mg
Outcome: AC

4. Fed Study (re-dose)
Clinical: PRACS Institute, Ltd.
Analytical: Mylan Pharmaceuticals Inc.

Strength: 25 mg
Outcome: AC

5. Dissolution Waiver

Strength: 12.5 mg
Outcome: AC

Outcome Decisions:
AC

3.1

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:	77-873 **SPONSOR:** Mylan Pharmaceuticals, Inc.
DRUG & DOSAGE FORM:	Paroxetine Hydrochloride Extended-release Tablets
STRENGTH(S):	25 mg and 12.5 mg
TYPES OF STUDIES:	Fasting and Fed
CLINICAL STUDY SITE(S):	PRACS Institute, Ltd.
ANALYTICAL SITE(S):	Mylan Pharmaceuticals Inc.
STUDY SUMMARY:	Fasting and fed studies are acceptable
DISSOLUTION:	Dissolution testing is acceptable

DSI INSPECTION STATUS

Inspection needed:	NO	**Inspection status:**	**Inspection results:**
First Generic	Yes		
New facility			
For cause			
Other			

Proposed Dissolution Method and Specifications from Original Submission Acceptable?
Yes _____ No X (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes X No ___

AMENDMENT DATE: Feb. 15, 2006

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: Bing V. Li **BRANCH:** I
INITIAL: BL DATE: 7/20/06

TEAM LEADER: Moheb H. Makary **BRANCH:** I
INITIAL: MHM DATE: 7/21/06

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: BMD DATE: 7/21/06

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-873

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

77-873
N-000

September 9, 2005

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

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

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 25MG

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: Paroxetine Hydrochloride Extended-release Tablets
This application consists of a total of 42 volumes and one CD-Rom.
- Archival Copy - 20 volumes.
- Review Copy – 20 volumes.
  - Technical Section For Chemistry - 2 volumes.
  - Technical Section For Pharmacokinetics - 18 volumes.
- Analytical Methods - 2 extra copies; 1 volume each.
- CD-Rom – eCover Letter, e356h, eTOC, eLabeling Components, Bioequivalence Summary Tables and data listings for the bioequivalence studies conducted in support of this application.

This application provides for the manufacture of Paroxetine Hydrochloride Extended-release Tablets, 25mg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

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

Department—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

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

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

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

MEMORANDUM

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

DATE : October 5, 2005

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 77-873 for Paroxetine Hydrochloride Extended-release Tablets, 25 mg to determine if the application is substantially complete for filing.

Mylan Pharmaceuticals, Inc. has submitted ANDA 77-873 for Paroxetine Hydrochloride Extended-release Tablets, 25 mg. It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Mylan Pharmaceuticals, Inc. on September 9, 2005 for its Paroxetine product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 77-873 **FIRM NAME** **Mylan Pharmaceuticals Inc.**

DRUG NAME Paroxetine HCl

DOSAGE FORM **ER tablets**
SUBJ: Request for examination of: Bioequivalence Study

Requested by: M. Shiner Date: 5 Oct 05
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

R. Lee Date: 7 Oct 05
Reviewer

for S. Shivanter Date: 10/7/05
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐	2	2	
Assay Methodology	☒	☐	1	1	
Procedure SOP	☒	☐	1	1	
Methods Validation	☒	☐	1	1	
Study Results Ln/Lin	☒	☐	2	2	
Adverse Events	☒	☐	2	2	
IRB Approval	☒	☐	2	2	
Dissolution Data	☒	☐	1	1	
Pre-screening of Patients	☒	☐	2	2	
Chromatograms	☒	☐	2	2	
Consent Forms	☒	☐	2	2	
Composition	☒	☐	1	1	
Summary of Study	☒	☐	2	2	
Individual Data & Graphs, Linear & Ln	☒	☐	2	2	
PK/PD Data Disk Submitted)	☒	☐	2	2	posted on EDR
Randomization Schedule	☒	☐	2	2	
Protocol Deviations	☒	☐	2	2	
Clinical Site	☒	☐	2	2	
Analytical Site	☒	☐	2	2	
Study Investigators	☒	☐	2	2	

Medical Records	☒	☐	2	2	
Clinical Raw Data	☒	☐	2	2	
Test Article Inventory	☒	☐	2	2	
BIO Batch Size	☒	☐	1	1	
Assay of Active Content Drug	☒	☐	1	1	in COAs
Content Uniformity	☒	☐	1	1	in COAs
Date of Manufacture	☒	☐	1	1	in Executed batch record
Exp. Date of RLD	☒	☐	1	1	in COA
BioStudy Lot Numbers	☒	☐	1	1	
Statistics	☒	☐	2	2	
Summary results provided by the firm indicate studies pass BE criteria	☒	☐	2	2	Yes, if reviewer agrees that the re-dosing studies indicate that a subject's data may be deleted
Waiver requests for other strengths / supporting data	☐	☒			N/A

Additional Comments regarding the ANDA:

Paroxetine HCl ER tablet is available in 3 strengths. The listed RLD is the 37.5 mg strength product. This application only involves the 25 mg strength product.

In addition to the fasted and fed studies contained in this submission, there is also a re-dosing study for the fasted and a re-dosing study for the fed study. There is sufficient information in the re-dosing studies to make a decision concerning the acceptability of dropping a subject in the respective main studies. Re-dosing study data is available electronically in the EDR.

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-873 **FIRM NAME:** MYLAN PHARMACEUTICALS, INC.

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: PAROXETINE

DOSAGE FORM: EXTENDED-RELEASED TABLETS, 25 MG

Bio Assignments:		Micro Review
☒ BPH	☐ BCE	☐
☐ BST	☒ BDI	

Random Queue: 10

Chem Team Leader: Susan Rosencrance PM: Tom Hinchliffe Labeling Reviewer: Michelle Dillahunt

Letter Date: SEPTEMBER 9, 2005	**Received Date:** SEPTEMBER 9, 2005
Comments: EC - 1 YES **On Cards:** YES **Therapeutic Code:** 2020100 ANTIDEPRESSANTS	
Archival Format: PAPER **Sections I** (356H Sections per EDR Email) **Review copy:** YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) **YES** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST **Iain Margand** **Date** **11/1/05**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date:	**Date:** 4 Nov 2005
ADDITIONAL COMMENTS REGARDING THE ANDA:	
Top 200 Drug Product:	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☒
Sec. II	**Basis for Submission** **NDA# : 20-936** Ref Listed Drug: PAXIL Firm: GLAXOSMITHKLINE ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** 1. Paragraph: IV patents '123, '132, '423, '291, '289, '084 2. Expiration of Patent: 9-17-2017 PIII patents '723, '177, '449 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use OK 2. Active ingredients OK 3. Route of administration OK 4. Dosage Form OK 5. Strength OK	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL Y 2. 1 RLD label and 1 RLD container label Y 3. 1 side by side labeling comparison with all differences annotated and explained Y 4. Was a proprietary name request submitted? No (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES pg. 50 **2. Request for Waiver of In-Vivo Study(ies): NA** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) N/A **4. Lot Numbers of Products used in BE Study(ies):** R1N0377 **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 25 MG a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES pg. 9533 FAST FED AUCt 81.3 – 110.0 95.6 – 119.8 Auc∞ 82.2 – 110.4 92.7 – 114.1 Cmax 84.8 – 114.5 95.5 – 123.9	☒

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation OK 2. Inactive ingredients as appropriate Inactive ingredients are acceptable per IIG	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers Y b. Type II DMF authorization letters or synthesis DMF# (b) (4) c. COA(s) specifications and test results from drug substance mfgr(s) Y d. Applicant certificate of analysis Y e. Testing specifications and data from drug product manufacturer(s) Y f. Spectra and chromatograms for reference standards and test samples Y g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified pg. 9663 b. Testing specifications (including identification and characterization) Y c. Suppliers' COA (specifications and test results) Y d. Applicant certificate of analysis Y	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address Y No testing of API or finished drug product 2. Functions Y 3. CGMP Certification/GLP Y 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) tablets 3.If sterile product: Aseptic fill / Terminal sterilization N/A 4.Filter validation (if aseptic fill) N/A 5. Reprocessing Statement pg. 9930	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation 2. In-process Controls - Specifications and data Y Ty: (b) (4) Ay: Packaged: 30 – (b) (4) 100 - 500 – (b) (4)	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) pg. 10071 2. Components Specification and Test Data (Type III DMF References) Y 3. Packaging Configuration and Sizes 75cc and 150cc bottles 4. Container/Closure Testing Y 5. Source of supply and suppliers address pg. 10072	☒

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data Y 2. Certificate of Analysis for Finished Dosage Form Y	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted Y 2. Post Approval Commitments pg. 10553 3. Expiration Dating Period 24 months 4. Stability Data Submitted a. 3 month accelerated stability data Y b. Batch numbers on stability records the same as the test batch R1N0377	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance 2. Finished Dosage Form 3. Same lot numbers	☒
Sec. XVII	**Environmental Impact Analysis Statement**	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) YES 4. Field Copy Certification (original signature) YES	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe

ANDA 77-873 Final Check List for Branch Chief

1) Check letter date and stamp date of ANDA vs. drafted letter.

2) Check for any NC arriving post stamp date but prior to Reg. Review.

3) Check for gross errors in letter.

4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

5) Check address and contact person on letter vs. 356h.

6) Check for any t-cons and verify date and correspondence date.

7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

8) Check for any comments or problems raised by reviewer on Check List.

9) If first generic, copy BE review and file.

10) Sign Check List.

11) Check electronic Orange Book to verify current patent information and correct RLD. PAI CR

12) Check for MOU patents

13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

14) Review Basis for Submission.

15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer. PIII → '423, '177 & '449 PIV to '123, '132, '423, '289, '291 & '084

16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

18) Pull USP information. (USP ____yes ____no)

19) Final Grammar review on letter.

20) Verify information in OGD Patent Tracking System.

21) EES slip.

22) Document in record book.

Signature Martin H. Gruin date NOV 2005

ANDA 77-873

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

NOV -7 2005

Dear Sir:

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

NAME OF DRUG: Paroxetine Hydrochloride Extended-release Tablets, 25 mg

DATE OF APPLICATION: September 9, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 9, 2005

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

CONTENTS OF THE NOTICE

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

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

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

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

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

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

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

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

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

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

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

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

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

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

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

- You must submit a copy of a copy of a court order or 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 Martin Shimer, Chief, Regulatory Support Branch, at (301)827-0503.

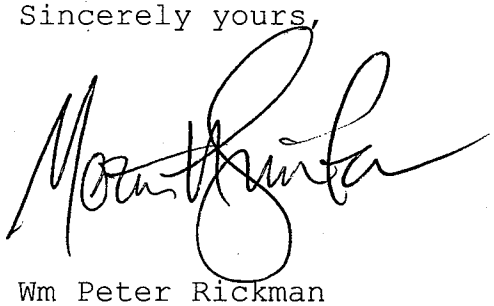
We will correspond with you further after we have had the opportunity to review the application.

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

Should you have questions concerning this application, contact:

Tom Hinchliffe
Project Manager
(301) 827-5771

Sincerely yours,



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

c: ANDA 77-873
DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement: HFD-613/MShimer, Chief, RSB _____ date 4 NOV 05
HFD-613/IMargand, CSO _____ date 11/1/05
Word File V:\Firmsam\Mylan\Ltrs&rev\77873.ack
FT/ 11/1/05
ANDA Acknowledgment Letter!

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

November 8, 2005

MAJOR AMENDMENT
(CMC, BIOWAIVER AND ELECTRONIC DATA ENCLOSED)

ORIG AMENDMENT
N/AC

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

RECEIVED
NOV 0 8 2005
OGD/CDER

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 25MG
ANDA 77-873
(Amendment to Provide for Addition of 12.5mg Strength)

Dear Mr. Buehler:

Mylan wishes to amend the above referenced application to provide for the manufacture of Paroxetine Hydrochloride Extended-release Tablets, 12.5mg, as a product line extension to Mylan's ANDA for Paroxetine Hydrochloride Extended-release Tablets, 25mg (ANDA 77-873) originally submitted on September 9, 2005.

The proposed strength is qualitatively identical (except for the addition of a colorant) and proportionally similar in composition to the 25mg strength, and will be manufactured, tested, packaged, and labeled using procedures and controls similar to those provided in Mylan's ANDA 77-873 submitted on September 9, 2005. The bioequivalence of Mylan's Paroxetine Hydrochloride Extended-release Tablets, 25mg and the reference listed drug, Paxil CR® Tablets, 25mg was demonstrated in Mylan's original submission. Based on the proportional similarity of the formulations of the 12.5mg strength to the 25mg strength, Mylan is requesting a waiver of *in vivo* bioequivalence testing requirements for the additional strength.

This amendment consists of 7 volumes as follows:
- Archival Copy - 2 volumes.
- Review Copy - 3 volumes.
  - Technical Section For Chemistry - 2 volumes.
  - Technical Section For Pharmacokinetics - 1 volume.
- Analytical Methods - 2 extra copies; 1 volume each.
- CD-Rom – eCover Letter, e356h, eTOC, eLabeling components, and Bioequivalence Summary Tables

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 the electronic labeling for Paroxetine Hydrochloride Extended-release Tablets. Please note that the enclosed labeling supersedes the draft labeling originally submitted on September 9, 2005. 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.

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

As an aid to the reviewer, this amendment has been assembled according to the traditional ANDA format. Only those documents that have been revised since the original submission and new documents in support of the additional strength are provided in this submission. Details of revisions made to previously submitted documents are fully described on the cover page preceding the document. The pagination from the original ANDA has been retained for documents that are identical to those submitted in the original application and have been resubmitted for the convenience of the reviewer. The enclosed Table of Contents provides a listing of the information being submitted in support of this amendment.

This amendment is being submitted in duplicate to the above referenced application. 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.

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

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

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

November 8, 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: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 25MG
ANDA 77-873
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to the Agency's letter dated November 7, 2005 notifying us that the ANDA has been found acceptable for filing (refer to Attachment A).

In accordance with 21 CFR 314.95(b) and as detailed in the Agency's November 7th letter, this amendment provides 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). A Patent Amendment is provided in Attachment B.

In accordance with the Agency's November 7, 2005 letter, Mylan will submit further documentation of receipt of the notice required by 21 CFR 314.95(e), as it pertains to the Paragraph IV patent certification contained in our original application submitted on September 9, 2005 for Paroxetine Hydrochloride Extended-release Tablets, 25mg upon receipt.

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
NOV 09 2005
OGD/CDER

G:\Project\ANDA\PAROXETINE HCl ER TABLETS\PATENT-AMENDMENT-110805.doc

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Regulatory Affairs	(304) 285-6407
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	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

December 16, 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: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. In accordance with 21 CFR 314.95(e), this amendment provides documentation of receipt of the notice required by 21 CFR 314.95(a) and (b), as it pertains to the Paragraph IV patent certification contained in our original ANDA submitted September 9, 2005 for the 25mg strength and our Amendment submitted on November 8, 2005 for the 12.5mg strength. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

The owner of the patents and the holder of the application for the listed drug were served with the required notice. Proof of delivery by Registered Mail, Return Receipt evidences receipt by GlaxoSmithKline on November 9, 2005, by SkyePharma AG, d/b/a Jagotec, GlaxoSmithKline, plc, and Glaxo Group, Ltd. d/b/a GlaxoSmithKline on November 10, 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

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

G:\Project\ANDA\PAROXETINE HCl ER TABLETS\PATENT-AMENDMENT-121605.doc

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Regulatory Affairs	(304) 285-6407
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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

DEC 16 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

RE: PAROXETINE HYDROCHLORIDE
EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA #77-873

PATENT AMENDMENT

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and the Agency's letter dated November 7, 2005, notifying Mylan Pharmaceuticals Inc. ("Mylan") that the ANDA has been found acceptable for filing.

In accordance with 21 CFR 314.95(e), this amendment provides documentation of receipt of notice, as it pertains to the Paragraph IV patent certification contained in our original application submitted on September 9, 2005 and the amendment submitted on November 8, 2005, for Paroxetine Hydrochloride Extended-release Tablets, 25mg and 12.5mg respectively. On November 8, 2005, Mylan requested FDA's permission to serve the required notice by Federal Express in lieu of the U.S. Postal Service. FDA approved this request and on November 8, 2005 the notice was sent *via* Federal Express. I have enclosed documentation of receipt by the owner(s) of the patents and the holder of the application for the listed drug claimed by said patents.

Proof of delivery by Federal Express (see attached) evidences receipt by GlaxoSmithKline on November 9, 2005. Proof of delivery by Federal Express (see attached) evidences receipt by SkyePharma AG, d/b/a Jagotec, GlaxoSmithKline, plc, and Glaxo Group, Ltd. d/b/a GlaxoSmithKline on November 10, 2005.

Sincerely,

Vince H. Suneja, Esq.
Assistant Regulatory Counsel

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

New Strength

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-873 **FIRM NAME**: MYLAN PHARMACEUTICALS INC.

RELATED APPLICATION(S): NA

First Generic Product Received? NO

Bio Assignments:		☐ **Micro Review**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

DRUG NAME: PAROXETINE HYDROCHLORIDE
DOSAGE FORM: EXTENDED- RELEASE TABLETS, 12.5 MG AND 25 MG (NEW STRENGTH 12.5 MG)

Random Queue: 10
Chem Team Leader: Ya, Naiqi PM: Thomas Hinchliffe Labeling Reviewer: Michelle Dillahunt

Letter Date: NOVEMBER 08, 2005	**Received Date**: NOVEMBER 08, 2005
Comments: EC- 2 YES **On Cards:** YES **Therapeutic Code:** 2020100 ANTIDEPRESSANTS	
Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)** **Review copy**: YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES – Cover letter & pg. 295	
Methods Validation Package (3 copies PAPER archive) **YES** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST Sandra J. Middleton **Date** 1/5/06	**Recommendation:** ☑ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: [signature]	**Date:** 6 Jan 2006
ADDITIONAL COMMENTS REGARDING THE ANDA: NONE	
Top 200 Drug Product:	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES ✓ (Statement regarding Rx/OTC Status) RX YES	☑
Sec. II	**Basis for Submission** **NDA# : 20-936** ✓ Ref Listed Drug: PAXIL Firm: GLAXO SMITH KLINE ANDA suitability petition required? NO If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☑
Sec. III	**Patent Certification** 1. Paragraph: IV – pg. 9 2. Expiration of Patent: 9-17-2017 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES – pg. 10	☑
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓	☑
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 30, 100 & 500 ct 1. 4 copies of draft (each strength and container) or 12 copies of FPL ✓ 2. 1 RLD label and 1 RLD container label ✓ 3. 1 side by side labeling comparison with all differences annotated and explained ✓ 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	☑
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) NO **2. Request for Waiver of In-Vivo Study(ies): Yes** – pg. 133 **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies):** **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☑
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED WAS DONE ON 25 MG ✓ a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES – pg. 142	☑

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation ✓ See Sheets attached 2. Inactive ingredients as appropriate ✓	☒ ✓

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers ✓ b. Type II DMF authorization letters or synthesis — (b) (4) c. COA(s) specifications and test results from drug substance mfgr(s) d. Applicant certificate of analysis e. Testing specifications and data from drug product manufacturer(s) f. Spectra and chromatograms for reference standards and test samples g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified — pg. 254 & 255 b. Testing specifications (including identification and characterization) c. Suppliers' COA (specifications and test results) ✓ d. Applicant certificate of analysis ✓ Same as original submission	☑
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) ✓ 2. CGMP Certification: YES — pg. 318 3. CFN numbers 1110315	☑
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address 2. Functions 3. CGMP Certification/GLP 4. CFN numbers Same as original	☑
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified ✓ (b) (4) 3.If sterile product: Aseptic fill / Terminal sterilization 4.Filter validation (if aseptic fill) 5. Reprocessing Statement — pg. 415	☑
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ✓ 2. In-process Controls - Specifications and data ✓	☑
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ✓ 2. Components Specification and Test Data (Type III DMF References) ✓ 3. Packaging Configuration and Sizes ✓ 4. Container/Closure Testing ✓ 5. Source of supply and suppliers address ✓	☑

Lot #	Master	Exhibit	Made	Packaged
12.5mg RIN1808	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data ✓ 2. Certificate of Analysis for Finished Dosage Form – pg	☑
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 24 months 4. Stability Data Submitted a. 3 month accelerated stability data ✓ b. Batch numbers on stability records the same as the test batch ✓	☑
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance ✓ 2. Finished Dosage Form ✓ 3. Same lot numbers ✓	☑
Sec. XVII	**Environmental Impact Analysis Statement** ✓	☑
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature): YES – pg 793 3. List of Convictions statement (original signature)	☑

OGD Template Revised 04/01/2004 /T.Hinchliffe

ANDA 77-883 Final Check List for Branch Chief

N/A 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

N/A 3) Check for gross errors in letter.

N/A 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

N/A 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

N/A 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. PAxil CR 37-5

✓ 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission. PAxil CR 20-936

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer. PIV → '723, '177 & '449 PII → '123, '132, '403, '289, '291 & '084 I-356 exp 8/12/05, I-405 exp. 8/28/06, D-91 exp 11/27/07

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ____yes ✓ no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature Martin Gruin date 6 January 2006

Middleton, Saundra T

From: Middleton, Saundra T
Sent: Monday, January 09, 2006 7:17 AM
To: Hinchliffe, Thomas; Dillahunt, Michelle; Fabian-Fritsch, Beth; Mazzella, Steven; Sigler, Aaron; Thompson, Christina
Cc: Shimer, Martin
Subject: New strength 77-873

We have accepted for filing the following new strength amendment:

ANDA: 77-873

Firm: Mylan Pharmaceuticals, Inc.

Drug: Paroxetine Hydrochloride

Dosage form: Extended-release

Strength: 12.5 mg

Date of amendment: November 8, 2005

Date received/acceptable for filing: November 8, 2005

Saundra

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

January 12, 2006

PATENT AMENDMENT

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

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
(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 our Amendment submitted on November 8, 2005 for the 12.5mg strength. Reference is also made to our Patent Amendment submitted on December 16, 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 A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

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

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

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JAN 13 2006
CGD / CDER

G:\Project\ANDA\PAROXETINE HCl ER TABLETS\PATENT-AMENDMENT-011206.doc

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

BIOEQUIVALENCY AMENDMENT

ANDA 77-873

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

FEB 0 8 2006

APPLICANT: Mylan Pharmaceuticals Inc.

TEL: 304-599-2595

ATTN: S. Wayne Talton

FAX: 304-285-6407

FROM: Keri Suh

PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on September 9, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Paroxetine Hydrochloride Extended-release Tablets, 12.5 mg and 25 mg.

Reference is also made to your amendment dated November 8, 2005.

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

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

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCY

ANDA: 77-873 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Paroxetine HCl ER tablets; 12.5 and 25 mg

The Division of Bioequivalence has completed its review of the dissolution testing portion of your application. The review of the bioequivalence studies and waiver request will be done at a later date.

1. We accept your proposed dissolution method based on your justification as follows:

   Apparatus I (basket) at 100 rpm
   750 ml of 0.1N HCl [acid stage]
   and 1000 ml of 0.05M Tris buffer, pH 7.5 [buffer stage]

   Based on the submitted data on your test products only, we wish to modify your proposed specifications:

   NMT [redacted] (b) (4) % dissolved in 2 hrs [acid stage]

   2 hrs: [redacted] (b) (4) %
   4 hrs: [redacted] %
   12 hrs: NLT [redacted] (b) (4) % dissolved [buffer stage]

   Please acknowledge the above specifications.

2. We acknowledge that you have submitted the study summaries in CTD format.

Sincerely yours,

Barbara P. Conner

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

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

February 15, 2006

N/AB

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)

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
RESPONSE TO AGENCY CORRESPONDENCE DATED FEBRUARY 8, 2006

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated February 8, 2006 (refer to Attachment C). In response to the February 8th comments from the Division of Bioequivalence, Mylan wishes to amend this application as follows:

The Division of Bioequivalence has completed its review of the dissolution testing portion of your application. The review of the bioequivalence studies and waiver request will be done at a later date.

FDA COMMENT 1: We accept your proposed dissolution method based on your justification as follows:

Apparatus 1 (basket) at 100 rpm
750 ml of 0.1N HCl [acid stage]
and 1000 ml of 0.05M Tris buffer, pH 7.5 [buffer stage]

Based on the submitted data on your test products only, we wish to modify your proposed specifications:

NMT (b) (4) % dissolved in 2 hours [acid stage]

2 hrs: (b) (4) %
4 hrs: %
12 hrs: NLT (b) (4) % dissolved [buffer stage]

Please acknowledge the above specifications.

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FEB 16 2006
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Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN RESPONSE: As requested, Mylan acknowledges our acceptance of the following dissolution method and specification for incorporation into our stability and quality control programs:

Apparatus:	1 (basket)
Speed:	100 rpm
Acid Stage:	
Volume:	750 mL
Medium:	0.1N HCl
Limits:	NMT (b) (4) % dissolved in 2 hours
Buffer Stage:	
Volume:	1000 mL
Medium:	0.05M Tris buffer, pH 7.5
Limits:	2 hours (b) (4) %
	4 hours %
	12 hours NLT (b) (4) % dissolved

Revised finished product specifications and Post-Approval Stability Protocols are provided in Attachments A and B, respectively.

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

Desk Copy: Keri Suh, Project Manager
Division of Bioequivalence

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

March 10, 2006

PATENT AND LABELING AMENDMENT
(ELECTRONIC LABELING AND PATENT 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

N/xP
N/AF

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
(Patent Amendment and Revised Labeling Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. We wish to amend this application to revise the patent certification previously submitted for U.S. Patent No. 5,789,449 from a 'Paragraph III Certification' to a 'Section viii Statement'. Provided in Attachment A is a Patent Amendment from our Legal Department which provides specifics regarding the enclosed information.

In accordance with the enclosed Patent Amendment and to labeling revisions approved on February 6, 2006 for the reference listed drug, Paxil CR® (GlaxoSmithKline), we have enclosed revised final printed labeling for Paroxetine Hydrochloride Extended-Release Tablets that excludes information related to the treatment of Premenstrual Dysphoric Disorder (PMDD) as it is covered by U.S. Patent No. 5,789,449 and 'Orange Book' code exclusivity I-405 (Treatment Of Premenstrual Dysphoric Disorder (PMDD) Using An Intermittent Dosing Regimen). A copy of the Agency's correspondence dated February 6, 2006 is provided herein as Letter1.pdf for the reviewer's reference. Please note that the enclosed draft outsert labeling supersedes the labeling previously submitted in our Major Amendment submitted on November 8, 2005. Container labels remain the same as those previously submitted in the original ANDA on September 9, 2005 (25 mg strength) and Major Amendment on November 8, 2005 (12.5 mg strength).

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 Paroxetine Hydrochloride Extended-Release Tablets as described in the electronic Table of Contents. As a review aid, Mylan has also included Microsoft Word versions of our proposed labeling components. To access these Word files, bookmarks are provided within the pdf versions.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Sales & Marketing	(304) 598-3232

Should a Structured Product Labeling (SPL) version of the Reference Listed Drug's labeling become available prior to receipt of ANDA approval, Mylan commits to submit a SPL version of our generic product labeling in an amendment to this application. If the SPL version becomes available post ANDA approval, Mylan commits to submit a SPL version of our generic product labeling in a Changes Being Effected Supplement, the next Annual report, or in a Post-Marketing Special Report as applicable.

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 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/dmy

Enclosures

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

MAR 10 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

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5 MG AND 25MG
ANDA #77-873

PATENT/EXCLUSIVITY AMENDMENT

STATEMENT PURSUANT TO 21 U.S.C. § 355(j)(2)(A)(viii)

U.S.PATENT NO.: 5,789,449

Dear Mr. Buehler:

Mylan Pharmaceuticals Inc. ("Mylan") previously submitted its patent certifications and exclusivity information for the above-referenced product. This current submission addresses Mylan's amendment of its previously submitted patent certification information for U.S. Patent No. 5,789,449. This amendment is being made consistent with 21 C.F.R. § 314.94(a)(12)(viii), which allows an applicant to amend its patent certification at any time before the effective date of the approval of the application.

Pursuant to Section 355(j)(2)(vii)(III) of the Federal Food, Drug and Cosmetic Act, Mylan originally submitted its patent certification information for U.S. Patent No. 5,789,449 (commonly referred to as a "Paragraph III Certification"). Mylan hereby amends its Paragraph III Certification to the following statement pursuant to 21 U.S.C. § 355(j)(2)(A)(viii) (commonly referred to as a "section viii statement").

> With respect to the listed drug referred to in its application for which information was filed under subsection (b) or (c) for this method of use patent, Mylan states that its labeling does not claim such methods of use.

As discussed in FDA's Final Rule for patent submission and patent listing requirements, Mylan's labeling "carves out" or "omits" from its proposed labeling for the referenced drug, the use claimed by U.S. Patent No. 5,789,449. FDA Final Rule, *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays of Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed* ("FDA Final Rule-2003"), 68 Fed. Reg. 36676, 36682 (June 18, 2003). According to FDA's Final Rule, "[FDA's] position has been that, for an ANDA applicant to file a section viii statement, it must

"carve out" from the proposed ANDA labeling, the labeling protected by the listed patent." Specifically, U.S. Patent No. 5,789,449 covers information in the approved labeling for "Premenstrual Dysphoric Disorder".

Interestingly, a review of the patent information published by FDA in the document entitled "Approved Drug Products With Therapeutic Equivalence Evaluations", 26th Edition as set forth in the "Electronic Orange Book" published at FDA's web site indicates that the patent use code assigned to U.S. Patent No. 5,789,449 is "U-286" which covers "Depression" and not "Premenstrual Dysphoric Disorder". In fact, according to the Electronic Orange Book, U. S. Patent No. 5,789,449 is also listed for the drug product, Zoloft® (sertraline hydrochloride), but with patent use code "U-460" which covers "Method of Treating Psychiatric Symptoms Associated with Premenstrual Disorders Using Sertraline". The assignment of an improper patent use code by the innovator or by FDA based on information provided by the innovator should not preclude an ANDA applicant from submitting an appropriate section viii statement. The statute requires an applicant to make a patent statement when a method of use patent "does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii); *see also* FDA Final Rule, *Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions*, 59 Fed. Reg. 50338 (October 3, 1994).

"Use codes are intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use. They are not meant to substitute for the applicant's review of the patent and the approved labeling." [1] FDA Final Rule-2003; 68 Fed. Reg. 36676, 36683. Thus, if an applicant has reviewed the patent and approved labeling, the assignment of a particular patent use code should not be determinative in the acceptance of a section viii statement. Accordingly, Mylan has reviewed the patent and approved labeling for the referenced drug and because Mylan has not sought to duplicate the labeling for which the innovator has submitted U.S. Patent No. 5,789,449, Mylan is submitting a section viii statement.

Mylan seeks approval to market its Paroxetine Hydrochloride Extended-release Tablets, 12.5mg and 25mg, upon completion of the regulatory review process; following the expiration of U.S. Patent Nos. 4,721,723 and 4,839,177 and their associated PED exclusivities; the expiration of exclusivity D-91; and prior to the expiration of U.S. Patent Nos. 5,422,123; 5,872,132; 5,900,423; 6,133,289; 6,121,291; 5,789,449 and 6,548,084; and exclusivity I-405.

Sincerely,

Vinde H. Suneja
Assistant Regulatory Counsel

1 Because Mylan is not disputing the accuracy or relevance of U.S. Patent No. 5,789,449, Mylan does not believe that the process outlined in 21 C.F.R. § 314.53(f) is necessary to follow.

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

ORIGINAL

April 13, 2006

TELEPHONE AMENDMENT
(CMC INFORMATION ENCLOSED)

ORIG AMENDMENT
N/AC

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: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
RESPONSE TO AGENCY CORRESPONDENCE DATED MARCH 10, 2006

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 March 10, 2006 (provided in Attachment Q). In response to the Agency's comments of March 10th, Mylan wishes to amend this application as follows:

A. Deficiencies:

FDA COMMENT 1:

[redacted] (b) (4)

MYLAN RESPONSE:

[redacted] (b) (4)

FDA COMMENT 2:

[redacted] (b) (4)

MYLAN RESPONSE:

[redacted] (b) (4)

Revised [redacted] (b) (4) are provided in Attachment B.

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APR 14 2006
OGD / CDER

Following this page, 3 pages withheld in full - (b)(4)

Department—Fax Number					
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Medical Unit	(304) 598-5445	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Research & Development	(304) 285-6419
				Sales & Marketing	(304) 598-3232

MYLAN RESPONSE: Mylan has been notified by [redacted] (b) (4) that an amendment that addresses all deficiencies noted by the Agency was submitted to DMF [redacted] (b) (4). A copy of [redacted] (b) (4) s letter to the Agency dated April 11th is provided in Attachment K for the convenience of the reviewer.

FDA COMMENT 3: Please remove all annotations from the ANDA that refer to [redacted] (b) (4), however, we will not consider it until a formal amendment is received.

MYLAN RESPONSE: As requested by the Agency, [redacted] (b) (4).

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

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosure

Desk Copy: Barbara Scott, Project Manager
Division of Chemistry II, Team 10

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

June 9, 2006

ORIG AMENDMENT
N-AC

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: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
RESPONSE TO AGENCY CORRESPONDENCE DATED JUNE 2, 2006

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 June 2, 2006 (provided in Attachment C). In response to the Agency's comments of June 2nd, Mylan wishes to amend this application as follows:

FDA COMMENT 1: Please include (b) (4)

MYLAN RESPONSE: As requested by the Agency and in accordance with (b) (4) are provided in Attachment B.

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

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

RECEIVED
JUN 12 2006
OGD / CDER

Enclosure
Desk Copy: Barbara Scott, Project Manager
Division of Chemistry II, Team 10

Department—Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
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Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

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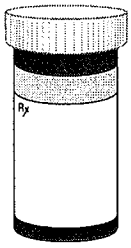
Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Mylan Pharmaceuticals Inc.
S. Wayne Talton

Fax: 304-285-6407 **Phone:**

From: Michelle Dillahunt
Fax: 301-827-7884 **Phone:** 301-827-5846

Number of Pages (including cover sheet): 3 **Date:** 6/28/06

Comments:

Attached are labeling deficiencies for ANDA 77-873 (Paroxetine Hydrochloride Extended-Release Tablets, 12.5 mg and 25 mg) for your drug application dated November 8, 2005 and March 10, 2006.

Please feel free to call me if you have any questions.

Sincerely,
Michelle Dillahunt

A6.1

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

ANDA Number: 77-873 Date of Submissions: November 8, 2005 and March 10, 2006

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Paroxetine Hydrochloride Extended-Release Tablets, 12.5 mg and 25 mg

---

Labeling Deficiencies:

1. CONTAINER - 30s, 100s, 500s

   a. Please ensure that you differentiate your product strengths by using boxing, contrasting colors, and/or some other means.

   b. Delete, "USP" from your statement on the side panel.

2. INSERT

   a. GENERAL

      (1) You have filed paragraph III certifications to the following patents, 4,721,723, 4,839,177 and 5,789,449, expiring December 13, 2005, June 29, 2007 and July 6, 2009, respectively. The patent '449' will expire after the expiration of the I-405 and D-91 exclusivities. However, you have carved out information relating to the two above exclusivities. Please revise and/or cllarify.

      (2) Change "paroxetine hydrochloride extended-release" to paroxetine hydrochloride extended-release tablets" throughout the insert.

   b. DESCRIPTION

      (1) Second and third paragraphs, delete reference to "USP".

      (2) Please indicate lactose type.

      (3) Label your product to indicate with which impurity tests the article complies as stated in the USP 29, monograph for paroxetine hydrochloride. Include this statement as the last paragraph in this section.

3. MEDICATION GUIDE

      (1) Please indicate how many patient medication guides will accompany each container size and how they will be presented.

      (2) Ensure that the medication guide that will be dispensed to the patients complies with 21 CFR 208.20.

Please revise your container labels and insert labeling, as instructed above. The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be

submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

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

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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

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

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

August 1, 2006

LABELING AMENDMENT
(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

N/AF
ORIG AMENDMENT

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
RESPONSE TO AGENCY CORRESPONDENCE DATED JUNE 28, 2006

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the labeling comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated June 28, 2006. A copy of the Agency's June 28th correspondence is provided on the enclosed CD-Rom as Letter.pdf.

CONTAINER:

FDA COMMENT 1.a: **Please ensure that you differentiate your product strengths by using boxing, contrasting colors, and/or some other means.**

MYLAN RESPONSE: Mylan's final printed container labels will contain contrasting colors to differentiate the two product strengths.

FDA COMMENT 1.b: **Delete, "USP" from your statement on the side panel.**

MYLAN RESPONSE: The statement of contents located on the left panel of Mylan's revised draft bottle label does not include reference to "USP".

INSERT:

FDA COMMENT 2.a.(1): GENERAL:

(1) You have filed paragraph iii certifications to the following patents, 4,721,723, 4.839,177 and 5,789,449, expiring December 13, 2005, June 29, 2007 and July 6, 2009, respectively. The patent '449' will expire after the expiration of the I-405 and D-91 exclusivities. However, you have carved out information relating to the two above exclusivities. Please revise and/or clarify.

RECEIVED
AUG 0 2 2006
OGD / CDER

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0468	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) 285-6482	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN RESPONSE: Mylan submitted a Patent and Labeling Amendment on March 10, 2006 in which we revised our Paragraph III certification to U.S. Patent No. 5,789,449 to a section viii statement. U.S. Patent no. 5,789,449 covers information in the approved labeling for treatment of symptoms associated with premenstrual disorders. In the March 10, 2006 Patent Amendment Mylan indicated that we would seek approval to market Paroxetine Hydrochloride Extended-release Tablets, 12.5 mg and 25 mg after the expiration of U.S. Patent Nos. 4,721,723, and 4.839,177 and the expiration of the D-91 exclusivity; however, we have carved out treatment of Premenstrual Dysphoric Disorder since it is associated with U.S. Patent 5,789,449, I-405 and D-91.

FDA COMMENT 2.a.(2): GENERAL:

(2) Change "paroxetine hydrochloride extended-release" to "paroxetine hydrochloride extended-release tablets" throughout the insert.

MYLAN RESPONSE: Mylan's revised draft outsert was revised throughout to change '(P)paroxetine hydrochloride extended-release" to "(P)paroxetine hydrochloride extended-release tablet(s)".

FDA COMMENT 2.b.(1): DESCRIPTION:

(1) Second and third paragraphs, delete references to "USP"

MYLAN RESPONSE: Mylan's revised draft outsert does not include references to "USP" in the second and third paragraphs of the 'DESCRIPTION' section.

FDA COMMENT 2.b.(2): DESCRIPTION

(2) Please indicate lactose type.

MYLAN RESPONSE: Mylan's list of inactive ingredients located in the 'DESCRIPTION' section of the outsert was revised to add 'monohydrate' to specify the lactose type.

FDA COMMENT 2.b.(3): DESCRIPTION

(3) Label your product to indicate with which impurity tests the article complies as stated in the USP 29, monograph for paroxetine hydrochloride. Include this statement as the last paragraph in this section.

MYLAN RESPONSE: Mylan has included the following statement as the last paragraph of the 'DESCRIPTION' section to indicate the impurity test to which our paroxetine hydrochloride complies within the current USP 29 monograph.

'Paroxetine hydrochloride complies with *USP Chromatographic Purity Test 1.*'

MEDICATION GUIDE:

FDA COMMENT 3.(1): **Please indicate how many patient medication guides will accompany each container size and how they will be presented.**

MYLAN REPONSE: Mylan's final printed outsert will contain one complete copy of the Medication Guide at the end of the prescribing information. Additional copies will be available for distribution to patients as (b) (4) Appropriate instructions have also been included for the pharmacist in the HOW SUPPLIED section of the outsert and on the center panel of Mylan's container labels to instruct the pharmacist to provide a Medication Guide to the patient.

FDA COMMENT 3.(2): **Ensure that the medication guide that will be dispensed to the patients complies with 21 CFR 208.20**

MYLAN RESPONSE: Mylan's Medication Guide complies with the Agency's class suicidality labeling language requirement for anti-depressants and to the general requirements for a medication guide defined 21§CFR 208.20.

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 Paroxetine hydrochloride Extended-release Tablets, 12.5 mg and 25 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, bookmarks are provided within the pdf versions.

Should a Structured Product Labeling (SPL) version of the Reference Listed Drug's labeling become available prior to receipt of ANDA approval, Mylan commits to submit a SPL version of our generic product labeling in an amendment to this application. If the SPL version becomes available post ANDA approval, Mylan commits to submit a SPL version of our generic product labeling in a Changes Being Effected Supplement, the next Annual report, or in a Post-Marketing Special Report as applicable.

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

Should you have any questions regarding this supplement, please contact the undersigned by telephone 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/dmy

Enclosure

Desk Copy Ms. Michelle Dillahunt, Labeling Reviewer
Division of Labeling and Program Support

A9.1

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

August 23, 2006

GENERAL CORRESPONDENCE

N/MC

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: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA #77-873
(GENERAL CORRESPONDENCE REGARDING U.S. PATENT NO. 5,789,449)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which is currently under review, and to our Patent and Labeling Amendment submitted on March 10, 2006 in which we changed our paragraph III certification to U.S. Patent No. 5,789,449 to a section viii statement. A copy of the cover letter and Patent Amendment from our March 10th correspondence is provided in Attachment A for your reference. As discussed in our March 10th Patent Amendment, the establishment and listing of patent use codes is not governed by any statutory provision, but rather is a practice created for convenience. "Use codes are intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use. They are not meant to substitute for the applicant's review of the patent and the approved labeling." FDA Final Rule-2003; 68 Fed. Reg. 36676, 36683.

Mylan has reviewed the patent and approved labeling for the referenced drug, and we believe that the listing of use code ("U-286") for U.S. Patent No. 5,789,449 in the "Patent and Exclusivity Data" section of the Electronic Orange Book is not appropriate as U-286 covers "Depression" which is an indication not claimed by the patent.

The patent is directed to a method of treating symptoms selected from the group consisting of anger, rejection, sensitivity, and lack of mental or physical energy. The patent does not cover a method for treating "depression", as indicated by use code U-286. In fact, the word "depression" is not found in any of the patent's eight claims.

Accordingly, Mylan submitted a section viii statement to U.S. Patent No. 5,789,449 and carved out of its labeling information for which U.S. Patent No. 5,789,449 was submitted– "Premenstrual Dysphoric Disorder". However, on August 14, 2006, we received a telephone call from Ian Margand, of your Office, regarding our March 10, 2006 Patent and Labeling Amendment. Dr. Margand indicated that if Mylan believes that there is an improper patent use code listing in the Electronic Orange Book, we must submit our request for correction in writing to the Drug Information Services Branch per 21 C.F.R. § 314.53(f); otherwise, the Agency will only be able to review our application in accordance with the current Electronic Orange Book listing.

We do not believe that the process outlined in 21 C.F.R. § 314.53(f) applies to Mylan in this situation and that FDA has the full authority to proceed without requiring the applicable new drug application/patent holder to correct the listing; however, as requested by the Agency, Mylan has initiated the process outlined in 21 C.F.R. § 314.53(f). A copy of our letter to the Drug Information Services Branch is provided in Attachment B.

We respectfully request that the Agency accept Mylan's section viii statement to U.S. Patent No. 5,789,449 regardless of the process initiated by Mylan or the application/patent holder's response to any FDA communication associated with Mylan's request.

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

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

Enclosures

Desk Copy: Ian Margand, Project Manager, Regulatory Support Branch, Office of Generic Drugs
Elizabeth Dickinson, Associate Chief Counsel for Drugs

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

October 25, 2006

Gary J. Buehler, R.Ph.
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
7519 Standish Place
Rockville, Maryland 20855

Re: **ANDA 77-873; Paroxetine Hydrochloride Extended-Release Tablets, 12.5 mg and 25 mg; U.S. Patent No. 5,789,449**

Dear Mr. Buehler:

We write to follow up on our two previous letters requesting FDA's acceptance of Mylan's amendment of its certification for the above-identified listed patent from a Paragraph III certification to a Section viii statement of non-applicable use. This amendment was submitted on March 10, 2006, to Mylan's ANDA for Paroxetine Hydrochloride Extended-Release Tablets, which is currently under review.

Mylan has submitted this Section viii statement to carve out the indication for premenstrual dysphoric disorder from the labeling of Paroxetine Extended-Release Tablets (Paxil CR), a drug primarily indicated for the treatment of depression. The carve-out is intended to avoid listed method of use U.S. Patent No. 5,789,449 ("the '449 patent", copy enclosed), which claims use of a serotonin re-uptake inhibitor to treat symptoms associated with premenstrual disorders. FDA's patent certification regulation (21 C.F.R. § 314.94(a)(12)(iii)), and the preamble to the agency's amended patent listing regulation (68 Fed. Reg. 36678, 36682, effective August 18, 2003), allow an ANDA applicant to submit a Section viii statement, carving out one of several labeled indications in order to avoid coverage by a listed method of use patent claiming the carved-out indication.

As noted in Mylan's amendment and related letters dated March 10 and August 23, 2006 (copies enclosed), the title and claims of the '449 patent recite that the patent covers use of an SSRI such as paroxetine to treat symptoms associated with premenstrual disorders. There is no mention of depression in any claims of the '449 patent. In fact, the prosecution history of the '449 patent includes arguments by the applicants that the symptoms of premenstrual disorders they claim are "different" from depression (pertinent pages enclosed).

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
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Corporate Services (304) 285-6482
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Information Systems (304) 285-6404
Label Control (800) 848-0463
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Quality Control (304) 598-5409
Regulatory Affairs (304) 285-6407
Research & Development (304) 285-6419
Sales & Marketing (304) 598-3232

Apparently, the only issue delaying FDA's acceptance of Mylan's Section viii statement is the "use code" for the '449 patent appearing in the Orange Book, "U-286 (Depression)." This code is manifestly inapplicable, based on the title and claims of the patent as described above.

The preamble to FDA's patent listing regulation is explicit. Despite a use code appearing in the Orange Book, the code is solely "intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use;" the code is "not meant to substitute for the applicant's review of the patent and the approved labeling." 68 Fed. Reg. 36676, 36683.* Following this directive, Mylan reviewed the '449 patent and determined that the patent only claims symptoms associated with premenstrual disorders. Accordingly, the premenstrual dysphoric disorder indication in the labeling qualifies for a carve-out, and the '449 patent is properly addressed by a Section viii statement.

In response to Mylan's amendment, we received a telephone call on August 14, 2006, from OGD's Dr. Ian Margand, in which he stated that Mylan has to submit a request for correction of the use code under the procedure in 21 C.F.R. § 314.53(f), which indicated to us that Mylan's Section viii statement will be only accepted if the request is granted and the code is changed. Such a request is neither an applicable nor a viable route. A use code is not "patent information" subject to listing or correction. The Hatch-Waxman Amendments define "patent information" as the patent number and expiration date of a patent claiming the pertinent drug or a method of its use. 21 U.S.C. § 355(b)(1). FDA's patent listing regulation defines "patent information" the same way, with the addition of the patent's issue date. 21 C.F.R. § 314.53(c)(2)(G). Use codes are nowhere mentioned in the statute or implementing regulations; they have been created by FDA for administrative purposes (see August 18, 2003 preamble noted above).

Nor does an ANDA applicant have to submit a request for correction as a condition precedent for acceptance of a Section viii statement. Purepac Pharmaceutical Co. v. Thompson, 238 F.Supp.2d 191, 199 (D.D.C. 2002), aff'd 354 F.3d 877 (D.C. Cir. 2004) (upholding a Section viii statement for a patent claiming an inapposite use, event though no § 314.53(f) request was filed).

Moreover, as you know, requests to correct patent information under the § 314.53(f) procedure are rarely if ever granted, since the NDA holder invariably refuses to affirm or deny existing Orange Book use codes on grounds (correctly or incorrectly) that it was not the source of the code, whereupon FDA makes no change to the incorrect information.

In response to Dr. Margand's call, on August 23, 2006, we reiterated our position that the FDA should accept our Section viii statement irrespective of the plainly incorrect use code listing. Solely to protect our interests, and without prejudice to our position that a request to correct is neither

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* See also 59 Fed. Reg. 50338, 50339 (preamble to FDA's original patent listing regulation): use codes are intended "to provide *some guidance* to applicants" regarding whether to file a patent certification or or a statement of non-applicable use. (emphasis supplied).

required nor appropriate, Mylan submitted, in the alternative, a request to correct under 21 C.F.R. § 314.53(f). Two months have passed since then without further word from FDA as to whether our Section viii statement has been accepted.

Acceptance of Mylan's Section viii statement is not only proper as a matter of law, but is also in the public interest (and within the mission of OGD to further availability of low-cost generic drugs). The '449 patent, with pediatric exclusivity, will not expire until July 6, 2009. Two other Orange Book patents, for which Mylan has filed paragraph III certifications, will expire by June 29, 2007, at which time our ANDA should be eligible for approval. (We were not sued on our paragraph IV certifications for the remaining listed patents). Thus, FDA's refusal to accept Mylan's Section viii statement and carve-out will delay introduction of a first generic alternative to Paxil CR® for more than two years.

Given the timing involved, it is critical that we understand FDA's position on this matter within the coming few weeks so that we can take whatever further steps may be necessary in order to secure our eligibility for approval in June 2007. Mylan's Paroxetine extended release ANDA product would be the first generic product approved as an equivalent to Paxil CR® and we trust the agency shares our desire for a prompt resolution and will make this matter a priority. We would be happy to meet with OGD or legal staff at their earliest convenience to address any questions they may have about this matter.

Sincerely yours,

Brian S. Roman

Brian S. Roman
Vice President and General Counsel

Enclosures

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

October 26, 2006

GENERAL CORRESPONDENCE
(TIME SENSITIVE REQUEST)

MC

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: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA #77-873
(GENERAL CORRESPONDENCE REGARDING U.S. PATENT NO. 5,789,449)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which is currently under review and to our Patent and Labeling Amendment submitted on March 10, 2006 in which we changed our paragraph III certification to U.S. Patent No. 5,789,449 to a section viii statement. Reference is also made to our General Correspondence submitted on August 23, 2006 regarding this matter. Copies of our March 10th and August 23rd correspondences are enclosed for your reference.

Mylan maintains our position that our section viii statement to U.S. Patent No. 5,789,449 is appropriate and should be found acceptable by the Agency. Provided in Attachment A is a letter of explanation from our Legal department and additional supportive documentation.

As concluded from the attached letter, the resolution of this matter is very time sensitive to Mylan and is considered a significant step in determining our path forward regarding this ANDA. We would, therefore, welcome the opportunity to have a telephone conference or face-to-face meeting with the Agency as soon as possible to further explain and discuss the rationale pertaining to our position on this issue.

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

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

Enclosures

Desk Copy: Martin Shimer, Branch Chief, Regulatory Support, Office of Generic Drugs

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) 285-6482	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Telephone Fax

ANDA 77-873

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301 827 7885

TO: Mylan Pharmaceuticals Inc.

TEL: 304-599-2595

ATTN: S. Wayne Talton

FAX: 304-285-6407

FROM: Michelle Dillahunt

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Paroxetine Hydrochloride Extended-Release Tablets, 12.5 mg and 25 mg.

Pages (including cover): 5

SPECIAL INSTRUCTIONS:

Labeling Comments

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

ANDA Number: 77-873 Date of Submission: August 1, 2006

Applicant's Name: Mylan Pharmaceuticals Inc.

Established Name: Paroxetine Hydrochloride Extended-Release Tablets, 12.5 mg and 25 mg

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Labeling Deficiencies:

1. CONTAINER - 30s, 100s, 500s

   a. Side panel, revise as follows; "Each extended-release tablet contains paroxetine hydrochloride equivalent to xx mg of paroxetine."

   b. Delete the statement, "(b) (4)"

2. INSERT/MEDICATION GUIDE

   a. Clinical Pharmacology, Clinical Trials, Social Anxiety Disorder, delete last paragraph, "(b) (4) (b) (4)…"

   b. WARNINGS

   (i) Add the following to appear after the subsection; Potential for Interaction With Monoamine Oxidase Inhibitors;

   Serotonin Syndrome

   The development of a potentially life-threatening serotonin syndrome may occur with use of paroxetine hydrochloride extended-release tablets, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

   The concomitant use of paroxetine hydrochloride extended–release tablets with MAOIs intended to treat depression is contraindicated (see CONTRAINDICATIONS and WARNINGS—Potential for Interaction With Monoamine Oxidase Inhibitors). If concomitant use of paroxetine hydrochloride extended-release tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see PRECAUTIONS—Drug Interactions).

   The concomitant use of paroxetine hydrochloride extended-release tablets with serotonin precursors (such as tryptophan) is not recommended (see PRECAUTIONS—Drug Interactions).

   Potential Interaction With Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes–type arrhythmias, and sudden death. This effect appears to be dose related.

   An in vivo study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

   (ii) Nonteratogenic Effects, add the following as the second, third and fourth paragraphs;

   Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants

exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.
There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.
When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

c. PRECAUTIONS

(i). Delete (b) (4) subsection.

(ii). Information for Patients, add the following as the first paragraph;
"Paroxetine hydrochloride extended-release tablets should not be chewed or crushed, and should be swallowed whole."

(iii). Clinical Worsening and Suicide Risk, delete last paragraph, " (b) (4) (b) (4) .."

(iv) Serotonergic Drugs, revise subsection as follows; "Based on the mechanism of action of paroxetine hydrochloride and the potential for serotonin syndrome, caution is advised when paroxetine hydrochloride extended-release tablets is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see WARNINGS—Serotonin Syndrome). The concomitant use of paroxtine extended release tablets with other SSRIs, SNRIs or tryptophan is not recommended (see PRECAUTIONS—Drug Interactions, Tryptophan).

(v) Triptans, revise subsection as follows; " There have been rare postmarketing reports of serotonin syndrome with the use of an SSRI and a triptan. If concomitant use of paroxetine hydrochloride extended-release tablets with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS—Serotonin Syndrome)"

d. ADVERSE REACTIONS, Other Events Observed During the Clinical Development of Paroxetine, second paragraph, second sentence, revise as follows; "…panic disorder and social anxiety disorder, multiple doses of paroxtetine hydrochloride extended-release tablets…"

e. MEDICATION GUIDE

Please provide a sample sheet electronically in final printed format of your (b) (4) medication guides.

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

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

-http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling and your last submission with all differences annotated and explained.

{See appended electronic signature page}

_____

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

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

/s/

Lillie Golson
2/5/2007 06:51:37 PM
Lillie Golson for Wm. Peter Rickman

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

February 16, 2007

LABELING AMENDMENT
(ELECTRONIC LABELING INFORMATION ENCLOSED)

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

ORIG AMENDMENT
N/AF

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
(RESPONSE TO THE AGENCY CORRESPONDENCE DATED FEBRUARY 5, 2007)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the labeling comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated February 5, 2007. A copy of the Agency's February 5th correspondence is provided on the enclosed CD-Rom as Letter.pdf for your reference.

In response to the Agency's February 5th correspondence, Mylan wishes to amend this application with Final Printed labeling which has been revised as follows:

1. CONTAINER: 30s, 100s and 500s

FDA COMMENT 1.a.: **Side panel, revise as follows; "Each extended-release tablet contains paroxetine hydrochloride equivalent to xx mg of paroxetine.".**

MYLAN RESPONSE: As requested by the Agency, the final printed container labels have been revised accordingly.

FDA COMMENT 1.b.: **Delete the statement, "** [redacted] (b) (4) (b) (4)

MYLAN RESPONSE: As requested by the Agency, the final printed container labels have been revised to delete this statement.

RECEIVED
FEB 2 0 2007
OGD / CDER

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
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		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

2. INSERT/MEDICATION GUIDE:

FDA COMMENT 2.a: **Clinical Pharmacology, Clinical Trials, Social Anxiety Disorder, delete last paragraph, "(b) (4)".**

MYLAN RESPONSE: As requested by the Agency, Mylan's final printed outsert has been revised to delete the referenced paragraph.

FDA COMMENT 2.b.i.: **WARNINGS: Add the following to appear after the subsection; Potential for Interaction with Monoamine Oxidase Inhibitors;**

Seritonin Syndrome: The development of a potentially life threatening serotonin syndrome may occur with the use of paroxetine hydrochloride extended-release tablets, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of paroxetine hydrochloride extended-release tablets with MAOIs intended to treat depression is contraindicated (see CONTRAINDICATIONS and WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors). If concomitant use of paroxetine hydrochloride extended-release tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see PRECAUTIONS: Drug Interactions).

The concomitant use of paroxetine hydrochloride extended-release tablets with serotonin precursors (such as tryptophan) is not recommended (see PRECAUTIONS: Drug Interactions).

Potential Interaction with Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as Torsade de pointes–type arrhythmias, and sudden death. This effect appears to be dose related.

An *in vivo* study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

MYLAN RESPONSE: As requested by the Agency, Mylan's final printed outsert has been revised to add the referenced subsection regarding the potential for interaction with Monoamine Oxidase Inhibitors.

FDA COMMENT 2.b.ii.: **WARNINGS: Nonteratogenic Effects, add the following as the second, third and fourth paragraphs;**

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately 6-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no collaborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

There have also been post-marketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

MYLAN RESPONSE: As requested by the Agency, Mylan's final printed outsert has been revised to add three new paragraphs regarding nonteratogenic effects.

FDA COMMENT 2.c.i.: **PRECAUTIONS: Delete** (b) (4) **subsection.**

MYLAN RESPONSE: As requested by the Agency, Mylan's final printed outsert has been revised to delete the referenced subsection.

FDA COMMENT 2.c.ii.: **PRECAUTIONS: Information for Patients, add the following as the first paragraph:**

"Paroxetine hydrochloride extended-release tablets should not be chewed or crushed, and should be swallowed whole."

MYLAN RESPONSE: As requested by the Agency, Mylan's final printed outsert has been revised to add the new precaution statement.

FDA COMMENT 2.c.iii.: **PRECAUTIONS: Clinical Worsening and Suicide Risk, delete last paragraph, "** (b) (4) (b) (4)**,**

MYLAN RESPONSE: As requested by the Agency, Mylan's final printed outsert has been revised to delete the referenced paragraph.

FDA COMMENT 2.c.iv.: **PRECAUTIONS: Serotonergic Drugs, revise subsection as follows;**

Based on the mechanism of action of paroxetine hydrochloride and the potential for serotonin syndrome, caution is advised when paroxetine hydrochloride extended-release tablets are coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible nonselective MAOI) lithium, tramadol, or St. John's Wort (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors: *Serotonin Syndrome*). The concomitant use of paroxetine extended-relaease tablets with other SSRI's, SNRIs or tryptophan is not recommended (see PRECAUTIONS: Drug Ineractions: *Trytophan*).

MYLAN RESPONSE: As requested by the Agency, Mylan's has revised the precaution subsection regarding serotonergic drugs.

FDA COMMENT 2.c.v.: **PRECAUTIONS: Triptans, revise subsection as follows;**

"There have been rare post-marketing reports of serotonin syndrome with the use of an SSRI and a triptan. If concomitant use of paroxetine hydrochloride extended-release tablets with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors: *Serotonin Syndrome*). "

MYLAN RESPONSE: As requested by the Agency, Mylan's has revised the precaution subsection regarding triptans.

FDA COMMENT 2.d.: **ADVERSE REACTIONS, Other Events Observed During the Clinical Development of Paroxetine, second paragraph, second sentence, revise as follows; "...panic disorder and social anxiety disorder, multiple doses of paroxetine hydrochloride extended-release tablets..."**

MYLAN RESPONSE: As requested by the Agency, Mylan's has revised our labeling accordingly.

FDA COMMENT 2.e: **MEDICATION GUIDE; Please provide a sample sheet electronically in final printed format of your (b) (4) medication guides.**

MYLAN RESPONSE: Please note that Mylan previously planned to distribute Medication Guides as (b) (4) However, we have recently re-entered in a contract agreement (b) (4) (b) (4) that uses (b) (4) as a vendor to create, manufacture and distribute the standard Medication Guides in tear-off pads to pharmacists and physicians. An electronic copy of this Medication Guide is provideded on the enclosed CD-Rom as Proposed MG.pdf.

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

Mylan commits to submit a Structured Product Labeling (SPL) version of our generic product labeling post approval in the first Annual Report or upon Agency request.

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

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

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/rr
Enclosure

Desk Copy: Michelle Dillahunt, Labeling Reviewer
Division of Labeling and Program Support

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

March 16, 2007

GRATUITOUS CHEMISTRY AMENDMENT
(CHEMISTRY INFORMATION ENCLOSED)

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

ORIG AMENDMENT
N-AA

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
(To Provide Revisions to the Master Batch Records)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Mylan wishes to revise the Master Batch Records to provide for the use of a new ink for imprinting tablets due to the discontinuation of the registered ink from our current supplier. In addition, we wish to [redacted] (b) (4) the replacement ink. As our ANDA is eligible to receive approval in June 2007, this change in our Master Batch Records is required to enable Mylan to produce launch quantities of this product.

The revisions to the Batch Records which are provided in Attachments A and B include:

- [redacted] (b) (4)

[redacted] (b) (4)

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MAR 19 2007
OGD / CDER

Department—Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

G:\Project\ANDA\PAROXETINE HCl ER TABLETS\GRATUITOUS AMENDMENT.doc

- [redacted] (b) (4) from Mylan and the supplier are provided in Attachment D.

The [redacted] (b) (4) statement for Paroxetine Hydrochloride Extended-release Tablets is provided in Attachment E.

Mylan plans to implement the use of the revised batch records upon approval of this application. Mylan commits to place the first lots of Paroxetine Hydrochloride Extended-release Tablets, 12.5mg and 25mg, [redacted] (b) (4), in our long-term stability program. Stability data for these lots will be included in future annual reports.

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

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/as

Enclosure

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

April 24, 2007

TELEPHONE AMENDMENT
(CHEMISTRY INFORMATION ENCLOSED)

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

ORIG AMENDMENT
N-000-AC

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5 MG AND 25 MG
ANDA 77-873
(Response to Agency Telephone Call Received April 12, 2007)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Reference is also made to a telephone call received on April 12, 2007 from Mr. Tom Hinchliffe, of your Office, in which he relayed additional chemistry comments concerning this application. In response to the Agency's comments of April 12th, Mylan wishes to amend this application as follows:

FDA COMMENT 1: (b) (4) in accordance with the current USP monograph.

MYLAN RESPONSE: As requested by the Agency, our (b) (4) are provided in Attachments A and B, respectively.

FDA COMMENT 2: With respect to the (b) (4) please explain why (b) (4).

MYLAN RESPONSE: (b) (4)

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APR 25 2007
OGD / CDER

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources		Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
					(304) 598-3232

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

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

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosure

ORIGINAL

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

May 3, 2007

TELEPHONE AMENDMENT
(CHEMISTRY INFORMATION ENCLOSED)

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

ORIG AMENDMENT
N-000-AC

RECEIVED
MAY 4 2007
OGD

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5 MG AND 25 MG
ANDA 77-873
(Response to Agency Telephone Call Received April 30, 2007)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. Reference is also made to a telephone call received on April 30, 2007 from Dr. Naiqi Ya, of your Office, in which he relayed an additional chemistry comment concerning this application. In response to Dr. Ya's telephone call, Mylan wishes to amend this application as follows:

FDA COMMENT 1: With respect to your (b) (4)

MYLAN RESPONSE: As requested by the Agency, Mylan has revised the (b) (4) is provided in Attachment A.

(b) (4)

As discussed with Dr. Ya, Mylan has recently (b) (4)

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 285-6482
Human Resources
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Assurance (304) 598-5407
Quality Control (304) 598-5409
Regulatory Affairs (304) 285-6407
Research & Development (304) 285-6419
(304) 598-3232

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

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

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosure

Desk Copy: Dr. Naiqi Ya, Team Leader
Division of Chemistry II, Team 10

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

May 14, 2007

LABELING AMENDMENT
(ELECTRONIC LABELING INFORMATION ENCLOSED)

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

ORIG AMENDMENT
N/A

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
(Labeling Revisions in Response to the Agency's Correspondence Dated May 3, 2007)

Dear Mr. Buehler:

Mylan wishes to amend the above referenced Abbreviated New Drug Application (ANDA) to provide final printed labeling (Outsert code PRXT:R2mc; Revised May 2007 with Medication Guide; Revised 5/2007) that has been revised to incorporate class labeling revisions contained in the Agency's email correspondence dated May 3, 2007. A copy of the Agency's correspondence dated May 3rd is provided herein as Letter.pdf for the reviewer's reference. Refer to the Comp.pdf file for a side by side comparison of all labeling revisions. In addition to including a complete copy of the revised Medication Guide at the end of the prescribing information, please note that Mylan is also (b) (4) (b) (4) as a vendor to create, manufacture and distribute the standard Medication Guides in tear-off pads to pharmacists and physicians. Please note that the (b) (4) (D) (4)

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 Paroxetine Hydrochloride Extened-release Tablets as described in the electronic Table of Contents. As a review aid, Mylan has also included Microsoft Word versions of our proposed labeling components.

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

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

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

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MAY 15 2007
OGD

Desk Copy: Michelle Dillahunt, Labeling Reviewer
Division of Labeling and Program Support

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

May 18, 2007

TELEPHONE AMENDMENT
(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-AF

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
(Response to the Agency's Telephone Call Received on May 17, 2007)

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 May 14, 2007. Reference is also made to a telephone call received on May 17, 2007 from Michelle Dillahunt, of your Office, in which she requested that we provide a copy of our current service agreement with (b) (4) who Mylan has contracted to produce and distribute the required Medication Guides for this product.

As requested, Attachment A contains a copy of the current service agreement with (b) (4). Please note that this agreement is currently undergoing a revision to adopt the new class labeling contained in the Agency's email correspondence dated May 3, 2007. The contract will be renewed and extended accordingly. A copy of the revised Medication Guide was previously included in our May 14, 2007 labeling amendment.

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

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Desk Copy: Michelle Dillahunt, Labeling Reviewer
Division of Labeling and Program Support

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Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Logel Center	(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) 285-6482	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-873 Applicant Mylan Pharmaceuticals Inc.
Drug Paroxetine Hydrochloride Extended-release Tablets Strength(s) 12.5 mg and 25 mg

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

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. Martin Shimer Chief, Reg. Support Branch	Date 15 March 2007 Initials MHS	Date _____ Initials _____

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = _____ NDA# _____
Patent/Exclusivity Certification: Yes ☒ No ☐
Date Checked _____
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒
Has case been settled: Yes ☐ No ☐
Date settled:
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
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: TA
Comments: Firm provided PIV certifications to the '123, '132, '423, '289, '291 and '405 patents. Mylan provided notice and was not sued within 45 days. Mylan has a PIII cert to the '723 which will expire on 6/29/07 with ped exclusivity. Mylan provided a MOU statement to the '449 patent which OGD was not initially inclined to accepting as the use code that appeared in the OB and the time Mylan originally submitted(March 06) their MOU was not conducive to permitting a carve-out. Mylan then availed themselves of the 314.53(f) process and GSK eventually requested a change in the use code that was associated with the '449 patent. This code u-788 which is now defined as METHOD OF TREATING PSYCHIATRIC SYMPTOMS ASSOCIATED WITH PREMENSTRUAL DISORDERS USING PAROXETINE may be omitted from the labeling. This ANDA currently eligible for TA due to PIII on '723.

2. Project Manager, Thomas Hinchliffe Team 10 Review Support Branch	Date _____ Initials _____	Date _____ Initials _____

Original Rec'd date September 9, 2005
Date Acceptable for Filing September 9, 2005
Patent Certification (type) IV
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver Yes ☐
EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 1/30/2007
Date of Office Bio Review 7/21/2006
Date of Labeling Approv. Sum 3/8/07
Labeling Acceptable Email Rec'd Yes ☐ No ☐
Labeling Acceptable Email filed Yes ☐ No ☐
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☒
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement

Reviewer:	Labeling Team Leader:
Date 3/9/07	Date 3/9/07
Name/Initials MD	Name/Initials LDG

Comments:
Per email 3/9/07

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 3/16/07

OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials DTR
Comments: Changes to TA ltr saved to V drive.

5. Div. Dir./Deputy Dir. Date 5/17/07
Chemistry Div. II Initials FF

Comments: (b) (4) (b) (4) revised (4/24 and 5/3 amendments). CMC ok.

6. Frank Holcombe **First Generics Only** Date 5/25/07
Assoc. Dir. For Chemistry Initials RR
Comments: (First generic drug review)
CMC ok- For Frank- Radhika Rajagopalan

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

8. Peter Rickman Date 5/29/07
Director, DLPS Initials WPR
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes ☐ No ☒; Petition: Yes☐ No☒
Comments: Firm provided PIVs to the '123, '132, '423, '289, '291 and '084 patents. Mylan provided notice and was not sued within the 45 day period. Mylan has a PIII to the '723 patent which expires on 6/29/2007 w/ ped exclusivity. Mylan provided an MOU statement to the '449 patent. W/H exclusivity D-91 and I-405 carved out of labeling; Labeling acceptable 3/8/2007; Bio acceptable 7/21/2006 per AP Summary (fasting and Fed studies 25 mg tablet); EER acceptable 1/30/2007; Okay for TA ONLY

OR

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

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

10. Project Manager, Thomas Hinchliffe Team 10 Date 5/30/07
Review Support Branch Initials TOH
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
5/30 Time notified of approval by phone 5/30 Time approval letter faxed

FDA Notification:
5/30 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
5/30/07 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Shimer, Martin Paroxetine

From: Shimer, Martin
Sent: Monday, January 08, 2007 1:34 PM
To: Hinchliffe, Thomas; Dillahunt, Michelle
Cc: West, Robert L; Ames, Timothy W
Subject: RE: 77-873 - Mylan - Paroxetine

Tom,

From what I recall Mylan disputes the accuracy of a use code as defined in the OB. I had advised Mylan to avail themselves of the 314.53(f) process to address any perceived inaccuracies. Unfortunately I don't believe that the innovator responded to the request from the OB. This leaves us in a situation where Mylan wishes to carve out information from their labeling which they believe more accurately depicts the claims of the patent but does not comport with the use code as defined in the OB. I had left some jackets with Dave Read a week or so ago asking him what he thought of Mylan's proposal. I'll follow up with him and let you know.

Marty

From: Hinchliffe, Thomas
Sent: Monday, January 08, 2007 1:09 PM
To: Shimer, Martin; Dillahunt, Michelle
Cc: West, Robert L; Ames, Timothy W
Subject: 77-873 - Mylan - Paroxetine

Hey Marty,

ANDA 77-873 has been on the AP matrix since June, only pending Labeling, and I understand there is some Regulatory issue (Use code and '449 patent I think???) holding up the continuation for review of labeling. Michelle told me about it back in August and I have still heard nothing about this being resolved. What is the status of this issue?

Let me know thanks,
Tom

Thomas Hinchliffe, PharmD
LCDR, U.S. Public Health Service
Project Manager
Office of Generic Drugs
Food and Drug Administration
HFD-617, Rm E230, MPN2
301-827-5771

Shimer, Martin

From: Holovac, Mary Ann
Sent: Thursday, January 11, 2007 9:47 AM
To: Shimer, Martin; Stewart, Kendra
Subject: RE: 314.53(f) submission from Mylan

No response. Ltr dated 8/23/6 from Mylan was mailed 9/11/06. I think someone else from your group asked about this fairly recently.

From: Shimer, Martin
Sent: Thursday, January 11, 2007 9:36 AM
To: Holovac, Mary Ann; Stewart, Kendra
Subject: 314.53(f) submission from Mylan

Mary Ann and Kendra,

Did you ever here anything back from the NDA sponsor regarding a 314.53(f) challenges that Mylan sent to the Agency in August of 06? More specifically the request dealt with the use code associated with the '449 patent covering NDA 20-936. Mylan believes the code is inaccurate.

Thanks,

Marty

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

/s/

Thomas Hinchliffe
5/30/2007 09:28:21 AM

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

June 11, 2007

MINOR AMENDMENT - (FINAL APPROVAL REQUESTED)

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-000-AM

RE: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
(Request for Final ANDA Approval)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which received Tentative Approval on May 30, 2007. A copy of the May 30, 2007 Tentative Approval letter has been provided in Attachment A for your reference. In accordance with the conditions outlined in the May 30, 2007 tentative approval letter and pursuant to 21 CFR 314.107(b)(3)(i)(A), Mylan hereby requests that final approval of ANDA 77-873 be granted upon expiration of the pediatric exclusivity associated with U.S. Patent No. 4,721,723 (i.e., June 29, 2007).

As required by the Tentative Approval Letter, this amendment provides notification that no changes have been made to chemistry, manufacturing and controls, or to any other conditions under which this application was tentatively approved.

With respect to labeling, final printed labeling for Mylan's outsert and Medication Guide remain the same as those previously submitted in our labeling amendment dated May 14, 2007. Final printed container labeling remains the same as those previously submitted in our labeling amendment dated February 16, 2007.

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

S. Wayne Talton
Vice President
Regulatory Affairs

RECEIVED
JUN 12 2007
OGD

SWT/dn
Enclosures

Desk Copy: Thomas Hinchliff, Project Manager
Division of Chemistry II, Team 10

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Locker Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	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

June 20, 2007

PATENT AMENDMENT

N.000.
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: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which was granted Tentative Approval on May 30, 2007.

This current patent amendment addresses a new patent filing by the holder of the Reference Listed Drug, Paxil CR® (GlaxoSmithKline), which has been listed in the FDA's "Orange Book" subsequent to our previous submission(s). Enclosed along with the 356h form, is a Patent Amendment letter from our Legal Department which provides specifics regarding the recently listed patent. The enclosed information is in addition to what has been previously submitted and comprises an update to reflect the newly filed patent 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

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

June 27, 2007

PATENT AMENDMENT

N.000,
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: PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 12.5MG AND 25MG
ANDA 77-873
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which is currently under review. Reference is also made to the patent certification information submitted in the original ANDA on September 9, 2005 and to our patent amendment submitted on June 20, 2007. Our June 20th patent amendment provided a paragraph IV certification to U.S. Patent No. 7,229,640 which was listed in the FDA's "Orange Book" subsequent to our original submission.

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 June 20, 2007 for Paroxetine Hydrochloride Extended-release Tablets, 12.5mg and 25mg. 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 Federal Express, Return Receipt evidences receipt on June 21 and 22, 2007. 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

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-873 Applicant Mylan Pharmaceuticals Inc.
Drug Paroxetine Hydrochloride Extended-release Tablets Strength(s) 12.5 mg and 25 mg

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

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. Martin Shimer Chief, Reg. Support Branch	Date_____ Initials_____	Date6/29/07 Initialsrlw/for

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD =_____ NDA#20-936
Date Checked Previously granted
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒
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:
Comments: Since TA issued on 5/30/2007 the holder of the NDA submitted the '640 patent for listing in the OB. Mylan addressed this patent with a PIV certification on June 21, 2007. As these drug products are governed under post-MMA requirements for notice and 30 month stays, there will be no opportunity for a 30 month stay as this patent was submitted after Mylan's ANDA was acknowledged. There also isn't an opportunity for the 45 day notice clock as the 45 day clock is only related to invocation of the 30 month stay. I spoke with Mylan(Wayne Talton) on 6/27/2007 and asked that he provide the FedEx tracking receipts to prove that notice was given with respect to this patent. Once OGD has obtained these FedEx receipts we will be able to Fully Approve this ANDA effective 6/29/2007. Applicant is eligible for 180 day exclusivity for these two drug products.

2. Project Manager, Thomas Hinchliffe Team 10 Review Support Branch	Date Initials_____	Date6/28/07 InitialsTOH

Original Rec'd date September 9, 2005
Date Acceptable for Filing September 9, 2005
Patent Certification (type) IV
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☒ Date 5/30/07
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments: PREVIOUSLY TA'd on 5/30/07 TA documentation im DFS….

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 1/30/2007
Date of Office Bio Review 7/21/2006
Date of Labeling Approv. Sum 3/8/07
Labeling Acceptable Email Rec'd Yes ☐ No ☐
Labeling Acceptable Email filed Yes ☐ No ☐
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☒

3. Labeling Endorsement

Reviewer:	Labeling Team Leader:
Date6/19/07	Date6/19/07
Name/Initialsldg	Name/Initialsldg

Comments:

From: Golson, Lillie D
Sent: Wednesday, June 20, 2007 12:53 PM

To: Hinchliffe, Thomas; Golson, Lillie D
Subject: FW: 77-873 Full Ap endorsement needed

Hi Tom,

From a labeling standpoint, this application is acceptable for approval. Please endorse the AP routing form on behalf of Michelle and me.

Thanks

Lillie

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 6/28/07
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials DTR
Comments:Changes to AP ltr saved to V drive.

5. Div. Dir./Deputy Dir. Date 6/28/07
Chemistry Div. II Initials RCA

Comments:CMC OK, see attached spreadsheet. NO CMC changes since TA 5/30/07

6. Frank Holcombe **First Generics Only** Date 6/29/07
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
This was completed on 5/25/07 at the time of the tentative approval.

7. Vacant Date _____
Deputy Dir., DLPS Initials _____
RLD = Paxil CR Extended-release Tablets, 12.5 mg (base) and 25 mg (base)
GlaxoSmithKline NDA 20-936 (001, 002)

8. Peter Rickman Date 6/29/07
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐
Comments:This ANDa was granted tentative approval on May 30, 2007. Final approval at that time was blocked by the '723 patent that is scheduled to expire on June 29, 2007. Refer to the administrative sign-off form created at that time.

On June 11, 2007, Mylan submitted a minor amendment to request final approval for this ANDA effective upon the expiration of the '723 patent on June 29, 2007. Mylan stated that no CMC changes had been made to the ANDA since receipt of the tentative aproval. On June 20, 2007, Mylan addressed the newly listed '640 patent. On June 27, 2007, Mylan submitted confirmation that the owner of the '640 patent and the NDA holder had received notice of Mylan's paragraph IV certification to the patent.

FPL remains acceptable for approval (as endorsed 6/20/07 by L.Golson above).

CMC remains acceptable for final approval 6/19/07.

OR

8. Robert L. West Date 6/29/07
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments:Acceptable EES dated 1/30/07 (Verified 6/29/07). No "OAI" Alerts noted.

Refer to the text found in the tentative approval letter dated May 30, 2007, as well as the summary provided above by Martin Shimer for the regulatory basis for approval of this ANDA. As noted by M.Shimer, Mylan is eligible for 180-day generic drug ecxlusivity for Paroxetine Hydrochloride Extended-release Tablets

12.5 mg and 25 mg.

With the expiration of the '723 patent, this ANDA is recommended for final approval.

9. Gary Buehler — Date 6/29/07
Director, OGD — Initials rlw/for
Comments:
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Thomas Hinchliffe Team 10 — Date6/29/07
Review Support Branch — Initials TOH
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
6/29/07Time notified of approval by phone 6/29/07Time approval letter faxed

FDA Notification:
6/29/07Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
6/29/07Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 020936 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020936	002	4721723	DEC 29,2006			
020936	002	4721723*PED	JUN 29,2007			
020936	002	4839177*PED	DEC 13,2006			
020936	002	5422123	JUN 06,2012			
020936	002	5422123*PED	DEC 06,2012			
020936	002	5789449	JAN 06,2009			U-788
020936	002	5789449*PED	JUL 06,2009			
020936	002	5872132	MAY 19,2015			
020936	002	5872132*PED	NOV 19,2015			
020936	002	5900423	MAY 19,2015			
020936	002	5900423*PED	NOV 19,2015			
020936	002	6121291	MAR 17,2017			U-286
020936	002	6121291*PED	SEP 17,2017			U-286
020936	002	6133289	MAY 19,2015			U-286
020936	002	6133289*PED	NOV 19,2015			U-286
020936	002	6548084	JUL 19,2016			
020936	002	6548084*PED	JAN 19,2017			
020936	002	7229640	JUL 19,2016		Y	U-816

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020936	002	D-91	JAN 27,2007
020936	002	I-405	AUG 28,2006

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).

2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.

3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply

4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

5. U.S. Patent Nos. RE 36481 and RE 36520 were relisted for Zocor (NDA 19-766) pursuant to the decision and related order in Ranbaxy Labs. v.Leavitt, No. 05-1838 (D.D.C. April 30, 2006). The '481 and '520 patents remained listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act were triggered and run. For additional information on this matter, please refer to Docket Nos. 2005P-0008 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.

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

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through May, 2007
Patent and Generic Drug Product Data Last Updated: June 28, 2007

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

/s/

Thomas Hinchliffe
6/29/2007 09:49:49 AM