

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-395

Name: Paroxetine Hydrochloride Oral Suspension,
10 mg (base)/5mL

Sponsor: Apotex Corp.

Approval Date: December 4, 2006

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-395

CONTENTS

Reviews / Information Included in this Review

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-395

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-395

DEC 4 2006

Apotex Corp.
Attention: Tammy McIntire
U.S. Agent for: Apotex Inc.
2400 N. Commerce Parkway, Suite 400
Weston, FL 33326

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Paroxetine Hydrochloride Oral Suspension, 10 mg (base)/5mL. This ANDA was received acceptable for filing on February 10, 2005.

Reference is also made to your amendments dated August 16 and August 30, 2005; June 14, July 7, August 4, and September 29, 2006.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is **approved**. The Division of Bioequivalence has determined your Paroxetine Hydrochloride Oral Suspension, 10 mg (base)/5mL to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Paxil Oral Suspension, 10 mg (base)/5mL of GlaxoSmithKline (GSK). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The reference listed drug (RLD) upon which you have based your ANDA, GSK's Paxil Oral Suspension 10 mg (base)/5mL, is subject to periods of patent protection. The following patents and expiration dates (with pediatric exclusivity added) are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
4,721,723 (the '723 patent)	June 29, 2007
5,789,449 (the '449 patent)	July 6, 2009
5,811,436 (the '436 patent)	March 22, 2016
5,872,132 (the '132 patent)	November 19, 2015
6,121,291 (the '291 patent)	September 17, 2017
6,133,289 (the '289 patent)	November 19, 2015
5,900,423 (the '423 patent)	November 19, 2015

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent listed above is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Paroxetine Hydrochloride Oral Suspension 10 mg (base)/5mL, 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 Apotex Inc. (Apotex) for infringement of one or more of the patents that were the subjects of the paragraph IV certifications. You have notified the agency that Apotex complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Apotex 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 180-day generic drug exclusivity, we note that Apotex was the first ANDA applicant using GSK's Paxil Oral Suspension 10 mg (base)/5mL as the RLD to submit a substantially complete ANDA with a paragraph IV certification to the patents listed above. Therefore, with this approval Apotex Corp. is eligible for 180-days of market exclusivity for Paroxetine Hydrochloride Oral Suspension, 10 mg (base)/5mL. 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(s) directly to:

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

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

Sincerely yours,



Gary Buehler 12/9/06
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-395
Division File
Field Copy
HFD-610/R. West
HFD-013
HFD-610/Orange Book Staff

WPM/ma - 12/9/2006

Approved Electronic Labeling Located at:

Container Labels: 250 mL

Satisfactory in FPL as of the May 3, 2006 submission.

file:///\\Cdsesub1\77395\N_000\2006-05-03\Labeling\paro_imsu_10mg5ml_lbl_225576.pdf

Carton:

file:///\\Cdsesub1\77395\N_000\2006-05-03\Labeling\paro_suor_10mg5ml_ctn_223538.pdf

Professional Package Insert Labeling:

Satisfactory in FPL as of the July 7, 2006 submission.

file:///\\Cdsesub1\77395\N_000\2006-07-07\Labeling\paro_imsu_10mg_5ml_ins_223529.pdf.pdf

Endorsements:

HFD-647/N.Samaan/10.05.06

N.Samaan 10-5-06

HFD-647/U.Venkataram/10.05.06

U.V. Venkataram

HFD-617/C.Wiseman/10.05.06

C. Wiseman 10/5/06

10/5/06

HFD-617/M.Dillahunt/See Attachment

HFD-613/L.Golson/ See Attachment

*cmc ok
10/25/06
RCA*

\\CDSNAS\OGDS11\FIRMSV:\FIRMSAM\Apotex\LTRS&REV\77395.ap.doc
F/T by caw/10.04.06

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-395

LABELING

PRESCRIBING INFORMATION

Rx Only

Paroxetine Hydrochloride Oral Suspension 10 mg/5 mL

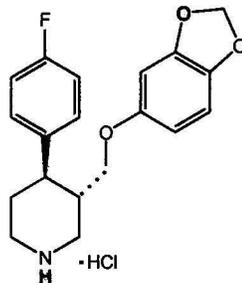
Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of paroxetine or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be 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. (See WARNINGS and PRECAUTIONS—Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Paroxetine Hydrochloride Oral Suspension is an orally administered psychotropic drug. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as *(-)-trans-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride anhydrous* and has the molecular formula of $C_{19}H_{20}FNO_3 \cdot HCl$. The molecular weight is 365.83 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



Paroxetine hydrochloride is a white to off-white crystalline powder, with a melting range of 116° to 120°C and a solubility at 5.4 mg/mL in water.

Each 5 mL of orange-colored suspension with an orange aroma contains paroxetine hydrochloride equivalent to paroxetine, 10 mg. Inactive ingredients consist of bitter blocker type flavor, FD&C Yellow No. 6, glycerin, methylparaben, microcrystalline cellulose and carboxymethylcellulose

sodium, natural orange blood sicilian flavor, propylene glycol, propylparaben, purified water, saccharin sodium, 30% simethicone emulsion and sorbitol solution.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The efficacy of paroxetine in the treatment of major depressive disorder, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) 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, α_1 -, α_2 -, beta-adrenergic-, dopamine (D_2)-, 5-HT₁-, 5-HT₂-, and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic, and α_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 mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets of paroxetine daily for 30 days. 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 is equally bioavailable from the oral suspension and tablet.

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n = 15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of C_{max} , T_{max} , C_{min} , and $T_{1/2}$ were 61.7 ng/mL (CV 45%), 5.2 hours (CV 10%), 30.7 ng/mL (CV 67%), and 21.0 hours (CV 32%), respectively. The steady-state C_{max} and C_{min} values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was

administered with food but the C_{max} was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.

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 is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets daily for 30 days of paroxetine. In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses 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 paroxetine doses of 20, 30, and 40 mg, 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 as a treatment for major depressive disorder has been established in 6 placebo-controlled studies of patients with major depressive disorder (aged 18 to 73). In these studies, paroxetine was shown to be significantly more effective than placebo in treating major depressive disorder by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness. Paroxetine was significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor, and anxiety factor.

A study of outpatients with major depressive disorder who had responded to paroxetine (HDRS total score <8) during an initial 8-week open-treatment phase and were then randomized to continuation on paroxetine or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking paroxetine (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Obsessive Compulsive Disorder

The effectiveness of paroxetine in the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies 1 and 2). Patients in all studies had moderate to severe OCD (DSM-III-R) with mean baseline ratings on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score ranging from 23 to 26. Study 1, a dose-range finding study where patients were treated with fixed doses of 20, 40, or 60 mg of paroxetine/day demonstrated that daily doses of paroxetine 40 and 60 mg are effective in the treatment of OCD. Patients receiving doses of 40 and 60 mg paroxetine experienced a mean reduction of approximately 6 and 7 points, respectively, on the YBOCS total score which was significantly greater than the approximate 4-point reduction at 20 mg and a 3-point reduction in the placebo-treated patients. Study 2 was a flexible-dose study comparing paroxetine (20 to 60 mg daily) with clomipramine (25 to 250 mg daily). In this study, patients receiving paroxetine experienced a mean reduction of approximately 7 points on the YBOCS total score, which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.

The following table provides the outcome classification by treatment group on Global Improvement items of the Clinical Global Impression (CGI) scale for Study 1.

Outcome Classification (%) on CGI-Global Improvement Item for Completers in Study 1				
Outcome Classification	Placebo (n = 74)	Paroxetine		
		20 mg (n = 75)	40 mg (n = 66)	60 mg (n = 66)
Worse	14%	7%	7%	3%
No Change	44%	35%	22%	19%
Minimally Improved	24%	33%	29%	34%
Much Improved	11%	18%	22%	24%
Very Much Improved	7%	7%	20%	20%

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

The long-term maintenance effects of paroxetine in OCD were demonstrated in a long-term extension to Study 1. Patients who were responders on paroxetine during the 3-month double-blind phase and a 6-month extension on open-label paroxetine (20 to 60 mg/day) were randomized to either paroxetine or placebo in a 6-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.

Panic Disorder

The effectiveness of paroxetine in the treatment of panic disorder was demonstrated in three 10- to 12-week multicenter, placebo-controlled studies of adult outpatients (Studies 1-3). Patients in all studies had panic disorder (DSM-III-R), with or without agoraphobia. In these studies, paroxetine was shown to be significantly more effective than placebo in treating panic disorder by at least 2 out of 3 measures of panic attack frequency and on the Clinical Global Impression Severity of Illness score.

Study 1 was a 10-week dose-range finding study; patients were treated with fixed paroxetine doses of 10, 20, or 40 mg/day or placebo. A significant difference from placebo was observed only for the 40 mg/day group. At endpoint, 76% of patients receiving paroxetine 40 mg/day were free of panic attacks, compared to 44% of placebo-treated patients.

Study 2 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) and placebo. At endpoint, 51% of paroxetine patients were free of panic attacks compared to 32% of placebo-treated patients.

Study 3 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) to placebo in patients concurrently receiving standardized cognitive behavioral therapy. At endpoint, 33% of the paroxetine-treated patients showed a reduction to 0 or 1 panic attacks compared to 14% of placebo patients.

In both Studies 2 and 3, the mean paroxetine dose for completers at endpoint was approximately 40 mg/day of paroxetine.

Long-term maintenance effects of paroxetine in panic disorder were demonstrated in an extension to Study 1. Patients who were responders during the 10-week double-blind phase and during a 3-month double-blind extension phase were randomized to either paroxetine (10, 20, or 40 mg/day)

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.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

Social Anxiety Disorder

The effectiveness of paroxetine in the treatment of social anxiety disorder was demonstrated in three 12-week, multicenter, placebo-controlled studies (Studies 1, 2, and 3) of adult outpatients with social anxiety disorder (DSM-IV). In these studies, the effectiveness of paroxetine compared to placebo was evaluated on the basis of (1) the proportion of responders, as defined by a Clinical Global Impression (CGI) Improvement score of 1 (very much improved) or 2 (much improved), and (2) change from baseline in the Liebowitz Social Anxiety Scale (LSAS).

Studies 1 and 2 were flexible-dose studies comparing paroxetine (20 to 50 mg daily) and placebo. Paroxetine demonstrated statistically significant superiority over placebo on both the CGI Improvement responder criterion and the Liebowitz Social Anxiety Scale (LSAS). In Study 1, for patients who completed to week 12, 69% of paroxetine-treated patients compared to 29% of placebo-treated patients were CGI Improvement responders. In Study 2, CGI Improvement responders were 77% and 42% for the paroxetine- and placebo-treated patients, respectively.

Study 3 was a 12-week study comparing fixed paroxetine doses of 20, 40, or 60 mg/day with placebo. Paroxetine 20 mg was demonstrated to be significantly superior to placebo on both the LSAS Total Score and the CGI Improvement responder criterion; there were trends for superiority over placebo for the 40 mg and 60 mg/day dose groups. There was no indication in this study of any additional benefit for doses higher than 20 mg/day.

Subgroup analyses generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

Generalized Anxiety Disorder

The effectiveness of paroxetine in the treatment of Generalized Anxiety Disorder (GAD) was demonstrated in two 8-week, multicenter, placebo-controlled studies (Studies 1 and 2) of adult outpatients with Generalized Anxiety Disorder (DSM-IV).

Study 1 was an 8-week study comparing fixed paroxetine doses of 20 mg or 40 mg/day with placebo. Doses of 20 mg or 40 mg of paroxetine were both demonstrated to be significantly superior to placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. There was not sufficient evidence in this study to suggest a greater benefit for the 40 mg/day dose compared to the 20 mg/day dose.

Study 2 was a flexible-dose study comparing paroxetine (20 mg to 50 mg daily) and placebo. Paroxetine demonstrated statistically significant superiority over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. A third study, also flexible-dose comparing paroxetine (20 mg to 50 mg daily), did not demonstrate statistically significant superiority of paroxetine over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, the primary outcome.

Subgroup analyses did not indicate differences in treatment outcomes as a function of race or gender. There were insufficient elderly patients to conduct subgroup analyses on the basis of age.

In a longer-term trial, 566 patients meeting DSM-IV criteria for Generalized Anxiety Disorder, who had responded during a single-blind, 8-week acute treatment phase with 20 to 50 mg/day of paroxetine, were randomized to continuation of paroxetine at their same dose, or to placebo, for up to 24 weeks of observation for relapse. Response during the single-blind phase was defined by having a decrease of ≥ 2 points compared to baseline on the CGI-Severity of Illness scale, to a score of ≤ 3 . Relapse during the double-blind phase was defined as an increase of ≥ 2 points compared to baseline on the CGI-Severity of Illness scale to a score of ≥ 4 , or withdrawal due to lack of efficacy. Patients receiving continued paroxetine experienced a significantly lower relapse rate over the subsequent 24 weeks compared to those receiving placebo.

Posttraumatic Stress Disorder

The effectiveness of paroxetine in the treatment of Posttraumatic Stress Disorder (PTSD) was demonstrated in two 12-week, multicenter, placebo-controlled studies (Studies 1 and 2) of adult outpatients who met DSM-IV criteria for PTSD. The mean duration of PTSD symptoms for the 2 studies combined was 13 years (ranging from .1 year to 57 years). The percentage of patients with secondary major depressive disorder or non-PTSD anxiety disorders in the combined 2 studies was 41% (356 out of 858 patients) and 40% (345 out of 858 patients), respectively. Study outcome was assessed by (i) the Clinician-Administered PTSD Scale Part 2 (CAPS-2) score and (ii) the Clinical Global Impression-Global Improvement Scale (CGI-I). The CAPS-2 is a multi-item instrument that measures 3 aspects of PTSD with the following symptom clusters: Reexperiencing/intrusion, avoidance/numbing and hyperarousal. The 2 primary outcomes for each trial were (i) change from baseline to endpoint on the CAPS-2 total score (17 items), and (ii) proportion of responders on the CGI-I, where responders were defined as patients having a score of 1 (very much improved) or 2 (much improved).

Study 1 was a 12-week study comparing fixed paroxetine doses of 20 mg or 40 mg/day to placebo. Doses of 20 mg and 40 mg of paroxetine were demonstrated to be significantly superior to placebo on change from baseline for the CAPS-2 total score and on proportion of responders on the CGI-I. There was not sufficient evidence in this study to suggest a greater benefit for the 40 mg/day dose compared to the 20 mg/day dose.

Study 2 was a 12-week flexible-dose study comparing paroxetine (20 to 50 mg daily) to placebo. Paroxetine was demonstrated to be significantly superior to placebo on change from baseline for the CAPS-2 total score and on proportion of responders on the CGI-I.

A third study, also a flexible-dose study comparing paroxetine (20 to 50 mg daily) to placebo, demonstrated paroxetine to be significantly superior to placebo on change from baseline for CAPS-2 total score, but not on proportion of responders on the CGI-I.

The majority of patients in these trials were women (68% women: 377 out of 551 subjects in Study 1 and 66% women: 202 out of 303 subjects in Study 2). Subgroup analyses did not indicate differences in treatment outcomes as a function of gender. There were an insufficient number of patients who were 65 years and older or were non-Caucasian to conduct subgroup analyses on the basis of age or race, respectively.

INDICATIONS AND USAGE

Major Depressive Disorder

Paroxetine is indicated for the treatment of major depressive disorder.

The efficacy of paroxetine in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see **CLINICAL PHARMACOLOGY - Clinical Trials**). A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: Change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The effects of paroxetine in hospitalized depressed patients have not been adequately studied.

The efficacy of paroxetine in maintaining a response in major depressive disorder for up to 1 year was demonstrated in a placebo-controlled trial (see **CLINICAL PHARMACOLOGY - Clinical Trials**). Nevertheless, the physician who elects to use paroxetine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Obsessive Compulsive Disorder

Paroxetine is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of paroxetine was established in two 12-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-III-R category of obsessive compulsive disorder (see **CLINICAL PHARMACOLOGY - Clinical Trials**).

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients assigned to paroxetine showed a lower relapse rate compared to patients on placebo (see **CLINICAL PHARMACOLOGY - Clinical Trials**). Nevertheless, the physician who elects to use paroxetine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Panic Disorder

Paroxetine is 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 was established in three 10- to 12-week trials in panic disorder patients whose diagnoses corresponded to the DSM-III-R 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 4 (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 was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see **CLINICAL PHARMACOLOGY - Clinical Trials**).

Nevertheless, the physician who prescribes paroxetine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Social Anxiety Disorder

Paroxetine is 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 1 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 was established in three 12-week trials in adult patients with social anxiety disorder (DSM-IV). Paroxetine has not been studied in children or adolescents with social phobia (see **CLINICAL PHARMACOLOGY - Clinical Trials**).

The effectiveness of paroxetine 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 for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Generalized Anxiety Disorder

Paroxetine is indicated for the treatment of Generalized Anxiety Disorder (GAD), as defined in DSM-IV. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The efficacy of paroxetine in the treatment of GAD was established in two 8-week placebo-controlled trials in adults with GAD. Paroxetine has not been studied in children or adolescents with Generalized Anxiety Disorder (see **CLINICAL PHARMACOLOGY - Clinical Trials**).

Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following 6 symptoms: Restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance.

The efficacy of paroxetine in maintaining a response in patients with Generalized Anxiety Disorder, who responded during an 8-week acute treatment phase while taking paroxetine and were then observed for relapse during a period of up to 24 weeks, was demonstrated in a placebo-controlled trial (see **CLINICAL PHARMACOLOGY - Clinical Trials**). Nevertheless, the physician who elects to use paroxetine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Posttraumatic Stress Disorder

Paroxetine is indicated for the treatment of Posttraumatic Stress Disorder (PTSD).

The efficacy of paroxetine in the treatment of PTSD was established in two 12-week placebo-controlled trials in adults with PTSD (DSM-IV) (see **CLINICAL PHARMACOLOGY - Clinical Trials**).

PTSD, as defined by DSM-IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response that involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include re-experiencing of the event in the form of intrusive thoughts, flashbacks, or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The efficacy of paroxetine in longer-term treatment of PTSD, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to prescribe paroxetine for extended periods should periodically re-evaluate 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 is contraindicated in patients with a hypersensitivity to paroxetine or any of the inactive ingredients in paroxetine.

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. There has been a longstanding concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be 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. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

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**, 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 health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for paroxetine should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

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 a monoamine oxidase inhibitor (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, 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 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 before starting an MAOI.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with use of paroxetine, 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 with MAOIs intended to treat depression is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS—Potential for Interaction With Monoamine Oxidase Inhibitors**).

If concomitant use of paroxetine 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 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 - Discontinuation of Treatment with Paroxetine**). 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 1.1-2.8). 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 US 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 0.8-2.9). 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 1.2-2.8). 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 an 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 an 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 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 – 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.

PRECAUTIONS

General

Activation of Mania/Hypomania

During premarketing testing, hypomania or mania occurred in approximately 1.0% of unipolar patients treated with paroxetine 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 paroxetine and 11.6% for the combined active-control groups. As with all drugs effective in the treatment of major depressive disorder, paroxetine should be used cautiously in patients with a history of mania.

Seizures

During premarketing testing, seizures occurred in 0.1% of patients treated with paroxetine, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Paroxetine 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

Recent clinical trials supporting the various approved indications for paroxetine employed a taper-phase regimen, rather than an abrupt discontinuation of treatment. The taper-phase regimen used in GAD and PTSD clinical trials involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped.

With this regimen in those studies, the following adverse events were reported at an incidence of 2% or greater for paroxetine and were at least twice that reported for placebo: Abnormal dreams, paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention.

During marketing of paroxetine and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring, upon the 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. 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. 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 agents 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 2 studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see **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 paroxetine in patients with certain concomitant systemic illness is limited. Caution is advisable in using paroxetine 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. A few cases of acute angle closure glaucoma associated with paroxetine therapy 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 is prescribed for patients with narrow angle glaucoma.

Paroxetine 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 the product's premarket testing. Evaluation of electrocardiograms of 682 patients who received paroxetine in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine 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

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of paroxetine and triptans, tramadol, or other serotonergic agents. 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 Using Antidepressants in Children and Teenagers 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 Medication Guide is attached to this Prescribing Information with a perforation for easy removal.

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 observe 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 paroxetine 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 does not affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with treatment with paroxetine in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication

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 paroxetine 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.

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 paroxetine. Consequently, concomitant use of paroxetine with tryptophan is not recommended (see ***Serotonin Syndrome***).

Monoamine Oxidase Inhibitors

See **CONTRAINDICATIONS and WARNINGS**.

Pimozide

In a controlled study of healthy volunteers, after paroxetine 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 is 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 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 paroxetine with other SSRIs, 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 and warfarin should be undertaken with caution (see **Drugs That Interfere With Hemostasis**).

Triptans

There have been rare postmarketing reports of serotonin syndrome with the use of an SSRI and a triptan. If concomitant use of paroxetine with a triptan is warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS - 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 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 after the 20 mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital

Phenobarbital induces many cytochrome P₄₅₀ (oxidative) enzymes. When a single oral 30 mg dose of paroxetine was administered at phenobarbital steady state (100 mg once daily for 14 days), paroxetine AUC and T_½ 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 of paroxetine is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin

When a single oral 30 mg dose of paroxetine was administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and T_½ were reduced (by an average of 50% and 35%, respectively) compared to 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 these drugs are coadministered; any subsequent adjustments should be guided by clinical effect (see **ADVERSE REACTIONS - Postmarketing 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 P₄₅₀ 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 dosing with paroxetine. In 1 study, daily dosing of 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 1 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 it is given with paroxetine.

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

Therefore, co-administration of paroxetine 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 P₄₅₀ isozymes that, unlike CYP2D6, show no evidence of saturation (see **PRECAUTIONS - 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 cytochrome 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 co-administration of tricyclic antidepressants (TCAs) with paroxetine, 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 co-administered with paroxetine (see **PRECAUTIONS - Drugs Metabolized by Cytochrome CYP2D6**).

Drugs Highly Bound to Plasma Protein

Because paroxetine is highly bound to plasma protein, administration of paroxetine 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.

Lithium

A multiple-dose study 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 paroxetine 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 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 paroxetine (30 mg once daily) increased steady-state AUC₀₋₂₄, 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 co-administration with paroxetine (30 mg once daily) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see **ADVERSE REACTIONS - Postmarketing Reports**).

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).

Theophylline

Reports of elevated theophylline levels associated with treatment with paroxetine 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.

Electroconvulsive Therapy (ECT)

There are no clinical studies of the combined use of ECT and paroxetine.

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 2.4 (mouse) and 3.9 (rat) times the maximum recommended human dose (MRHD) for major depressive disorder, social anxiety disorder, GAD, and PTSD on a mg/m² basis. Because the MRHD for major depressive disorder is slightly less than that for OCD (50 mg versus 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. 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 5 *in vitro* and 2 *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 2.9 times the MRHD for major depressive disorder, social anxiety disorder, GAD, and PTSD or 2.4 times the MRHD for OCD 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 (9.8 and 4.9 times the MRHD for major depressive disorder, social anxiety disorder, and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m² basis).

Pregnancy

Pregnancy Category D. See **WARNINGS – Usage in Pregnancy: *Teratogenic and Nonteratogenic 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 is 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, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of paroxetine 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 paroxetine 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 paroxetine in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received paroxetine 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 **Discontinuation of Treatment With Paroxetine**).

Geriatric Use

In worldwide premarketing clinical trials with paroxetine, 17% of patients treated with paroxetine (approximately 700) were 65 years of age 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**).

ADVERSE REACTIONS

Associated With Discontinuation of Treatment: Twenty percent (1,199/6,145) of patients treated with paroxetine in worldwide clinical trials in major depressive disorder and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients treated with paroxetine in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD, and PTSD, respectively, discontinued treatment due to an adverse event. The most common events ($\geq 1\%$) 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 compared to placebo) included the following:

	Major Depressive Disorder		OCD		Panic Disorder		Social Anxiety Disorder		Generalized Anxiety Disorder		PTSD	
	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo
CNS												
Somnolence	2.3%	0.7%	—		1.9%	0.3%	3.4%	0.3%	2.0%	0.2%	2.8%	0.6%
Insomnia	—	—	1.7%	0%	1.3%	0.3%	3.1%	0%			—	—
Agitation	1.1%	0.5%	—								—	—
Tremor	1.1%	0.3%	—				1.7%	0%			1.0%	0.2%
Anxiety	—	—	—				1.1%	0%			—	—
Dizziness	—	—	1.5%	0%			1.9%	0%	1.0%	0.2%	—	—
Gastrointestinal												
Constipation	—		1.1%	0%							—	—
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%	4.0%	0.3%	2.0%	0.2%	2.2%	0.6%
Diarrhea	1.0%	0.3%	—								—	—
Dry mouth	1.0%	0.3%	—								—	—
Vomiting	1.0%	0.3%	—				1.0%	0%			—	—
Flatulence							1.0%	0.3%			—	—
Other												
Asthenia	1.6%	0.4%	1.9%	0.4%			2.5%	0.6%	1.8%	0.2%	1.6%	0.2%
Abnormal ejaculation ¹	1.6%	0%	2.1%	0%			4.9%	0.6%	2.5%	0.5%	—	—
Sweating	1.0%	0.3%	—				1.1%	0%	1.1%	0.2%	—	—
Impotence ¹	—		1.5%	0%							—	—
Libido Decreased							1.0%	0%			—	—

Where numbers are not provided the incidence of the adverse events in patients treated with paroxetine was not $>1\%$ or was not greater than or equal to 2 times the incidence of placebo.

1. Incidence corrected for gender.

Commonly Observed Adverse Events

Major Depressive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 1) were: Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders.

Obsessive Compulsive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that of placebo, derived from Table 2) were: Nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

Panic Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 2) were: Asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders, and impotence.

Social Anxiety Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 2) were: Sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital disorders, and impotence.

Generalized Anxiety Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 3) were: Asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

Posttraumatic Stress Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 3) were: Asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders, and impotence.

Incidence in Controlled Clinical Trials

The prescriber should be aware that the figures in the tables following 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 populations studied.

Major Depressive Disorder

Table 1 enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 mg to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder¹			
Body System	Preferred Term	Paroxetine (n=421)	Placebo (n=421)
Body as a Whole	Headache	18%	17%
	Asthenia	15%	6%
Cardiovascular	Palpitation	3%	1%
	Vasodilation	3%	1%
Dermatologic	Sweating	11%	2%
	Rash	2%	1%
Gastrointestinal	Nausea	26%	9%
	Dry Mouth	18%	12%
	Constipation	14%	9%
	Diarrhea	12%	8%
	Decreased Appetite	6%	2%
	Flatulence	4%	2%
	Oropharynx Disorder ²	2%	0%
	Dyspepsia	2%	1%
Musculoskeletal	Myopathy	2%	1%
	Myalgia	2%	1%
	Myasthenia	1%	0%
Nervous System	Somnolence	23%	9%
	Dizziness	13%	6%
	Insomnia	13%	6%
	Tremor	8%	2%
	Nervousness	5%	3%
	Anxiety	5%	3%
	Paresthesia	4%	2%
	Libido Decreased	3%	0%
	Drugged Feeling	2%	1%
	Confusion	1%	0%
Respiration	Yawn	4%	0%
Special Senses	Blurred Vision	4%	1%
	Taste Perversion	2%	0%

Body System	Preferred Term	Paroxetine (n=421)	Placebo (n=421)
Urogenital System	Ejaculatory Disturbance ^{3,4}	13%	0%
	Other Male Genital Disorders ^{3,5}	10%	0%
	Urinary Frequency	3%	1%
	Urination Disorder ⁶	3%	0%
	Female Genital Disorders ^{3,7}	2%	0%

1. Events reported by at least 1% of patients treated with paroxetine are included, except the following events which had an incidence on placebo \geq paroxetine: Abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly "cold symptoms" or "URI"), trauma, and vomiting.
2. Includes mostly "lump in throat" and "tightness in throat".
3. Percentage corrected for gender.
4. Mostly "ejaculatory delay".
5. Includes "anorgasmia", "erectile difficulties", "delayed ejaculation/orgasm" and "sexual dysfunction", and "impotence".
6. Includes mostly "difficulty with micturition" and "urinary hesitancy".
7. Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm".

Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder

Table 2 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on paroxetine who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg to 60 mg/day or among patients with panic disorder on paroxetine who participated in placebo-controlled trials of 10- to 12-weeks duration in which patients were dosed in a range of 10 mg to 60 mg/day or among patients with social anxiety disorder on paroxetine who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg to 50 mg/day.

Body System	Preferred Term	Obsessive Compulsive Disorder		Panic Disorder		Social Anxiety Disorder	
		Paroxetine (n=542)	Placebo (n=265)	Paroxetine (n=469)	Placebo (n=324)	Paroxetine (n=425)	Placebo (n=339)
Body as a Whole	Asthenia	22%	14%	14%	5%	22%	14%
	Abdominal Pain	—	—	4%	3%	—	—
	Chest Pain	3%	2%	—	—	—	—
	Back pain	—	—	3%	2%	—	—
	Chills	2%	1%	2%	1%	—	—
	Trauma	—	—	—	—	3%	1%
Cardiovascular	Vasodilation	4%	1%	—	—	—	—
	Palpitation	2%	0%	—	—	—	—

Table 2. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder¹ (Cont'd)

Body System	Preferred Term	Obsessive Compulsive Disorder		Panic Disorder		Social Anxiety Disorder	
		Paroxetine (n=542)	Placebo (n=265)	Paroxetine (n=469)	Placebo (n=324)	Paroxetine (n=425)	Placebo (n=339)
Dermatologic	Sweating	9%	3%	14%	6%	9%	2%
	Rash	3%	2%	—	—	—	—
Gastrointestinal	Nausea	23%	10%	23%	17%	25%	7%
	Dry mouth	18%	9%	18%	11%	9%	3%
	Constipation	16%	6%	8%	5%	5%	2%
	Diarrhea	10%	10%	12%	7%	9%	6%
	Decreased Appetite	9%	3%	7%	3%	8%	2%
	Dyspepsia	—	—	—	—	4%	2%
	Flatulence	—	—	—	—	4%	2%
	Increased Appetite	4%	3%	2%	1%	—	—
	Vomiting	—	—	—	—	2%	1%
Musculoskeletal	Myalgia	—	—	—	—	4%	3%
Nervous System	Insomnia	24%	13%	18%	10%	21%	16%
	Somnolence	24%	7%	19%	11%	22%	5%
	Dizziness	12%	6%	14%	10%	11%	7%
	Tremor	11%	1%	9%	1%	9%	1%
	Nervousness	9%	8%	—	—	8%	7%
	Libido Decreased	7%	4%	9%	1%	12%	1%
	Agitation	—	—	5%	4%	3%	1%
	Anxiety	—	—	5%	4%	5%	4%
	Abnormal Dreams	4%	1%	—	—	—	—
	Concentration Impaired	3%	2%	—	—	4%	1%
	Depersonalization	3%	0%	—	—	—	—
	Myoclonus	3%	0%	3%	2%	2%	1%
	Amnesia	2%	1%	—	—	—	—
Respiratory System	Rhinitis	—	—	3%	0%	—	—
	Pharyngitis	—	—	—	—	4%	2%
	Yawn	—	—	—	—	5%	1%
Special Senses	Abnormal Vision	4%	2%	—	—	4%	1%
	Taste Perversion	2%	0%	—	—	—	—

Table 2. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder¹ (Cont'd)

Body System	Preferred Term	Obsessive Compulsive Disorder		Panic Disorder		Social Anxiety Disorder	
		Paroxetine (n=542)	Placebo (n=265)	Paroxetine (n=469)	Placebo (n=324)	Paroxetine (n=425)	Placebo (n=339)
Urogenital System	Abnormal Ejaculation ²	23%	1%	21%	1%	28%	1%
	Dysmenorrhea	—	—	—	—	5%	4%
	Female Genital Disorder ²	3%	0%	9%	1%	9%	1%
	Impotence ²	8%	1%	5%	0%	5%	1%
	Urinary Frequency	3%	1%	2%	0%	—	—
	Urination Impaired	3%	0%	—	—	—	—
	Urinary Tract Infection	2%	1%	2%	1%	—	—

¹ Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients treated with paroxetine are included, except the following events which had an incidence on placebo \geq paroxetine: [OCD]: Abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder, rhinitis, and sinusitis. [panic disorder]: Abnormal dreams, abnormal vision, chest pain, cough increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired, and vasodilation. [social anxiety disorder]: Abdominal pain, depression, headache, infection, respiratory disorder, and sinusitis.

² Percentage corrected for gender.

Generalized Anxiety Disorder and Posttraumatic Stress Disorder

Table 3 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on paroxetine who participated in placebo-controlled trials of 8-weeks duration in which patients were dosed in a range of 10 mg/day to 50 mg/day or among PTSD patients on paroxetine who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg/day to 50 mg/day.

Table 3. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder and Posttraumatic Stress Disorder¹

Body System	Preferred Term	Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
		Paroxetine (n=735)	Placebo (n=529)	Paroxetine (n=676)	Placebo (n=504)
Body as a Whole	Asthenia	14%	6%	12%	4%
	Headache	17%	14%	—	—
	Infection	6%	3%	5%	4%
	Abdominal Pain	—	—	4%	3%
	Trauma	—	—	6%	5%

Table 3. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder and Posttraumatic Stress Disorder ¹ (Cont'd)					
Body System	Preferred Term	Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
		Paroxetine (n=735)	Placebo (n=529)	Paroxetine (n=676)	Placebo (n=504)
Cardiovascular	Vasodilation	3%	1%	2%	1%
Dermatologic	Sweating	6%	2%	5%	1%
Gastrointestinal	Nausea	20%	5%	19%	8%
	Dry Mouth	11%	5%	10%	5%
	Constipation	10%	2%	5%	3%
	Diarrhea	9%	7%	11%	5%
	Decreased Appetite	5%	1%	6%	3%
	Vomiting	3%	2%	3%	2%
	Dyspepsia	—	—	5%	3%
Nervous System	Insomnia	11%	8%	12%	11%
	Somnolence	15%	5%	16%	5%
	Dizziness	6%	5%	6%	5%
	Tremor	5%	1%	4%	1%
	Nervousness	4%	3%	—	—
	Libido Decreased	9%	2%	5%	2%
	Abnormal Dreams	—	—	3%	2%
Respiratory System	Respiratory Disorder	7%	5%	—	—
	Sinusitis	4%	3%	—	—
	Yawn	4%	—	2%	1%
Special Senses	Abnormal Vision	2%	1%	3%	1%
Urogenital System	Abnormal Ejaculation ²	25%	2%	13%	2%
	Female Genital Disorder ²	4%	1%	5%	1%
	Impotence ²	4%	3%	9%	1%

¹ Events reported by at least 2% of GAD and PTSD in patients treated with paroxetine are included, except the following events which had an incidence on placebo \geq paroxetine. [GAD]: Abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis. [PTSD]: Back pain, headache, anxiety, depression, nervousness, respiratory disorder, pharyngitis, and sinusitis.

² Percentage corrected for gender.

Dose Dependency of Adverse Events: A comparison of adverse event rates in a fixed-dose study comparing 10, 20, 30, and 40 mg/day of 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 use of paroxetine, as shown in the following table:

Body System	Preferred Term	Placebo (n = 51)	Paroxetine			
			10 mg (n = 102)	20 mg (n = 104)	30 mg (n = 101)	40 mg (n = 102)
Body as a Whole	Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology	Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal	Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
	Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
	Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
	Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
	Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System	Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
	Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
	Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
	Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
	Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
	Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses	Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System	Abnormal Ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
	Impotence	0.0%	1.9%	4.3%	6.4%	1.9%
	Male Genital Disorders	0.0%	3.8%	8.7%	6.4%	3.7%

* Rule for including adverse events in table: Incidence at least 5% for 1 of paroxetine groups and \geq twice the placebo incidence for at least 1 paroxetine group.

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of paroxetine in the treatment of OCD, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned. No new adverse events were observed in the group treated with 60 mg of paroxetine compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 10, 20, and 40 mg of paroxetine in the treatment of panic disorder, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in patients receiving 60 mg of paroxetine compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of paroxetine in the treatment of social anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned.

In a fixed-dose study comparing placebo and 20 and 40 mg of paroxetine in the treatment of generalized anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned, except for the following adverse events: Asthenia, constipation, and abnormal ejaculation.

In a fixed-dose study comparing placebo and 20 and 40 mg of paroxetine in the treatment of posttraumatic stress disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned, except for impotence and abnormal ejaculation.

Adaptation to Certain Adverse Events

Over a 4- to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less to other effects (e.g., dry mouth, somnolence, and asthenia).

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 selective serotonin reuptake inhibitors (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.

In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD, panic disorder, social anxiety disorder, GAD, and PTSD are displayed in Table 5.

	Paroxetine	Placebo
n (males)	1446	1042
Decreased Libido	6-15%	0-5%
Ejaculatory Disturbance	13-28%	0-2%
Impotence	2-9%	0-3%
n (females)	1822	1340
Decreased Libido	0-9%	0-2%
Orgasmic Disturbance	2-9%	0-1%

There are no adequate and well-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 had minimal (about 1 pound) weight loss versus smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with paroxetine in controlled clinical trials.

ECG Changes

In an analysis of ECGs obtained in 682 patients treated with 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 placebo-controlled clinical trials, patients treated with paroxetine exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the paroxetine-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

Hallucinations

In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients receiving placebo.

Other Events Observed During the Premarketing Evaluation of Paroxetine

During its premarketing assessment in major depressive disorder, multiple doses of paroxetine were administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure to 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. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder, 542, 469, 522, 735, and 676 patients, respectively, received multiple doses of paroxetine. 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 standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9,089 patients exposed to multiple doses of paroxetine who experienced an event of the type cited on at least 1 occasion while receiving paroxetine. All reported events are included except those already listed in Tables 1 to 3, those reported in terms so general as to be uninformative and those events where a drug cause was remote. 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 1 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. Events of major clinical importance are also described in the **PRECAUTIONS** section.

Body as a Whole

Infrequent Allergic reaction, chills, face edema, malaise, neck pain; rare: Adrenergic syndrome, cellulitis, monilliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer.

Cardiovascular System

Frequent: Hypertension, tachycardia; *infrequent:* Bradycardia, hematoma, hypotension, migraine, syncope; *rare:* Angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System

Infrequent: Bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* Aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

Endocrine System

Rare: Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis.

Hemic and Lymphatic Systems

Infrequent: Anemia, leukopenia, lymphadenopathy, purpura; *rare:* Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional

Frequent: Weight gain; *infrequent:* Edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; *rare:* Alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

Musculoskeletal System

Frequent: Arthralgia; *infrequent:* Arthritis, arthrosis; *rare:* Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

Nervous System

Frequent: Emotional lability, vertigo; *infrequent:* Abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; *rare:* Abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome,

fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome.

Respiratory System

Infrequent: Asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, stridor, voice alteration.

Skin and Appendages

Frequent: Pruritus; *infrequent:* Acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* Angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis; herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses

Frequent: Tinnitus; *infrequent:* Abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* Amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage, taste loss, visual field defect.

Urogenital System

Infrequent: Amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis.

Postmarketing Reports

Voluntary reports of adverse events in patients taking paroxetine 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 paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Paroxetine is not a controlled substance.

Physical and Psychologic Dependence

Paroxetine has 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 (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Since the introduction of paroxetine in the United States, 342 spontaneous cases of deliberate or accidental overdose 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 non-fatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdose 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 overdose 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 who are taking or have recently taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see **PRECAUTIONS - Drugs Metabolized by Cytochrome CYP2D6**).

In managing overdose, 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 should be administered as a single daily dose with or without food, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the effectiveness of paroxetine 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 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with paroxetine 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 needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of paroxetine has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

Obsessive Compulsive Disorder

Usual Initial Dosage

Paroxetine should be administered as a single daily dose with or without food, usually in the morning. The recommended dose of paroxetine in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10 mg/day increments. Dose changes should occur at intervals of at least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine in the treatment of OCD. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see **CLINICAL PHARMACOLOGY - Clinical Trials**). OCD 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.

Panic Disorder

Usual Initial Dosage

Paroxetine should be administered as a single daily dose with or without food, usually in the morning. The target dose of paroxetine in the treatment of panic disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to 60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy

Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see **CLINICAL PHARMACOLOGY - Clinical Trials**). 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 should be administered as a single daily dose with or without food, usually in the morning. The recommended and initial dosage is 20 mg/day. In clinical trials the effectiveness of paroxetine was demonstrated in patients dosed in a range of 20 to 60 mg/day. While the safety of paroxetine has been evaluated in patients with social anxiety disorder at doses up to 60 mg/day, available information does not suggest any additional benefit for doses above 20 mg/day (see **CLINICAL PHARMACOLOGY - Clinical Trials**).

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with paroxetine should remain on it. Although the efficacy of paroxetine 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.

Generalized Anxiety Disorder

Usual Initial Dosage

Paroxetine should be administered as a single daily dose with or without food, usually in the morning. In clinical trials the effectiveness of paroxetine was demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended starting dosage and the established effective dosage is 20 mg/day. There is not sufficient evidence to suggest a greater benefit to doses higher than 20 mg/day. **Dose changes should occur in 10 mg/day** increments and at intervals of at least 1 week.

Maintenance Therapy

Systematic evaluation of continuing paroxetine for periods of up to 24 weeks in patients with Generalized Anxiety Disorder who had responded while taking paroxetine during an 8-week acute treatment phase has demonstrated a benefit of such maintenance (see **CLINICAL PHARMACOLOGY - Clinical Trials**). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Posttraumatic Stress Disorder

Usual Initial Dosage

Paroxetine should be administered as a single daily dose with or without food, usually in the morning. The recommended starting dosage and the established effective dosage is 20 mg/day. In 1 clinical trial, the effectiveness of paroxetine was demonstrated in patients dosed in a range of 20 to 50 mg/day. However, in a fixed dose study, there was not sufficient evidence to suggest a greater benefit for a dose of 40 mg/day compared to 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at intervals of at least 1 week.

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with paroxetine should remain on it. Although the efficacy of paroxetine beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, PTSD 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 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 is 10 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 40 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. Similarly, at least 14 days should be allowed after stopping paroxetine before starting an MAOI.

Discontinuation of Treatment with Paroxetine

Symptoms associated with discontinuation of paroxetine have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine is 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.

NOTE: SHAKE SUSPENSION WELL BEFORE USING.

HOW SUPPLIED

Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL is an orange-colored, orange-flavored suspension with an orange aroma, in 250 mL, white opaque HDPE induction sealed bottles with a child resistant white polypropylene cap.

NDC 60505-0374-1

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

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL
33326

223529

September 2006

MEDICATION GUIDE

R Only

Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. *No one committed suicide in these studies*, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with:

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child. After starting an antidepressant, your child should generally see his or her healthcare provider:

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.

3. You Should Watch for Certain Signs if Your Child is Taking an Antidepressant

Contact your child's healthcare provider right away if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®)* has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®)*, sertraline (Zoloft®)*, fluvoxamine, and clomipramine (Anafranil®)*.

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

*The following are registered trademarks of their respective manufacturers: Prozac®/Eli Lilly and Company; Zoloft®/Pfizer Pharmaceuticals; Anafranil®/Mallinckrodt Inc.

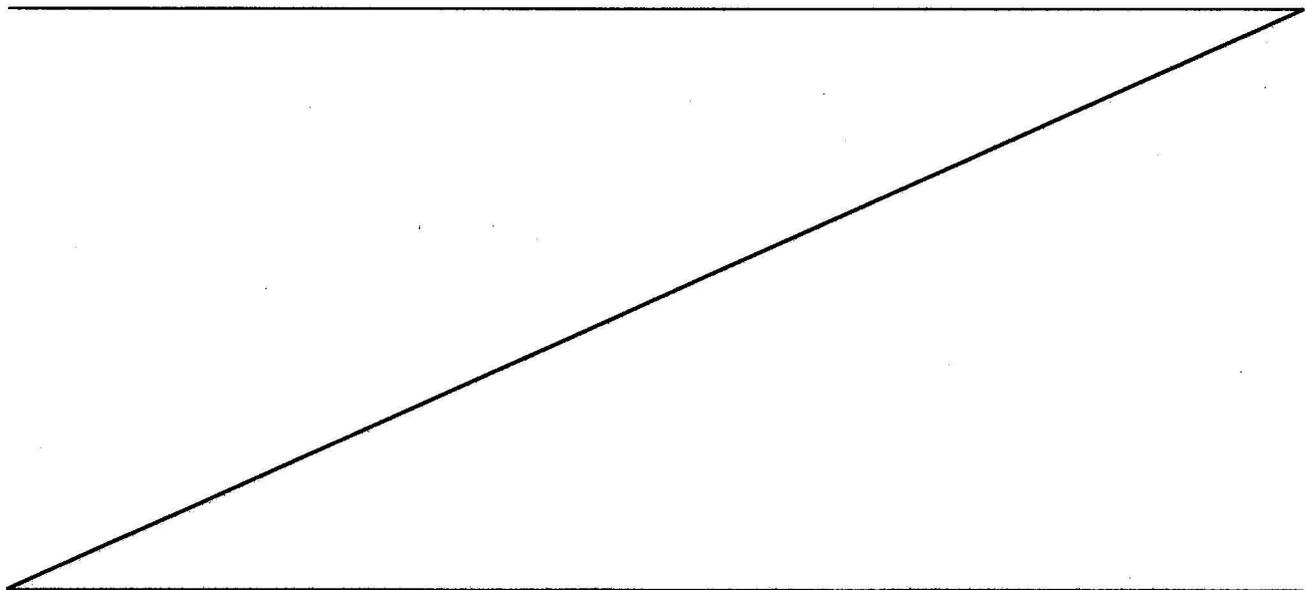
This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL
33326

223529

September 2006



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-395

LABELING REVIEWS

THIS APPROVAL SUMMARY SUPERSEDES THE APPROVAL SUMMARY FROM THE 7/7/06 SUBMISSION
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-395

Date of Submission: September 29, 2006

Applicant's Name: Apotex Corp.

Established Name: Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL

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

Container: 250 mL
 Satisfactory in FPL as of the May 3, 2006 submission.

Carton 1 x 250 mL
 Satisfactory in FPL as of the May 3, 2006 submission.

Professional Package Insert Labeling/Medication Guide
 Satisfactory in FPL as of the September 29, 2006 submission.

Revisions needed post approval:

Container and Carton:

Include an asterisk (*) after the strength and before "Each 5 mL contains...." statement.

BASIS OF APPROVAL:

Patent Data – NDA 20-710

No	Expiration	Use Code	Use	File
6133289	November 19, 2015	U-358	Depression/OCD /PD/SAD	IV
5811436	March 22, 2016			IV
6121291	September 17, 2017	U-286	Depression	IV
6121291	September 17, 2017	U-431	Method for treating PTSD	IV
4721723	June 29, 2007	U-12	Depression	IV
5872132	November 19, 2015		Depression & other disorders - SSRIs	IV
5900423	November 19, 2015		Depression & other disorders - SSRIs	IV
5789449	July 6, 2009	U-285	Depression & SAD/social phobia	IV

Exclusivity Data - NDA 20-710

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There are no unexpired exclusivities listed in the Orange book Database	

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Paxil®

NDA Number: 20-710

NDA Drug Name: Paxil® (paroxetine hydrochloride) Oral Suspension

NDA Firm: SmithKline Beecham

Date of Approval of NDA Insert and supplement #: 8-22-06 (NDA 20-710/S-018, S-019)

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

NOTES/QUESTIONS TO THE CHEMIST:**FOR THE RECORD:**

1. This review was based on the labeling for Paxil® Suspension (NDA 20-7101/S-018,S-019) SmithKline Beecham; approved 8/22/06.
2. Patents/exclusivities:

Patent Data – NDA 20-710

No	Expiration	Use Code	Use	File
6133289	November 19, 2015	U-358	Depression/OCD /PD/SAD	IV
5811436	March 22, 2016			IV
6121291	September 17, 2017	U-286	Depression	IV
6121291	September 17, 2017	U-431	Method for treating PTSD	IV
4721723	June 29, 2007	U-12	Depression	IV
5872132	November 19, 2015			IV
5900423	November 19, 2015			IV
5789449	July 6, 2009	U-285	Depression & SAD/social phobia	IV

Exclusivity Data - NDA 20-710

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There are no unexpired exclusivities listed in the Orange book Database	

3. Apotex Inc. is the manufacturer (Section 3.2P. 3.1.7012, V. B 1.2).
4. The inactives are listed accurately in the DESCRIPTION section (p 8, section 2.3, p.1 V B 1.2).
5. Storage/dispensing:

NDA: Store at or below 25°C (77°F).

ANDA: Store at 20 - 25 °C (68-77°F) [see USP Controlled Room Temperature]"
Keep tightly closed. Shake well before using.
6. Product line

NDA: 250 mL
ANDA: 250 mL
7. The drug product is packaged in an HDPE bottle and polypropylene CR cap (Section 3.2 P.2.4 V.B 1.2).
8. The medication guide is attached to the insert, which will be dispensed to the patient.

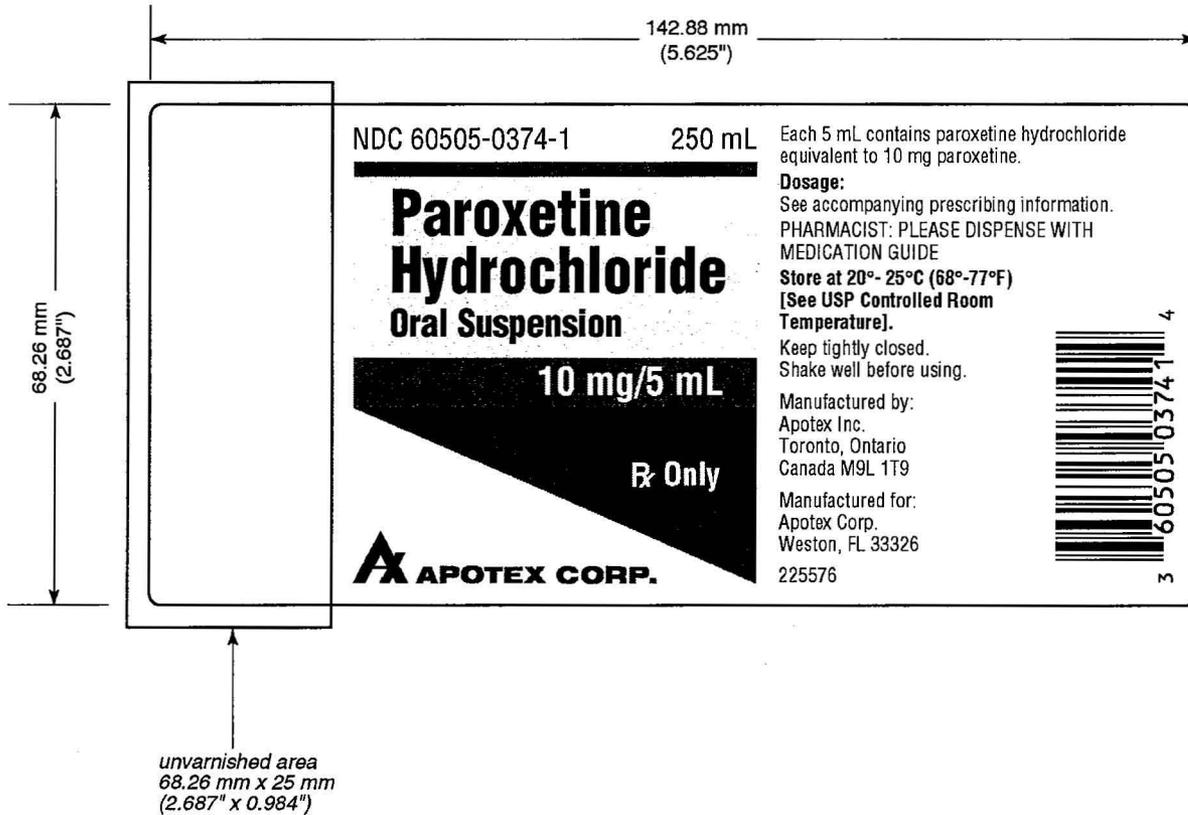
Date of Review: 10-5-06**Date of Submission: 9-29-06****Primary Reviewer: Michelle Dillahunt****Date:****Team Leader: Lillie Golson****Date:**

PRINTED PACKAGING MATERIAL PROOF

Copy of

Date April 10, 2006

(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
10/12/2006 03:38:59 PM
MEDICAL OFFICER

Lillie Golson
10/13/2006 11:44:38 AM
MEDICAL OFFICER .
Lillie Golson for Wm. Peter Rickman

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

ANDA Number: 77-395

Date of Submission: May 3, 2006

Applicant's Name: Apotex Corp.

Established Name: Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL

Labeling Deficiencies:

INSERT

Due to revisions to the current insert labeling for Paxil Tablets (combined insert with Paxil Suspension), approved May 3, 2006, please make the following changes:

1. PRECAUTIONS

- a. Add the following paragraph to appear after the "Discontinuation of Treatment with Paroxetine" subsection;

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.

- b. Add the following paragraph to appear after the "Abnormal Bleeding" subsection;

Serotonin Syndrome: The development of a serotonin syndrome may occur in association with treatment with paroxetine, particularly with concomitant use of serotonergic drugs and with drugs which may have impaired metabolism of paroxetine. Symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia, and tremor. The concomitant use of paroxetine with serotonin precursors (such as tryptophan) is not recommended (see WARNINGS, Potential for Interaction with Monoamine Oxidase Inhibitors and PRECAUTIONS, Drug Interactions).

- c. Drug Interactions, Tryptophan, add the following to follow the last sentence; "(see Serotonin Syndrome)".

- d. Add the following paragraph to appear after the "Pimozide" subsection;

Serotonergic Drugs: Based on the mechanism of action of paroxetine and the potential for serotonin syndrome, caution is advised when PAXIL is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see Serotonin Syndrome).

- e. Triptans, add the following to follow the last sentence; "(see Serotonin Syndrome)".

- f. Pediatric Use, add the following as the second and third paragraphs;

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with paroxetine 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 paroxetine in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received paroxetine 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 Discontinuation of Treatment With Paroxetine)

2. HOW SUPPLIED

- a. Add the established name to precede the description of your product.
- b. Include the flavor of your product to be in accordance with the reference listed drug.

Please revise your insert labeling, as instructed above and submit in final print. 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

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: 250 mL

Satisfactory in FPL as of the May 3, 2006 submission.

file:///C:/Cdsesub1/n77395/N_000/2006-05-03/Labeling/paro_imsu_10mg5ml_lbl_225576.pdf

Carton:

file:///C:/Cdsesub1/n77395/N_000/2006-05-03/Labeling/paro_suur_10mg5ml_ctn_223538.pdf

Professional Package Insert Labeling:

Satisfactory in FPL as of the submission.

BASIS OF APPROVAL:**Patents/exclusivities:****Patent Data – NDA 20-710**

No	Expiration	Use Code	Use	File
6133289	November 19, 2015	U-358	Depression/OCD /PD/SAD	IV
5811436	March 22, 2016			IV
6121291	September 17, 2017	U-286	Depression	IV
6121291	September 17, 2017	U-431	Method for treating PTSD	IV
4721723	June 29, 2007	U-12	Depression	IV
5872132	November 19, 2015		Depression & other disorders - SSRIs	IV
5900423	November 19, 2015		Depression & other disorders - SSRIs	IV
5789449	July 6, 2009	U-285	Depression & SAD/social phobia	IV

Exclusivity Data - NDA 20-710

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There are no unexpired exclusivities listed in the Orange book Database	

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Paxil®

NDA Number: 20-710

NDA Drug Name: Paxil® (paroxetine hydrochloride) Oral Suspension

NDA Firm: SmithKline Beecham

Date of Approval of NDA Insert and supplement #: 3-09-06 (NDA 20-031/S-046) (See FTR #1)

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:

FOR THE RECORD:

1. This review was based on the labeling for Paxil® Tablets (NDA 20-031/S-046) SmithKline Beecham; approved 3/9/06. The last approved labeling for Paxil Suspension (NDA 20-710/S-015,S-016 is 2/6/06. I used the Paxil®tablets insert since this insert includes information on the oral suspension.

2. Patents/exclusivities:

Patent Data – NDA 20-710

No	Expiration	Use Code	Use	File
6133289	November 19, 2015	U-358	Depression/OCD /PD/SAD	IV
5811436	March 22, 2016			IV
6121291	September 17, 2017	U-286	Depression	IV
6121291	September 17, 2017	U-431	Method for treating PTSD	IV
4721723	June 29, 2007	U-12	Depression	IV
5872132	November 19, 2015			IV
5900423	November 19, 2015			IV
5789449	July 6, 2009	U-285	Depression & SAD/social phobia	IV

Exclusivity Data - NDA 20-710

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There are no unexpired exclusivities listed in the Orange book Database	

3. Apotex Inc. is the manufacturer (Section 3.2P. 3.1.7012, V. B 1.2).
4. The inactives are listed accurately in the DESCRIPTION section (p 8, section 2.3, p.1 V B 1.2).
5. Storage/dispensing:
NDA: Store at or below 25°C (77°F).
ANDA: Store at 20 - 25 °C (68-77°F) [see USP Controlled Room Temperature]"
Keep tightly closed. Shake well before using.
6. Product line
NDA: 250 mL
ANDA: 250 mL
7. The drug product is packaged in an HDPE bottle and polypropylene CR cap (Section 3.2 P.2.4 V.B 1.2).

Date of Review: 5-31-06

Date of Submission: 5/3/06

Primary Reviewer: Michelle Dillahunt

Date: 6/8/06

Team Leader: Lillie Golson

Date: 6/5/06

cc:

ANDA: 77-395
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSAM\Apotex\LTRS&REV\77395.na2.labeling.doc
Review

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

ANDA Number: 77-395

Date of Submission: July 7, 2006

Applicant's Name: Apotex Corp.

Established Name: Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL

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: 250 mL

Satisfactory in FPL as of the May 3, 2006 submission.

file:///C:/cdsesub1/n77395/N_000/2006-05-03/Labeling/paro_imsu_10mg5ml_lbl_225576.pdf

Carton:

file:///C:/cdsesub1/n77395/N_000/2006-05-03/Labeling/paro_suor_10mg5ml_ctn_223538.pdf

Professional Package Insert Labeling:

Satisfactory in FPL as of the July 7, 2006 submission.

file:///c:/cdsesub1/N77395/N_000/2006-07-07/Labeling/paro_imsu_10mg_5ml_ins_223529.pdf.pdf

Revisions needed post approval:

INSERT

PRECAUTIONS, Abnormal Bleeding, relocate "Abnormal Bleeding" subsection to appear following the "Serotonin Syndrome" subsection.

BASIS OF APPROVAL:

Patent Data – NDA 20-710

No	Expiration	Use Code	Use	File
6133289	November 19, 2015	U-358	Depression/OCD /PD/SAD	IV
5811436	March 22, 2016			IV
6121291	September 17, 2017	U-286	Depression	IV
6121291	September 17, 2017	U-431	Method for treating PTSD	IV
4721723	June 29, 2007	U-12	Depression	IV
5872132	November 19, 2015		Depression & other disorders - SSRIs	IV
5900423	November 19, 2015		Depression & other disorders - SSRIs	IV
5789449	July 6, 2009	U-285	Depression & SAD/social phobia	IV

Exclusivity Data - NDA 20-710

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There are no unexpired exclusivities listed in the Orange book Database	

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Paxil®

NDA Number: 20-710

NDA Drug Name: Paxil® (paroxetine hydrochloride) Oral Suspension

NDA Firm: SmithKline Beecham

Date of Approval of NDA Insert and supplement #: 3-09-06 (NDA 20-031/S-046) (See FTR #1)

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

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:

FOR THE RECORD:

1. This review was based on the labeling for Paxil® Tablets (NDA 20-031/S-046) SmithKline Beecham; approved 3/9/06. The last approved labeling for Paxil Suspension (NDA 20-710/S-015,S-016 is 2/6/06. I used the Paxil ®tablets insert since this insert includes information on the oral suspension and the revisions applied to both dosage forms.

2. Patents/exclusivities:

Patent Data – NDA 20-710

No	Expiration	Use Code	Use	File
6133289	November 19, 2015	U-358	Depression/ OCD /PD/SAD	IV
5811436	March 22, 2016			IV
6121291	September 17, 2017	U-286	Depression	IV
6121291	September 17, 2017	U-431	Method for treating PTSD	IV
4721723	June 29, 2007	U-12	Depression	IV
5872132	November 19, 2015			IV
5900423	November 19, 2015			IV
5789449	July 6, 2009	U-285	Depression & SAD/social phobia	IV

Exclusivity Data - NDA 20-710

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There are no unexpired exclusivities listed in the Orange book Database	

3. Apotex Inc. is the manufacturer (Section 3.2P. 3.1.7012, V. B 1.2).

4. The inactives are listed accurately in the DESCRIPTION section (p 8, section 2.3, p.1 V B 1.2).
5. Storage/dispensing:
NDA: Store at or below 25°C (77°F).
ANDA: Store at 20 - 25 °C (68-77°F) [see USP Controlled Room Temperature]"
Keep tightly closed. Shake well before using.
6. Product line
NDA: 250 mL
ANDA: 250 mL
7. The drug product is packaged in an HDPE bottle and polypropylene CR cap (Section 3.2 P.2.4 V.B 1.2).

Date of Review: 7-31-06

Date of Submission: 7/7/06

Primary Reviewer: Michelle Dillahunt

Date: 8/1/06

Team Leader: Lillie Golson

Date: 8/2/06

cc:

ANDA: 77-395
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSAM\Apotex\LTRS&REV\77395.ap1.labeling.doc
Review

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

ANDA Number: 77-395

Date of Submission: February 9, 2005

Applicant's Name: Apotex Corp.

Established Name: Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL

Labeling Deficiencies

1. CONTAINER - 250 mL

Include a statement; "PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE" on the principal display panel.

2. CARTON - 250 mL

See comment under CONTAINER.

3. INSERT

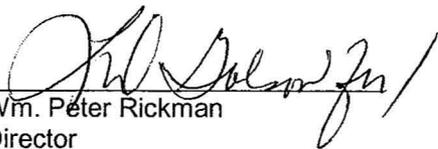
a. GENERAL

Revise your insert labeling to be in accord with the reference listed drug, Paxil® Oral Suspension, approved 7-13-05. You should address all patents and exclusivities listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") and revise your labeling accordingly.

Please revise your labels and labeling, as instructed above, and submit final print. The electronic labeling rule published December 11, 2003, (68 FR 69009) that requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (<http://www.fda.gov/cder/guidance/5004fnl.htm>). The guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- <http://www.fda.gov/cder/cdernew/listserv.html> or <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 the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.


Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs

Attachment: RLD insert

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:

Satisfactory in FPL as of the submission.

Professional Package Insert Labeling:

Satisfactory in draft as of the submission. (electronic)

BASIS OF APPROVAL:

Patents/exclusivities:

Patent Data – NDA 20-710

No	Expiration	Use Code	Use	File
6133289	November 19, 2015	U-358	Depression/OCD /PD/SAD	IV
5811436	March 22, 2016			IV
6121291	September 17, 2017	U-286	Depression	IV
6121291	September 17, 2017	U-431	Method for treating PTSD	IV
4721723	June 29, 2007	U-12	Depression	IV
5872132	November 19, 2015		Depression & other disorders - SSRIs	IV
5900423	November 19, 2015		Depression & other disorders - SSRIs	IV
5789449	July 6, 2009	U-285	Depression & SAD/social phobia	IV

Exclusivity Data - NDA 20-710

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There are no unexpired exclusivities listed in the Orange book Database	

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Paxil®

NDA Number: 20-710

NDA Drug Name: Paxil® (paroxetine hydrochloride) Oral Suspension

NDA Firm: SmithKline Beecham

Date of Approval of NDA Insert and supplement #: 7-13-05 (S-042) (See FTR #1)

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 28		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:

FOR THE RECORD:

1. This review was based on the labeling for Paxil® Tablets (NDA 20-031/S-042, S-045) SmithKline Beecham; approved 7/13/05 and 1/12/05. There are no recent labeling supplement approvals for NDA 20-710 Paxil® Oral Suspension. I have used the Paxil® tablets insert since this insert includes information on the oral suspension.

S-042 provides for revisions to the PRECAUTIONS-Drugs Metabolized by Cytochrome P450IID and CLINICAL PHARMACOLOGY section. Because S-042 was submitted before the revisions for the suicidality language were approved, I am using the language in S-045 for the suicidality information.

I have created a model combining both supplements to be used by the generics.

2. Patents/exclusivities:

Patent Data – NDA 20-710

No	Expiration	Use Code	Use	File
6133289	November 19, 2015	U-358	Depression/OCD /PD/SAD	IV
5811436	March 22, 2016			IV
6121291	September 17, 2017	U-286	Depression	IV
6121291	September 17, 2017	U-431	Method for treating PTSD	IV
4721723	June 29, 2007	U-12	Depression	IV
5872132	November 19, 2015			IV
5900423	November 19, 2015			IV
5789449	July 6, 2009	U-285	Depression & SAD/social phobia	IV

Exclusivity Data - NDA 20-710

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There are no unexpired exclusivities listed in the Orange book Database	

3. **Apotex Inc. is the manufacturer (Section 3.2P. 3.1.7012, V. B 1.2).**
4. **The inactives are listed accurately in the DESCRIPTION section (p 8, section 2.3, p.1 V B 1.2).**
5. **Storage/dispensing:**
NDA: Store at or below 25°C (77°F).
ANDA: Store at 20 - 25 °C (68-77°F) [see USP Controlled Room Temperature]"
Keep tightly closed. Shake well before using.
6. **Product line**
NDA: 250 mL
ANDA: 250 mL
7. **The drug product is packaged in an HDPE bottle and polypropylene CR cap (Section 3.2 P.2.4 V.B 1.2).**

Date of Review: 9-1-05

Date of Submission: 2/9/05

Primary Reviewer: Michelle Dillahunt

Date: *9/2/05*

Team Leader: Lillie Golson

Date: *9/7/05*

CC:

ANDA: 77-395
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSAM\Apotex\LTRS&REV\77395.na1.labeling.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-395

CHEMISTRY REVIEWS

#3



CHEMISTRY REVIEW



ANDA 77-395

**Paroxetine Hydrochloride
Oral Suspension, 10 mg/5 mL
(First Generic)**

Apotex Corp.

**Nashed I. Samaan, Ph.D.
CD II, OGD**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary.....	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	
A. Reviewer's Signature.....	
B. Endorsement Block.....	
C. CC Block.....	
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	9
S DRUG SUBSTANCE [Name, Manufacturer].....	9
P DRUG PRODUCT [Name, Dosage form].....	15
A APPENDICES.....	27
R REGIONAL INFORMATION.....	27
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	28
A. Labeling & Package Insert.....	28
B. Environmental Assessment Or Claim Of Categorical Exclusion.....	29
III. List Of Deficiencies To Be Communicated.....	



Chemistry Review Data Sheet

1. ANDA: 77-395
2. REVIEW #: 3
3. REVIEW DATE: 09-12-06
4. REVIEWER: Nashed I. Samaan, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	11-18-04
Refuse to Receive	01-14-05
Amendment	02-09-05
Date (received) acceptable for filing	02-10-05
CMC deficiency letter (Rev. # 1)	08-18-05
Minor amendment	12-23-05
CMC deficiency letter (Rev. # 2)	07-26-06

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor amendment (subject of this review)	08-04-06

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Corp
Address	2400 North Commerce Parkway, Suite 400 Weston, FL 33326
Representative	Tammy McIntire
Telephone	(954) 349-4217
Fax	(905) 508-2359

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION:

Chemistry Review Data Sheet

The RLD is GlaxoSmithKline's Paxil® (Paroxetine HCl) Oral Suspension, 10mg/5ml (NDA 20-710, approved on Jun 25, 1997).

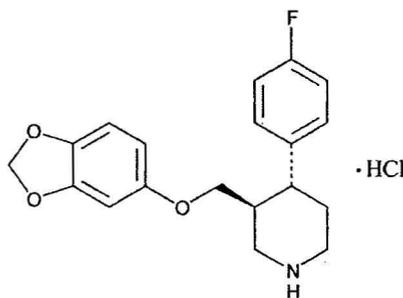
10. PHARMACOL. CATEGORY: Antidepressants
11. DOSAGE FORM: Oral Suspension
12. STRENGTH/POTENCY: 10 mg/5 mL
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Paroxetine HCl

Piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-, hydrochloride, (3*S*-*trans*)-(-)-(3*S*,4*R*)-4-(*p*-Fluorophenyl)-3-[(3,4-methylenedioxy)phenoxy]methyl]piperidine HCl [78246-49-8].

Formula: C₁₉H₂₀FNO₃·HCl

Molecular Weight: 365.83



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS LOA PP # *
12770	II	Apotex Corp.	Paroxetine HCl (anhydrous) (DS)	1	Adequate	09-12-06 By N. Samaan	Section 1.4.1
(b) (4)				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
							Section 1.4.1
				1	Adequate	6-20-05 N. Samaan	Section 1.4.1

* Copies of LOA are enclosed in vol. 1 under "letter of authorization" Section 1.4.1

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Satisfactory	09-12-06	N. Samaan
Labeling	Acceptable	08-02-06	M. Dillahunt
Bioequivalence	Acceptable	07-31-06	Sikta Pradhan
Microbiology	N/A		
EES	Acceptable	07-06-06	S. Adams
Methods Validation	Not required		
EA	Categorical Exclusion		Per 21 CFR
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

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

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

Executive Summary Section

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

The 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)****1. Drug Substance:**

Paroxetine Hydrochloride is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'fluorophenyl)-3S-(3'-4-methylenedioxyphenoxy) methyl] piperidine hydrochloride anhydrous and has the molecular formula of C₁₉H₂₀FN₃.HCl. The molecular weight is 365.83 (anhydrous) (329.4 as free base). It is a white to off-white crystalline powder, with a melting range of 116° to 120°C. Freely soluble in ethanol and methanol. Slightly soluble in water and octanol.

(b) (4)

2. Drug product

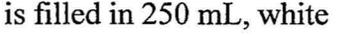
Executive Summary Section

The drug product is based on the approved listed drug GlaxoSmithKline's Paxil® (Paroxetine HCl) Oral Suspension, 10mg/5ml (NDA 20-710, approved date Jun 25, 1997

a. Product Description:

Paroxetine Hydrochloride Oral Suspension is an orally administered psychotropic drug. Each 5 mL of orange-colored suspension with an orange aroma contains Paroxetine hydrochloride equivalent to Paroxetine, 10 mg. Inactive ingredients consist of bitter blocker type flavor, FD&C Yellow No.6, glycerin, methylparaben, microcrystalline cellulose and carboxymethyl cellulose sodium, natural orange blood Sicilian flavor, propylene glycol, propylparaben, purified water, saccharin sodium, 30% simethicone emulsion and sorbitol solution.

The drug product is manufactured by addition of  (b) (4)

 is filled in 250 mL, white opaque HDPE induction sealed bottles.

b. Packaging:

Paroxetine Hydrochloride Oral Suspension is orange-colored suspension with an orange aroma, 10 mg/5 mL in 250 mL, white opaque HDPE induction sealed bottles with a child resistant white polypropylene cap.

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

Oral administration for the treatment of major depressive disorder,

Storage conditions: store at controlled room temperature 20–25°C (68–77° F).

Tentative expiration dating: 24 months based on 6 months accelerated data.

C. Basis for Approvability or Not-Approval Recommendation

The application is APPROVABLE.

Chemistry : Satisfactory on 09-12-06

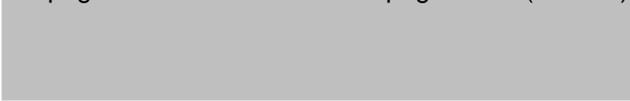
Labeling : Satisfactory on 08-02-06

Bioequivalence: Satisfactory on 07-31-06

Microbiology : N/A

EES : Acceptable on 07-06-06

33 pages are withheld after this page as b4 (CCI/TS)





CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

cc: ANDA 77-395
DUP
Field Copy

Endorsement:

HFD-647/Nashed I. Samaan Ph.D./ 09-12-06

HFD-647/U.V. Venkataram Ph.D./ 09.13.06

HFD-617/ C. Wiseman /10.04.06

Nashed I. Samaan 10-5-06

U.V. Venkataram

C. Wiseman

10/5/06

10/5/06

F/T by: caw

V:\FIRMSAMAPOTEXLTRS&REV\77395N03_RNS

TYPE OF LETTER:

Recommend approval

2 pages are withheld following this page as b4
(CCI/TS)



ANDA 77-395

**Paroxetine Hydrochloride
Oral Suspension, 10 mg/5 mL
(First Generic)**

Apotex Corp.

**Nashed I. Samaan, Ph.D.
CD II, OGD**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary.....	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used	8
C. Basis for Approvability or Not-Approval Recommendation	9
III. Administrative.....	
A. Reviewer's Signature	
B. Endorsement Block	
C. CC Block.....	
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Name, Manufacturer].....	10
P DRUG PRODUCT [Name, Dosage form]	18
A APPENDICES.....	36
R REGIONAL INFORMATION.....	36
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	37
A. Labeling & Package Insert.....	37
B. Environmental Assessment Or Claim Of Categorical Exclusion.....	38
III. List Of Deficiencies To Be Communicated.....	



Chemistry Review Data Sheet

1. ANDA: 77-395
2. REVIEW #: 2
3. REVIEW DATE: 06-30-06
4. REVIEWER: Nashed I. Samaan, Ph.D
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	11-18-04
Refuse to Receive	01-14-05
Amendment	02-09-05
Date (received) acceptable for filing	02-10-05
CMC deficiency letter (Rev. # 1)	08-18-05

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor amendment (subject of this review)	12-23-05

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Corp
Address	2400 North Commerce Parkway, Suite 400 Weston, FL 33326
Representative	Tammy McIntire
Telephone	(954) 349-4217
Fax	(905) 508-2359

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

The RLD is GlaxoSmithKline's Paxil® (Paroxetine HCl) Oral Suspension, 10mg/5ml (NDA 20-710, approved on Jun 25, 1997).

10. PHARMACOL. CATEGORY: Antidepressants
11. DOSAGE FORM: Oral Suspension
12. STRENGTH/POTENCY: 10 MG/5 ML
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

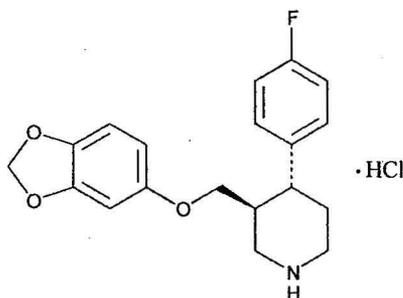
Chemical Name: Paroxetine HCl

Piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-, hydrochloride, (3*S*-*trans*)-.

(-)-(3*S*,4*R*)-4-(*p*-Fluorophenyl)-3-[(3,4-methylenedioxy)phenoxy]methyl]piperidine HCl [78246-49-8].

Formula: C₁₉H₂₀FNO₃·HCl

Molecular Weight: 365.83





CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS LOA PP # *
12770	II	Apotex Corp.	Paroxetine HCl (anhydrous) (DS)	1	Adequate	06-30-06 (IR)	Section 1.4.1
(b) (4)				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
							Section 1.4.1
				1	Adequate	6-20-05 N. Samaan	Section 1.4.1

* Copies of LOA are enclosed in vol. 1 under "letter of authorization" Section 1.4.1

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Not Satisfactory	06-30-06	N. Samaan
Labeling	Acceptable	05-25-06	M. Dillahunt
Bioequivalence	Pending		
Microbiology	N/A		
EES	Acceptable	07-06-06	S. Adams
Methods Validation	Not required		
EA	Categorical Exclusion		Per 21 CFR
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for A/NDA 77- 395

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is not approvable, Minor CMC regarding viscosity and Bio review .

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)

1. Drug Substance:

Paroxetine Hydrochloride is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'fluorophenyl)-3S-(3'-4-methylenedioxyphenoxy)methyl] piperidine hydrochloride anhydrous and has the molecular formula of C₁₉H₂₀FN₀₃.HCl. The molecular weight is 365.83 (anhydrous) (329.4 as free base). It is a white to off-white crystalline powder, with a melting range of 116° to 120°C. Freely soluble in ethanol and methanol. Slightly soluble in water and octanol.

(b) (4)

Executive Summary Section

(b) (4)

2. Drug product

The drug product is based on the approved listed drug GlaxoSmithKline's Paxil® (Paroxetine HCl) Oral Suspension, 10mg/5ml (NDA 20-710, approved date Jun 25, 1997

a. Product Description:

Paroxetine Hydrochloride Oral Suspension is an orally administered psychotropic drug. Each 5 mL of orange-colored suspension with an orange aroma contains paroxetine hydrochloride equivalent to paroxetine, 10 mg. Inactive ingredients consist of bitter blocker type flavor, FD&C Yellow No.6, glycerin, methylparaben, microcrystalline cellulose and carboxymethylcellulose sodium, natural orange blood Sicilian flavor, propylene glycol, propylparaben, purified water, saccharin sodium, 30% simethicone emulsion and sorbitol solution.

The drug product is manufactured by addition of

(b) (4)

is filled in 250 mL, white opaque HDPE induction sealed bottles.

b. Packaging:

Paroxetine Hydrochloride Oral Suspension is orange-colored suspension with an orange aroma, 10 mg/5 mL in 250 mL, white opaque HDPE induction sealed bottles with a child resistant white polypropylene cap.

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

Oral administration for the treatment of major depressive disorder,

Storage conditions: store at controlled room temperature 20–25°C (68–77° F).

Tentative expiration dating: 24 months based on 6 months accelerated data.



Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The application is NOT APPROVABLE.

Chemistry : Not Satisfactory on 06-30-06 (revised 7-20-06)
Labeling : Satisfactory on 05-25-06
Bioequivalence: Pending.
Microbiology : N/A
EES : Acceptable on 07-06-06

31 pages after this page are withheld as b4 (CCI/TS)



Chemistry Assessment Section

**cc: ANDA 77-395
DUP
DIV COPY
Field Copy**

Endorsement:

HFD-647/Nashed I. Samaan Ph.D./ 06-30-06 (revised 7-20-06)
HFD-647/U.V. Venkataram Ph.D./ 07.21.06 (07.24.06 – corrections to final)
HFD-617/ C. Wiseman /07.21.06

F/T by: caw

V:\FIRMSAM\APOTEX\LTRS&REV\77395N02_RNS

TYPE OF LETTER:

Minor Amendment



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

A. Reviewer's Signature Nashed I. Samaan, Ph.D., 06-30-06

B. Endorsement Block

HFD-647/Nashed I. Samaan Ph.D./ 06-30-06 (revised 7-20-06) *Nashed 7-21-06*

HFD-647/U.V. Venkataram Ph.D./ 07.21.06 *U.V. Venkataram*

HFD-617/ C. Wiseman /07.21.06

C. Wiseman 7/25/06

7/24/06

C. CC Block

F/T by: caw

V:FIRMSAMAPOTEXLTRS&REV77395N02_RNS

TYPE OF LETTER:

Minor Amendment

3 pages are withheld following this page
as b4

#1



CHEMISTRY REVIEW



ANDA 77-395

**Paroxetine Hydrochloride
Oral Suspension, 10 mg/5 mL
(First Generic)**

Apotex Corp.

**Nashed I. Samaan, Ph.D.
CD II, OGD**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary.....	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used	8
C. Basis for Approvability or Not-Approval Recommendation	9
III. Administrative.....
A. Reviewer's Signature
B. Endorsement Block
C. CC Block.....
Chemistry Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	11
S DRUG SUBSTANCE [Name, Manufacturer].....	11
P DRUG PRODUCT [Name, Dosage form]	18
A APPENDICES.....	31
R REGIONAL INFORMATION.....	31
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	33
A. Labeling & Package Insert.....	33
B. Environmental Assessment Or Claim Of Categorical Exclusion.....	33
III. List Of Deficiencies To Be Communicated.....



Chemistry Review Data Sheet

1. ANDA: 77-395
2. REVIEW #: 1
3. REVIEW DATE: 07-11-05
4. REVIEWER: Nashed I. Samaan, Ph.D
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	11-18-04
Refuse to Receive	01-14-05
amendment	02-09-05
Date (received) acceptable for filing	02-10-05

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (acceptable for filing)	02-10-05

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Corp
Address	616 Heathrow Drive Lincolnshire, IL 60069
Representative	Kalpesh Shroff
Telephone	(847) 279-7740
Fax	(847) 353-2982

8. DRUG PRODUCT NAME/CODE/TYPE:

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

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

The RLD is GlaxoSmithKline's Paxil® (Paroxetine HCl) Oral Suspension, 10mg/5ml (NDA 20-710, approved on Jun 25, 1997).

10. PHARMACOL. CATEGORY: Antidepressants

11. DOSAGE FORM: Oral Suspension

12. STRENGTH/POTENCY: 10 MG/5 ML

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

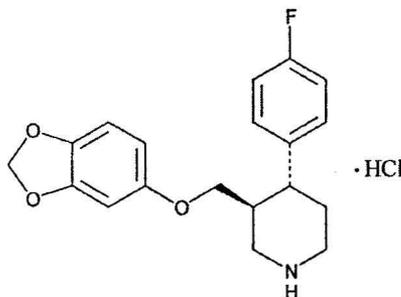
Chemical Name: Paroxetine HCl

Piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-, hydrochloride, (3*S*-*trans*)-.

(-)-(3*S*,4*R*)-4-(*p*-Fluorophenyl)-3-[(3,4-methylenedioxy)phenoxy]methyl]piperidine HCl [78246-49-8].

Formula: C₁₉H₂₀FNO₃·HCl

Molecular Weight: 365.83





CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS LOA PP # *
12770	II	Apotex Corp.	Paroxetine HCl (anhydrous) (DS)	1	Adequate on 12-13 -99	06-13-05 (IR)	Section 1.4.1
(b) (4)				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
				4	N/A		Section 1.4.1
							Section 1.4.1
			1	Adequate	6-20-05 N. Samaan	Section 1.4.1	

* Copies of LOA are enclosed in vol. 1 under "letter of authorization" Section 1.4.1

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Chemistry	Minor	08-10-05	N. Samaan
Labeling	Pending		
Bioequivalence	Deficient	05-19-05	Phelicia B. Bush
Microbiology	N/A		
EES	Pending		
Methods Validation	Not required		
EA	Categorical Exclusion		Per 21 CFR
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for A/NDA 77- 395

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is NOT APPROVABLE at this stage. The deficiencies are listed in the letter.

Chemistry : Not Approvable, MINOR
Labeling : Pending
Bioequivalence: Deficient on 5-19-05 by Phelicia B. Bush
Microbiology : N/A
EES : Pending

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)

1. Drug Substance:

Paroxetine Hydrochloride is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'fluorophenyl)-3S-(3'-4-methylenedioxyphenoxy)methyl] piperidine hydrochloride anhydrous and has the molecular formula of $C_{19}H_{20}FN_3 \cdot HCl$. The molecular weight is 365.83 (anhydrous) (329.4 as free base). It is a white to off-white crystalline powder, with a melting range of 116° to 120°C. Freely soluble in ethanol and methanol. Slightly soluble in water and octanol.

(b) (4)

Executive Summary Section



(b) (4)

2. Drug product

The drug product is based on the approved listed drug GlaxoSmithKline's Paxil® (Paroxetine HCl) Oral Suspension, 10mg/5ml (NDA 20-710, approved date Jun 25, 1997

a. Product Description:

Paroxetine Hydrochloride Oral Suspension is an orally administered psychotropic drug. Each 5 mL of orange-colored suspension with an orange aroma contains paroxetine hydrochloride equivalent to paroxetine, 10 mg. Inactive ingredients consist of bitter blocker type flavor, FD&C Yellow No.6, glycerin, methylparaben, microcrystalline cellulose and carboxymethylcellulose sodium, natural orange blood Sicilian flavor, propylene glycol, propylparaben, purified water, saccharin sodium, 30% simethicone emulsion and sorbitol solution.

The drug product is manufactured by addition of

(b) (4)

is filled in 250 mL, white opaque HDPE induction sealed bottles.

b. Packaging:

Paroxetine Hydrochloride Oral Suspension is orange-colored suspension with an orange aroma, 10 mg/5 mL in 250 mL, white opaque HDPE induction sealed bottles with a child resistant white polypropylene cap.

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

Oral administration for the treatment of major depressive disorder,

Storage conditions: store at controlled room temperature 20–25°C (68–77° F).



Executive Summary Section

Tentative expiration dating: 24 months based on 6 months accelerated data.

C. Basis for Approvability or Not-Approval Recommendation

The application is NOT APPROVABLE at this stage. The deficiencies are listed in the letter.

Chemistry : Not Approvable, MINOR
Labeling : Pending
Bioequivalence: Deficient on 5-19-05 by Phelicia B. Bush
Microbiology : N/A
EES : Pending



Executive Summary Section

III. Administrative

A. Reviewer's Signature Nashed I. Samaan, Ph.D., 07-11-05

B. Endorsement Block

HFD-647/Nashed I. Samaan Ph.D./ 07-11-05 & 08-10-05
HFD-647/U.V. Venkataram Ph.D./
HFD-617/ C. Wiseman /8.16.05

Nashed I. Samaan
8-16-05

C. CC Block: ANDA 77- 395
ANDA DUP
DIV FILE
Field Copy

F/T by: cw/8.16.05

V:\FIRMSAM\APOTEX\LTRS&REV\77395N01.RNS

TYPE OF LETTER: NOT APPROVABLE – MINOR

26 pages are withheld after this page as b4
(CCI/TS)



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

A. Reviewer's Signature Nashed I. Samaan, Ph.D., 07-11-05

B. Endorsement Block

HFD-647/Nashed I. Samaan Ph.D./ 07-11-05 & 08-10-05 *Nashed I. Samaan 8-16-05*

HFD-647/U.V. Venkataram Ph.D./ 8.11.05

HFD-617/ C. Wiseman /8.17.05

*U.V. Venkataram
8/18/05*

*C. Wiseman
8/17/05*

C. CC Block

F/T by: cw/8.17.05

V:\FIRMSAM\APOTEX\LTRS&REV\77395N01.RNS

TYPE OF LETTER: NOT APPROVABLE – MINOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-395

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-395
Drug Product Name	Paroxetine Hydrochloride Oral Suspension
Strength	10 mg/5 mL
Applicant Name	Apotex Inc.
Submission Date(s)	June 14, 2006
Amendment Date(s)	
First Generic	Yes
Reviewer	Sikta Pradhan
File Location	V:\firmsam\apotex\ltrs&rev\77395A0606.doc

Review of an Amendment

I. Executive Summary

The firm had submitted a single-dose, 2-way crossover fasting bioequivalence (BE) study and a fed bioequivalence study, comparing the test product, Paroxetine Hydrochloride Oral Suspension 10 mg/5 mL, with the RLD product, Paxil® Oral Suspension, 10 mg/5 mL of GlaxoSmithKline. The fasting and fed BE studies were acceptable. But the dissolution testing was found incomplete. The firm was advised to clarify if each dosage unit used for dissolution testing was taken from 12 separate bottles as recommended for oral suspensions. The firm was also advised to acknowledge its acceptance of the FDA-recommended specification of NLT (b) (4) (Q) in 30 minutes. The application was incomplete.

In the amendments dated June 14, 2006, the firm has reported additional dissolution data. The dissolution testing was conducted according to the condition specified by the Agency. Each dosage unit used for dissolution testing was taken from 12 separate bottles as recommended for oral suspensions. The firm has also provided acceptable information on the potency, content uniformity and lot sizes as requested by the Division of Bioequivalence.

The firm has accepted the FDA-recommended dissolution method and specifications. The application is now complete with no deficiencies.

AMENDMENT REVIEW

1. Agency Comment: We acknowledge that you have accepted the following dissolution method:

The dissolution testing should be conducted in 900 mL of Simulated Gastric Fluid without pepsin at 37°C using USP Apparatus 2 (paddle) at 100 rpm. The test product should meet the following specification: Not less than (b)(4)%(Q) of the labeled amount dissolved in 30 minutes.

Firm's Response: The dissolution testing will be conducted as per the dissolution method outlined above.

2. Agency Comment: Your dissolution testing is incomplete. It is not clear from the data submitted if each dosage unit used for dissolution testing was taken from the same bottle or from different bottles. Please note that 12 dosage units should be from 12 separate bottles. If the dosage units were not taken from separate bottles, please conduct and submit dissolution testing on the test and reference products taking each dosage unit from separate bottles. In your response, please also acknowledge your acceptance of the FDA-recommended dissolution specification.

Firm's Response: As requested, the dissolution testing has been conducted on 12 dosage units from 12 separate bottles for both the test and reference products. The comparative dissolution data are provided below.

In Vitro Dissolution (Amendment Submitted on June 14, 2006, Attachment 4)

Source of Method (USP, FDA or Firm)	FDA*
Medium	Simulated gastric fluid without pepsin
Volume (mL)	900 mL @ 37° C
USP Apparatus type	2 (paddle)
Rotation (rpm)	100
Firm's proposed specifications	None
FDA-recommended specifications	NLT (b)(4), (Q) in 30 min.

Test: Paroxetine HCl Oral Suspension				Reference: Paxil ^R		
Lot No GL6385				Lot No 16P15		
Strength: 10 mg/5 mL				Strength: 10 mg/5 mL		
No. of Units: 12				No. of Units: 12		
Time (min)	Mean	Range	% CV	Mean	Range	% CV
0						
5	89.3	(b)(4)	1.9	56.6	(b)(4)	10.2
10	94.1		1.0	86.4		5.3
15	94.1		1.1	91.6		3.0
20	94.3		1.6	93.0		2.3
30	95.0		1.3	94.3		2.0
45	95.0		1.1	95.2		1.7

*There is no USP dissolution method for this drug product

Comment: The dissolution testing is acceptable. The firm has acknowledged its acceptance of the FDA-recommended dissolution method and specification.

3. Agency Comment: Please provide potency and content uniformity of the test and potency of the reference listed drug used in the bioequivalence studies. Please also provide the bio-batch size and the production batch size of the test product.

Firm's Response: As requested, the potency and content uniformity of the test product and potency of the reference listed drug product used in the bioequivalence studies have been provided in the table below.

<u>Products</u>	<u>Content Uniformity</u>	<u>Potency</u>
Test	(b) (4)	(b) (4)
Reference		(b) (4)

The batch size of the bio-batch and the production batch (bulk Batch No. GL6384/ Finished Product Batch No. is (b) (4)

4. Agency Comment: From the Tables of Reanalysis of Study (both fasting and fed) Samples you provided, it is not clear if those reanalyzed values were used in the statistical analysis. Please clarify.

Firm's Response: All samples referred to in Table 8 "Reanalysis of Study Samples" in the studies (both fasting and fed) were reanalyzed because there was no acceptable original value. In these studies the reanalysis generated the only reportable value that there is no recalculation value to consider. Therefore, in all cases the reanalyzed sample values were used in the statistical analysis.

Reviewer's Comments

The firm responses to the Agency comments are acceptable. The in vivo and in vitro bioequivalence studies conducted on the test product are acceptable. Therefore, the application is acceptable with no deficiency.

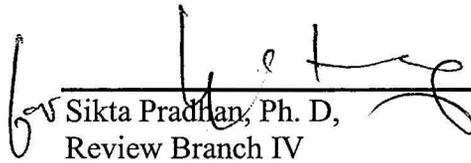
Recommendations

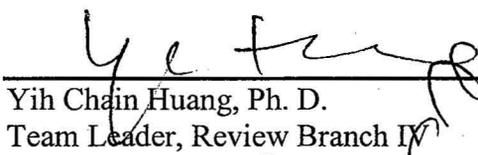
1. The single-dose, fasting and non-fasting bioequivalence studies (20 mg dose) conducted by Apotex Inc. on the test product, Paroxetine Oral Suspension, 10 mg/5 mL, lot # GL6385, comparing it with the reference product, Paxil® Oral Suspension, 10 mg/5 mL, lot # X103P15 of GlaxoSmithKline, are acceptable.
2. The dissolution testing conducted by Apotex Inc. on the test product, Paroxetine Suspension, 10 mg/5 mL, lot # GL6385, comparing it with the reference product, Paxil® Suspension, 10 mg/5 mL, lot # X103P15 of

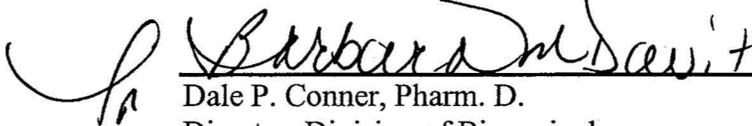
GlaxoSmithKline is also acceptable. The firm has acknowledged its acceptance of the FDA-recommended dissolution method and specification.

The dissolution testing should be conducted in 900 mL of Simulated gastric fluid without pepsin at 37°C using USP apparatus 2 (paddle) at 100 rpm.

The test product should meet the following specification: NLT (b) (4) (Q) dissolved in 30 minutes.


Sikta Pradhan, Ph. D.
Review Branch IV
Date 7/31/2006


Yih Chai Huang, Ph. D.
Team Leader, Review Branch IV
Date 7/31/2006


Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Date 7/31/06

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-395

APPLICANT: Apotex Inc.

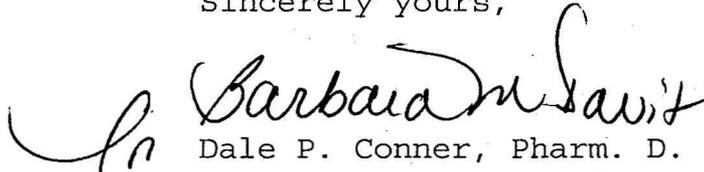
DRUG PRODUCT: Paroxetine Oral Suspension, 10 mg/5 mL

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

1. We acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in 900 mL of Simulated Gastric Fluid without pepsin at 37°C using USP Apparatus 2 (paddle) at 100 rpm. The test product should meet the following specification: Not less than (b) (4) (Q) of the labeled amount of drug is dissolved in 30 minutes.

Sincerely yours,



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

CC: ANDA 77-395
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

HFD-650 / Bio Drug File
HFD-650 / Reviewer: S. Pradhan

Endorsements: (Final with Dates)

HFD-650/ S. Pradhan

HFD-650/ Y. Huang

HFD-650/ D. Conner

HFD-650/ Fritsch

YKH 7/3/2006
BMD 7/31/06

Sh

V:\FIRMSAM\Apotex\ltrs&rev\77395A0606.doc
Printed in final on

BIOEQUIVALENCE - Acceptable

Submission date: June 14, 2006

1. STUDY Amendment (STA)

Strength: 10 mg/5 mL

(New dissol data) *OK*

Acceptable: **AC**

OUTCOME DECISIONS: AC: Acceptable

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-395
Drug Product Name	Paroxetine Hydrochloride Oral Suspension
Strength	10 mg/5 mL
Applicant Name	Apotex Inc.
Submission Date(s)	November 18, 2004 February 9, 2005 ✓
Amendment Date(s)	August 16, 2005 (Dissolution Amendment) ✓
First Generic	Yes
Reviewer	Sikta Pradhan
File Location	V:\firmsam\apotex\ltrs&rev\77395N1104.doc

I. Executive Summary

The firm has submitted a single-dose, 2-way crossover fasting bioequivalence (BE) study and a fed bioequivalence study, comparing the test product, Paroxetine Hydrochloride Oral Suspension 10 mg/5 mL, with the RLD product, Paxil® Oral Suspension, 10 mg/5 mL of GlaxoSmithKline. The fasting study was performed in 36 healthy male subjects at a dose of 10mL of 10 mg/5mL. The in vivo fasting study results for Paroxetine (point-estimate, 90% CI for AUC_t 1.00, 91.34-108.54; AUC_{inf} 1.00, 92.10-109.38; C_{max} 0.99, 91.71-107.38) demonstrate the test product's bioequivalence in the fasted state. The fed study was conducted in 35 healthy male subjects. The point-estimates and 90% CI of the fed study are as follows: for AUC_t, 1.04, 97.74-110.28; AUC_{inf}, 1.06, 99.63-113.38; C_{max}, 1.01, 94.79-108.48. The fed BE study is also acceptable.

The dissolution testing was reviewed previously (77395D1104.doc) and the firm was advised to conduct the dissolution testing using the FDA-recommended method. The dissolution testing data in the dissolution amendment submitted on August 16, 2005 are acceptable. However, the dissolution testing is incomplete. The firm should be advised to acknowledge its acceptance of the FDA-recommended specification of NLT (b) (4) (Q) in 30 minutes. The firm also needs to clarify if each dosage unit used for dissolution testing was taken from 12 separate bottles as recommended for oral suspensions. The application is incomplete.

II. Table of Contents

I.	Executive Summary.....	1
II.	Table of Contents.....	1
III.	Submission Summary.....	2
A.	Drug Product Information.....	2
B.	PK/PD Information.....	3

C.	Contents of Submission	4
D.	Pre-Study Bioanalytical Method Validation.....	5
1.	Single-dose Fasting Bioequivalence Study.....	6
2.	Single-dose Fed Bioequivalence Study	7
E.	Formulation	8
F.	In Vitro Dissolution (Amendment Submitted on August 16, 2005).....	8
G.	Waiver Request(s).....	8
H.	Deficiency Comments	8
I.	Recommendations.....	9
IV.	Appendix	10
A.	Individual Study Reviews.....	10
1.	Single-dose Fasting Bioequivalence Study.....	10
a)	Study Design.....	10
b)	Clinical Results	12
c)	Bioanalytical Results	15
d)	Pharmacokinetic Results.....	16
2.	Single-dose Fed Bioequivalence Study	19
a)	Study Design.....	19
b)	Clinical Results.....	21
c)	Bioanalytical Results	25
B.	Formulation Data.....	29
C.	Consult Reviews	30
D.	SAS Output.....	31
E.	Additional Attachments	31

III. Submission Summary

A. Drug Product Information

Test Product	Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL
Reference Product	Paxil® Oral Suspension, 10 mg/5 mL
RLD Manufacturer	GlaxoSmithKline
NDA No.	020710
RLD Approval Date	June 25, 1997
Indication	Treatment of major depressive disorder, obsessive compulsive disorder, panic disorder, and social anxiety.

B. PK/PD Information

(Source: PDR)

Bioavailability	Paroxetine is equally bioavailable from the oral suspension and tablet. Paroxetine HCl is completely absorbed after oral dosing of a solution of the hydrochloride salt. (Absolute bioavailability is not reported in PDR.)
Food Effect	AUC was only slightly increased (6%) when drug was administered with food but the C_{max} was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.
T_{max}	5.2 hours after its ingestion (dose; 30 mg/day for 10 days)
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.
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	Plasma elimination half- life is 21 Hours (dose; 30 mg/day for 10 days)
Relevant OGD or DBE History	<ul style="list-style-type: none"> • The Division of Bioequivalence has reviewed a number of acceptable biostudies (ANDAs #75-566, 75-716, (b) (4), 76-618, 76-968, etc.) on Paroxetine HCl tablets. (No review or control document found on suspension.) • The FDA recommends that ANDA sponsors for Paroxetine HCl tablets conduct two bioequivalence studies under fasting and non-fasting conditions on highest strength and the lower strengths are eligible for biowaivers • Conduct dissolution testing in 900 mL Simulated gastric fluid without pepsin using USP apparatus 2 (paddle) at 100 rpm. The test product should meet

the following specification: NLT (b) (4) (Q) of labeled amount of drug is dissolved in 30 minutes.

Agency Guidance None
 Drug Specific Issues (if any) None

C. Contents of Submission

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

D. Pre-Study Bioanalytical Method Validation

PARO-IMSU-01NB01-2FA
Internal Study Code: PX1543

Information Requested	Data
Bioanalytical method validation report location	Section 16.6
Analyte	Paroxetine
Internal Standard (IS)	(b) (4)
Method description	Liquid-liquid extraction, followed by MS detection after reversed phase HPLC on a C18 column
Limit of quantitation	0.050 ng/mL
Average recovery of drug	68.72 %
Average recovery of IS	79.14 %
Standard curve concentrations	(b) (4) ng/mL
QC concentrations	QC A: 0.150 ng/mL QC B: 17.518 ng/mL QC C: 35.035 ng/mL
QC Intraday precision range	QC A: 4.6 to 9.8 % QC B: 2.6 to 8.8 % QC C: 1.0 to 10.1 %
QC Intraday accuracy range	QC A: -12.0 to 2.0 % QC B: -10.8 to 6.2 % QC C: -9.5 to 0.7 %
QC Interday precision range	6.1 to 8.2 %
QC Interday accuracy range	-4.7 to -1.0 %
Bench-top stability	26 hours @ room temperature
Stock stability	102 days @ 4°C (Paroxetine) 60 days @ 4°C (Internal Std)
Processed stability	147.5 hours @ 4°C
Freeze-thaw stability	3 cycles
Long-term storage stability	188 days @ -30°C set point freezer
Dilution integrity	Diluted 2 fold and 4 fold
Selectivity	Results demonstrate freedom from any reasonably expected interferences.

Note: Dilution integrity: Diluted 2 fold (CV%=3.1; % Nominal=107.7) and Diluted 4 fold (CV%=3.7; Nominal=111.5) Vol.1.7, p1037.

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	PARO-IMSU-01NB01-2FA
Study Design	Randomized, single-dose, 2-way crossover study under fasting conditions
No. of subjects enrolled	36 + 3 alternates
No. of subjects completing	37
No. of subjects analyzed	36 (per protocol)
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 36 Female: 0
Test product	Peroxetine HCl Oral suspension
Reference product	Paxil ^R Oral suspension
Strength tested	10 mg/5 mL
Dose	20 mg (10 mL)

Summary of Statistical Analysis (N=36)		
Parameter	Point Estimate	90% Confidence Interval
AUC _{0-t}	1.00	91.34-108.54
AUC _∞	1.00	92.10-109.38
C _{max}	0.99	91.71-107.38

Table of Reanalysis of Study Samples (Provided by the firm)

PARO-IMSU-01NB01-2FA Internal Study Code: PX1543 Additional information in Table 16.5.8.6 and Volume 5, p.474								
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
B - Analysis Incomplete	1	0	0.08	0	0	0	0	0
C - Poor Chromatography	3	0	0.23	0	0	0	0	0
Total	4	0	0.31	0	0	0	0	0

Note: The firm did not provide any conclusive information (neither in the table above nor in jacket, vol.1.3, p.474), if the re-assayed values were used in the SAS analysis.

Did use of recalculated plasma concentration data change study outcome? Not known

2. Single-dose Fed Bioequivalence Study

Study No.	PARO-IMSU-01NB02-2FE
Study Design	Randomized, single-dose, 2-way crossover study under fed conditions
No. of subjects enrolled	36 + 4 alternates
No. of subjects completing	39
No. of subjects analyzed	35*
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 35 Female: 0
Test product	Paroxetine HCl Oral Suspension
Reference product	Paxil ^R Oral Suspension
Strength tested	10 mg/ 5 mL
Dose	20 mg (10 mL)

* As per protocol, 36 subjects' data were analyzed. However, Subject #27 had pre-dose levels at the second period that were more than 5% of his C_{max} for that period, and therefore, this subject's data were not included in PK analysis.

Summary of Statistical Analysis (N=35)		
Parameter	Point Estimate	90% Confidence Interval
AUC _{0-t}	1.04	97.74-110.28
AUC _∞	1.06	99.63-113.38
C _{max}	1.01	94.79-108.48

Table of Reanalysis of Study Samples (provided by Firm)

PARO-IMSU-01NB02-2FE Internal Study Code: PX1720 Additional information in Table 16.5.8.6 and Volume 8, p.450								
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
G - Highest/Lowest standards missing from the regression	2	1	0.15	0.08	0	0	0	0
C - Poor Chromatography	0	1	0	0.08	0	0	0	0
Total	2	2	0.15	0.16	0	0	0	0

Note: The firm should provide information if the reassayed values were used in the SAS analysis.

E. Formulation

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

F. In Vitro Dissolution (Amendment Submitted on August 16, 2005)

Source of Method (USP, FDA or Firm)	FDA*
Medium	Simulated gastric fluid without pepsin
Volume (mL)	900 mL @ 37 ^o C
USP Apparatus type	2 (paddle)
Rotation (rpm)	100
Firm's proposed specifications	None
FDA-recommended specifications	NLT (b) (4) (Q) in 30 min.
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving
Is method acceptable?	Yes
If not then why?	

* There is no USP dissolution method for this drug product

Comment: The dissolution testing is incomplete. The firm needs to acknowledge its acceptance of the dissolution specification. The firm also needs to clarify if each dosage unit used for dissolution testing was taken from 12 separate bottles as recommended for oral suspensions.

G. Waiver Request(s) N/A

H. Deficiency Comments

1. The firm should provide potency and content uniformity of the test drug and potency of the reference listed drug used in the bioequivalence studies. The firm should also provide the Bio-batch size and the production batch size of the test product.
2. From the Tables of Reanalysis of Study Samples, it is not clear whether those reassayed values were used in the statistical analysis. The firm should clarify this.

3. The dissolution testing data using the FDA-recommended method are acceptable. However, the firm needs to acknowledge its acceptance of the FDA-recommended dissolution specification.

4. It is not clear from the submitted dissolution data if each dosage unit used for the dissolution testing was taken from the same bottle or from different bottles. The firm should note that 12 dosage units should be from 12 separate bottles. If the dosage units were not taken from separate bottles, the firm should conduct additional dissolution testing on the test and reference products taking each dosage unit from a separate bottle and submit the data for review.

I. Recommendations

1. The single-dose, fasting and non-fasting bioequivalence studies (20 mg dose) conducted by Apotex Inc. on the test product, Paroxetine Oral Suspension, 10 mg/5 mL, lot # GL6385, comparing it with the reference product, Paxil® Oral Suspension, 10 mg/5 mL, lot # X103P15 of GlaxoSmithKline, are incomplete due to the deficiencies cited above.

2. The dissolution testing conducted by Apotex Inc. on the test product, Paroxetine Suspension, 10 mg/5 mL, lot # GL6385, comparing it with the reference product, Paxil® Suspension, 10 mg/5 mL, lot # X103P15 of GlaxoSmithKline is incomplete. The firm should acknowledge its acceptance of the FDA-recommended dissolution specification.

The dissolution testing should be conducted in 900 mL of Simulated gastric fluid without pepsin at 37°C using USP apparatus 2 (paddle) at 100 rpm.

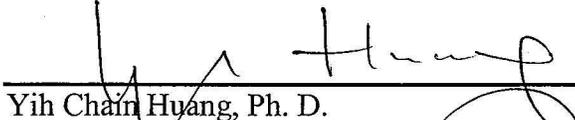
The test product should meet the following specification: NLT (b) (4) (Q) dissolved in 30 minutes.



Sikta Pradhan, Ph. D.
Review Branch IV

3/14/06

Date



Yih-Cham Huang, Ph. D.
Team Leader, Review Branch IV

3/15/2006

Date



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

3/17/06

Date

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	PARO-IMSU-01NB02-2FE
Study Title	A Relative Bioavailability Study of Paroxetine Oral Suspension, 10 mg/5 mL Under Fasting Conditions
Clinical Site	Apotex, Inc. Biomedical Division 465 Garyray Drive, Toronto, Ontario, Canada, M9L1P9
Principal Investigator	David Satok, M.D.
Study/Dosing Dates	Period I: 07/24/04 and Period II: 08/07/04
Analytical Site	Apotex, Inc. Biomedical Division 440 Garyray Drive, Toronto, Ontario, Canada, M9L1P7
Analytical Director	(b) (6)
Analysis Dates	August 18, 2004 – September 8, 2004
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	47 Days (Long-term storage stability was documented for 188 days.)

Treatment ID	Test	Reference
Test or Reference	A	B
Product Name	Paroxetine HCl Oral Suspension, 10 mg/5 mL	Paxil® Oral Suspension, 10 mg/5 mL
Manufacturer	Novex	GlaxoSmithKline
Batch/Lot No.	GL6385	X103P15
Manufacture Date	--	N/A
Expiration Date	Dec./2005	Dec./2006
Strength	19 mg/5 mL	10 mg/5 mL
Dosage Form	Suspension	Suspension
Batch Size	Not provided	N/A
Production Batch Size	Not provided	N/A
Potency	Not provided	Not provided
Content Uniformity (mean, %CV)	Not provided	Not provided
Formulation	See Appendix Section IV B	
Dose Administered	20 mg (10 mL)	20 mg (10 mL)
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	2 Weeks
Randomization Scheme	AB:2, 4, 6, 8, 10, 12, 13, 15, 18, 19, 22, 24, 26, 27, 29, 33, 34, 38, 39 BA:1, 3, 5, 7, 9, 11, 14, 16, 17, 20, 21, 23, 25, 28, 31, 32, 35, 36, 37, 40
Blood Sampling Times	0 and at 1, 2, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hrs post dose.
Blood Volume Collected/Sample	1x7 mL
Blood Sample Processing/Storage	Plasma was separated and stored at -30°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hrs
Length of Confinement	10 hrs prior to drug administration until 24 hr blood draw
Safety Monitoring	Yes, vital signs were measured prior to dosing and at 6 hr post dose.

- No Subject was entered as #30

•
Comments on Study Design: Acceptable

b) Clinical Results
Table 1 Demographics of Study Subjects (N=37)

Study No. PARO-IMSU-01NB01-2FA-(0) (Internal Code: PX1543)		
	Treatment Groups	
	Test Product N = 37	Reference Product N = 37
Age (years)		
Mean ± SD	33.03 ± 7.62	33.03 ± 7.62
Range	21 – 48	21 – 48
Groups		
<18	0 (%)	0 (%)
18 – 40	30 (81.1%)	30 (81.1%)
41 – 64	7 (18.9%)	7 (18.9%)
65 – 75	0 (%)	0 (%)
>75	0 (%)	0 (%)
Sex		
Female	0 (%)	0 (%)
Male	37 (100%)	37 (100%)
Race		
Asian	2 (5.4%)	2 (5.4%)
Black	8 (21.6%)	8 (21.6%)
Caucasian	14 (37.9%)	14 (37.9%)
Hispanic	9 (24.3%)	9 (24.3%)
Other	4 (10.8%)	4 (10.8%)
Other Factors	<i>PX03 withdrew during P1 due to timing of adverse event (diarrhea)</i> <i>PX13 withdrew during P1 due to timing of adverse event (diarrhea)</i>	

[N = number of subject; % (to one decimal place) = (N ÷ total number of subject dosed with test or reference TA) x 100%]

Table 2 Dropout Information

Subject No.	Reason	Period	Replaced?
3 & 13	Were withdrawn due to diarrhea	During Period 1	#3 was replaced by #38 and #13 was replaced by #37

Table 3 Study Adverse Events

System/Adverse Events	Reported Incidence by Treatment Groups			
	Fasted Bioequivalence Study Study Code: PARO-MSU-01NB01-2FA (Internal code: PX1543)		Fed Bioequivalence Study Study Code: PARO-MSU-01NB02-2FE (Internal code: PX1720)	
	Test	Reference	Test	Reference
Cardiac disorders				
Heart rate increased	1 (2.6%)			1 (2.5%)
Heart rate Decreased	2 (5.2%)		1 (2.5%)	2 (5.0%)
Gastrointestinal Disorders				
Abdominal Pain		1 (2.6%)		
Abdominal Discomfort			1 (2.6%)	1 (2.5%)
Nausea				
Loose stool	1 (2.6%)			
Diarrhea	1 (2.6%)		2 (5.1%)	1 (2.5%)
Flatulence		6 (15.4%)		1 (2.5%)
Abnormal stools		2 (5.2%)		1 (2.5%)
Dry mouth				1 (2.5%)
General disorder and administration site conditions				
Fatigue	1 (2.6%)			
Asthemia			1 (2.6%)	
Venipuncture site bruise		1 (2.6%)		
Venipuncture site Pain		1 (2.6%)		
Venipuncture site reaction			2 (5.1%)	
Venipuncture site swelling			1 (2.6%)	1 (2.5%)
Chest discomfort				
Injury, poisoning and procedural complications				
Injury			1 (2.6%)	1 (2.5%)
Periorbital hematoma				1 (2.5%)
Blister				1 (2.5%)
Nervous system disorders				
Dizziness	1 (2.6%)		1 (2.6%)	1 (2.5%)
Headache	1 (2.6%)	1 (2.6%)		
Dysgeusia	1 (2.6%)		1 (2.6%)	
Somnolence			1 (2.6%)	1 (2.5%)
Hypoesthesia			1 (2.6%)	1 (2.5%)
Syncope			1 (2.6%)	
Respiratory, thoracic, mediastinal disorders				
Nasal congestion				1 (2.5%)
Yawning	1 (2.6%)			
Rhinorrhoea				2 (5%)

Page 1 of 2

Table 4 Protocol Deviations

Except deviations to the blood-draw schedule, no significant protocol deviations were reported.

The adverse events occurred from the test and reference products are comparable.

Comments on Dropouts/Adverse Events/Protocol Deviations: As judged by the investigator the adverse events and protocol deviations did not compromise the integrity of the study.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Parent			Metabolite
QC Conc. (ng/mL)	0.150	17.535	35.070	
Inter day Precision (%CV)	8.4	7.8	8.3	
Inter day Accuracy (%)	103.3	99.5	96.5	
Cal. Standards Conc. (ng/mL)				
	0.050 - 50.100			
Inter day Precision (%CV)	2.0 – 5.1			
Inter day Accuracy (%)	95.7 – 103.7			
Linearity Range (range of R² values)	R ² ≥ 0.9934 – 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 L200.108 Sample Analysis (Chromatographic)

Table 7 Additional Comments on Repeat Assays: It is not clear from the reassay table whether the firm has used the reassayed values in its statistical analysis. The firm should clarify this.

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	Not known at this stage
Does the reviewer agree with the outcome of the repeat assays?	No, Firm has been requested to clarify the repeat analysis.
If no, reason for disagreement	

Summary/Conclusions, Study Assays: Incomplete

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters (N=36)

Mean **Peroxitine** plasma concentrations are presented in Table 11

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI (ng.h/mL)	146.38	220.20	150.26	210.87	0.97
AUCT (ng.h/mL)	119.91	155.39	127.86	160.16	0.94
C_{MAX} (ng/mL)	5.68	88.42	6.08	99.53	0.94
KE (1/h)	0.06	24.71	0.06	22.81	1.00
LAUCI	74.63	1.37	74.35	1.47	1.00
LAUCT	70.62	1.43	70.92	1.53	1.00
LC_{MAX}	4.15	20.37	4.18	21.87	0.99
THALF (h)	13.16	61.65	12.85	54.74	1.02
T_{MAX} (h)	6.00	25.82	6.50	19.62	0.92

Table 9 Peroxitine Geometric Means and 90% Confidence Intervals

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI (ng.h/mL)	146.39	150.26	0.97	90.30	104.54
AUCT (ng.h/mL)	119.91	127.86	0.94	85.74	101.83

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
C _{MAX} (ng/mL)	5.68	6.08	0.94	85.79	101.36
LAUCI	74.63	74.35	1.00	92.10	109.38
LAUCT	70.62	70.92	1.00	91.34	108.54
LC _{MAX}	4.15	4.18	0.99	91.71	107.38

Table 10 Additional Study Information: Peroxetine

Root mean square error, AUC _{0-t}	0.216450
Root mean square error, AUC _∞	0.215704
Root mean square error, C _{max}	0.197831
Ke and AUC _i determined for how many subjects?	All subjects
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C _{max}	None
Were the subjects dosed as more than one group?	No

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

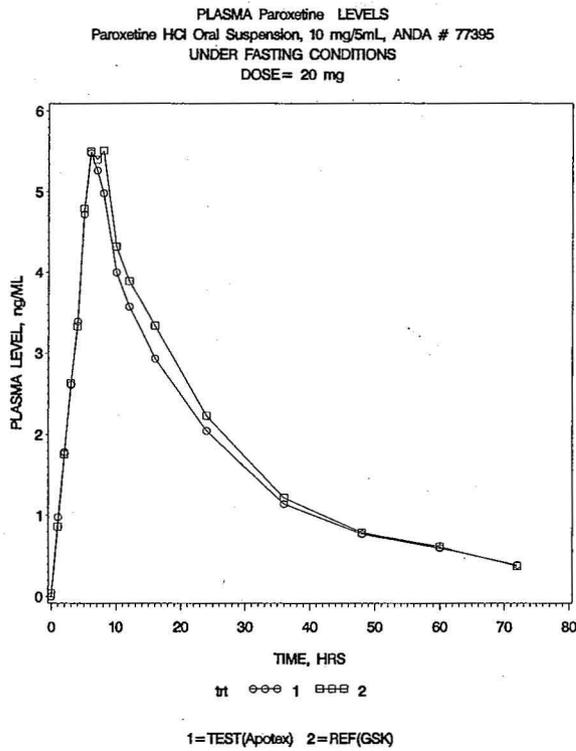
Table 11 Mean Peroxetine Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00		0.04	600.00	0.00
1	0.98	56.79	0.86	71.15	1.14
2	1.78	70.96	1.76	94.45	1.02
3	2.61	80.99	2.63	106.97	0.99
4	3.39	95.11	3.33	104.57	1.02
5	4.72	88.72	4.79	94.38	0.99
6	5.48	90.62	5.50	97.01	1.00
7	5.26	89.66	5.40	89.98	0.98
8	4.98	94.48	5.51	107.80	0.90
10	4.00	102.77	4.32	104.10	0.93
12	3.57	111.86	3.89	118.48	0.92
16	2.93	117.84	3.33	136.00	0.88

	MEAN1	CV1	MEAN2	CV2	RMEAN12
24	2.04	144.37	2.23	155.23	0.92
36	1.14	242.99	1.22	228.69	0.94
48	0.77	293.12	0.79	297.02	0.98
60	0.60	404.09	0.61	396.57	0.97
72	0.39	437.80	0.37	431.95	1.05

Unit=ng/mL, n=36

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



2. Single-dose Fed Bioequivalence Study

b) Study Design

Study Information	
Study Number	PARO-IMSU-01NB02-2FE
Study Title	A Relative Bioavailability Study of Paroxetine Oral Suspension, 10 mg/5 mL Under Fed Conditions
Clinical Site	Apotex, Inc. Biomedical Division 465 Garyray Drive, Toronto, Ontario, Canada, M9L1P9
Principal Investigator	David Satok, M.D.
Study/Dosing Dates	Period I: 07/24/04 and Period II: 08/07/04
Analytical Site	Apotex, Inc. Biomedical Division 440 Garyray Drive, Toronto, Ontario, Canada, M9L1P7
Analytical Director	(b) (6)
Analysis Dates	August 18, 2004 – September 8, 2004
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	47 Days

Treatment ID	Test	Reference
Test or Reference	A	B
Product Name	Paroxetine HCl Oral Suspension, 10 mg/5 mL	Paxil® Oral Suspension, 10 mg/5 mL
Manufacturer	(b) (4)	GlaxoSmithKline
Batch/Lot No.	GL6385	X103P15
Manufacture Date	--	N/A
Expiration Date	Dec./2005	Dec./2006
Strength	19 mg/5 mL	10 mg/5 mL
Dosage Form	Suspension	Suspension
Batch Size	Not provided	N/A
Production Batch Size	Not provided	N/A
Potency	Not provided	Not provided
Content Uniformity (mean, %CV)	Not provided	Not provided
Formulation	See Appendix Section B	
Dose Administered	20 mg (10 mL)	20 mg (10 mL)
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	2 Weeks
Randomization Scheme	AB:1, 4, 7, 8, 9, 12, 13, 14, 18, 19, 21, 23, 26, 27, 29, 31, 33, 36, 38, 40 BA:2, 3, 5, 6, 10, 11, 15, 16, 17, 20, 22, 24, 25, 28, 30, 32, 34, 35, 37, 39
Blood Sampling Times	0 and at 1, 2, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hrs post dose.
Blood Volume Collected/Sample	1x7 mL
Blood Sample Processing/Storage	Plasma was separated and stored at -30 ⁰ C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 12
Length of Fasting	10 hrs
Length of Confinement	10 hrs prior to drug administration until 24 hr blood draw
Safety Monitoring	Yes, vital signs were measured prior to dosing and at 6 hr post dose.
Standard Breakfast	Yes, 30 minutes before dosing

Comments on Study Design: Acceptable

Study No. PARO-IMSU-01NB01-2FA-(0) (Internal Code: PX1543)		
	Treatment Groups	
	Test Product N = 37	Reference Product N = 37
Age (years)		
Mean \pm SD	33.03 \pm 7.62	33.03 \pm 7.62
Range	21 – 48	21 – 48
Groups		
<18	0 (%)	0 (%)
18 – 40	30 (81.1%)	30 (81.1%)
41 – 64	7 (18.9%)	7 (18.9%)
65 – 75	0 (%)	0 (%)
>75	0 (%)	0 (%)
Sex		
Female	0 (%)	0 (%)
Male	37 (100%)	37 (100%)
Race		
Asian	2 (5.4%)	2 (5.4%)
Black	8 (21.6%)	8 (21.6%)
Caucasian	14 (37.9%)	14 (37.9%)
Hispanic	9 (24.3%)	9 (24.3%)
Other	4 (10.8%)	4 (10.8%)
Other Factors	<i>PX03 withdrew during P1 due to timing of adverse event (diarrhea)</i> <i>PX13 withdrew during P1 due to timing of adverse event (diarrhea)</i>	

e) Clinical Results
Table 12 Demographics of Study Subjects (N=39) *

[N = number of subject; % (to one decimal place) = (N + total number of subject dosed with test or reference TA) x 100%]

*Subject #16 was not dosed in second period.

Table 13 Dropout Information:

Subject No.	Reason	Period	Replaced?
1	Due to diarrhea	After Period 2	Yes, by Subj. #38
16		After Period 1	Yes, by Subj. #37

Forty (40) subjects completed period 1, and thirty-nine (39) subjects completed period 2. Subject #16 was withdrawn on the evening of period 2 check-in due to a black eye and trauma to the right shoulder, which were not likely produced by the reference drug.

Subject #1 was withdrawn after completion of period 2, due to diarrhea that occurred during period 2, as the timing of this event could potentially interfere with the absorption of the drug.

As per protocol, 36 subjects' data were analyzed; Subject #39 and Subject #40 were not analyzed. However, Subject #27 had pre-dose levels at the second period that were more than 5% of his C_{max} for that period, and therefore, this subject's data were not included in PK analysis.

Table 14 Study Adverse Events

System/Adverse Events	Reported incidence by Treatment Groups			
	Fasted Bioequivalence Study Study Code: PARO-IMSU-01NB01-2FA (Internal code: PX1543)		Fed Bioequivalence Study Study Code: PARO-IMSU-01NB02-2FE (Internal code: PX1720)	
	Test	Reference	Test	Reference
Cardiac disorders				
Heart rate increased	1 (2.6%)			1(2.5%)
Heart rate Decreased	2 (5.2%)		1(2.6%)	2 (5.0%)
Gastrointestinal Disorders				
Abdominal Pain		1 (2.6%)		
Abdominal Discomfort			1 (2.6%)	
Nausea			1 (2.6%)	1 (2.5%)
Loose stool	1(2.6%)			
Diarrhea	1(2.6%)	6 (15.4%)	2 (5.1%)	1(2.5%)
Flatulence		2 (5.2%)		1 (2.5%)
Aphthous stomatitis				1 (2.5%)
Dry mouth				1 (2.5%)
General disorder and administration site conditions				
Fatigue	1(2.6%)			
Asthenia			1 (2.6%)	
Venipuncture site bruise		1 (2.6%)		
Venipuncture site Pain		1(2.6%)		
Venipuncture site reaction			2 (5.1%)	
Venipuncture site swelling			1(2.6%)	
Chest discomfort				1 (2.5%)
Injury, poisoning and procedural complications				
Injury			1(2.6%)	1 (2.5%)
Periorbital haematoma				1 (2.5%)
Blister				1 (2.5%)
Nervous system disorders				
Dizziness	1 (2.6%)		1 (2.6%)	1 (2.5%)
Headache	1(2.6%)	1 (2.6%)		
Dysgeusia	1(2.6%)		1(2.6%)	
Somnolence			1(2.6%)	1 (2.5%)
Hypoaesthesia			1(2.6%)	1 (2.5%)
Syncope			1(2.6%)	
Respiratory, thoracic, mediastinal disorders				
Nasal congestion				1 (2.5%)
Yawning	1(2.6%)			
Rhinorrhoea				2 (5%)

Table 15 Protocol Deviations

Deviations to the blood-draw schedule are shown on page 92 of Vol. 1.5. Except deviations to the blood-draw schedule, no significant protocol deviations were reported.

Comments on Dropouts/Adverse Events/Protocol Deviations:

The adverse events occurred from the test and reference products are comparable.

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

f) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Parent			Metabolite
QC Conc. (ng/mL)	0.150	17.535	35.070	
Inter day Precision (%CV)	11.0	9.9	9.2	N/A
Inter day Accuracy (%)	103.3	105.9	97.6	
Cal. Standards Conc. (ng/mL)				
	0.050 – 50.100			
Inter day Precision (%CV)	4.0 – 7.4			
Inter day Accuracy (%)	97.5-102.2			
Linearity Range (range of R² values)	R ² ≥ 0.9935 – 0.9986			

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 17 SOP's dealing with analytical repeats of study samples

SOP ABM-BL-0155 Assay Failure Investigation Effective Date: 6/15/04

SOP ABM-BL-0156 Chromatography Acceptance Effective Date: 6/15/04

Table 18 Additional Comments on Repeat Assays: Firm has been requested to clarify the repeat analysis.

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	Not known at this stage
Does the reviewer agree with the outcome of the repeat assays?	No, Firm has been requested to clarify the repeat analysis.
If no, reason for disagreement	

Summary/Conclusions, Study Assays: Incomplete

Pharmacokinetic Results

Table 19 Paroxetine Arithmetic Mean Pharmacokinetic Parameters (N=35)

Mean plasma Paroxetine concentrations are presented in Table22

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI (ng.h/mL)	175.83	137.88	161.69	130.12	1.09
AUCT (ng.h/mL)	138.90	117.07	136.84	121.68	1.02
C_{MAX} (ng/mL)	5.60	84.85	5.58	85.95	1.00
KE (1/h)	0.05	35.62	0.05	32.64	0.97
LAUCI	81.15	1.55	76.98	1.65	1.05
LAUCT	73.02	1.64	70.13	1.75	1.04
LC_{MAX}	3.83	24.27	3.77	25.53	1.02
THALF (h)	16.88	63.63	15.00	42.47	1.13
T_{MAX} (h)	6.49	25.20	6.26	25.77	1.04

Table 20 Paroxetine Geometric Means and 90% Confidence Intervals

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI (ng.h/mL)	175.35	158.03	1.11	102.37	119.55
AUCT (ng.h/mL)	138.47	136.75	1.01	94.71	107.80
C_{MAX} (ng/mL)	5.59	5.57	1.00	93.33	107.16
LAUCI	80.78	76.00	1.06	99.63	113.38
LAUCT	72.72	70.04	1.04	97.74	110.28
LC_{MAX}	3.82	3.77	1.01	94.79	108.48

Table 21 Additional Study Information:

Root mean square error, AUC _{0-t}	0.149052
Root mean square error, AUC _{0-l}	0.154660
Root mean square error, C _{max}	0.166702
Ke and AUC _i determined for how many subjects?	All subjects
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	Subject #21 and Subject #25
-first measurable drug concentration as C _{max}	None
Were the subjects dosed as more than one group?	No

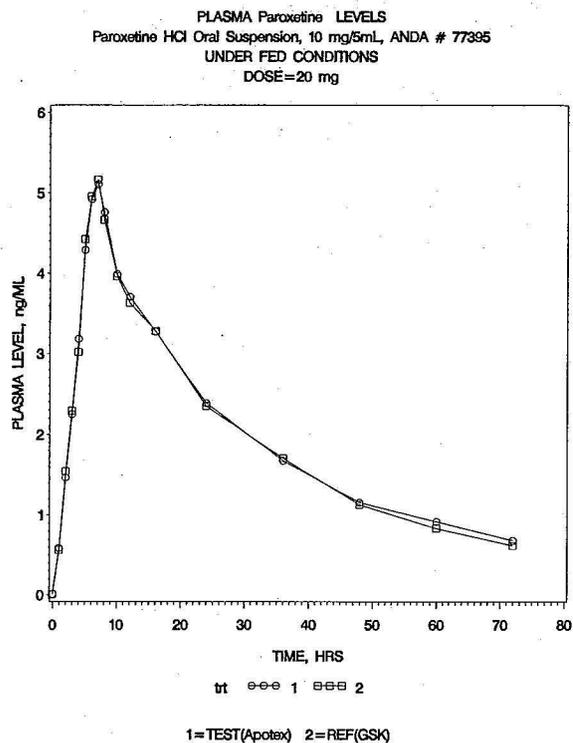
Comments on Pharmacokinetic Analysis: None

Table 22 Mean Plasma Paroxetine Concentrations, Single-Dose Fed Bioequivalence Study (N=35)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.01	591.61	0.00	591.61	2.22
1	0.59	78.12	0.56	95.41	1.04
2	1.47	68.94	1.54	141.14	0.95
3	2.25	70.97	2.29	88.59	0.98
4	3.18	82.22	3.02	89.03	1.06
5	4.29	79.65	4.42	82.87	0.97
6	4.92	80.03	4.95	81.57	0.99
7	5.11	88.99	5.17	92.27	0.99
8	4.76	91.91	4.66	93.27	1.02
10	3.99	87.86	3.96	90.89	1.01
12	3.71	94.55	3.63	106.74	1.02
16	3.27	103.49	3.28	108.04	1.00
24	2.39	117.43	2.35	122.22	1.02
36	1.68	147.27	1.70	157.61	0.98
48	1.16	165.81	1.13	162.90	1.02
60	0.92	188.12	0.83	185.08	1.10
72	0.68	204.22	0.62	206.88	1.10

Unit = ng/mL

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



Summary and Conclusions, Single-Dose Fed Bioequivalence Study: Incomplete

B. Formulation Data

Strength (Label Claim):	10 mg/5 mL	
Ingredient	Amount (g/L)	Amount (%) (w/v)
Paroxetine Hydrochloride		(b) (4)
Bitter Blocker Type Flavour (b) (4)		
FD & C Yellow No. 6 (b) (4)		
Glycerin USP		
Methylparaben NF		
Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF (b) (4)		
Natural Orange Blood Sicilian Flavour (b) (4)		
Propylene Glycol USP/EP		
Propylparaben NF		
Saccharin Sodium USP		
30% Simethicone Emulsion USP (b) (4)		
Sorbitol Solution USP (b) (4)		
Purified Water USP/EP		
TOTAL:		100.0%

Dissolution Data

There is no USP method for this product, but there is an FDA-recommended method. The firm conducted dissolution testing with a non-FDA-recommended and submitted the dissolution testing data to the Agency for review on November 19, 2004. The dissolution data was not acceptable and the firm was recommended to conduct the dissolution testing using FDA-recommended method (Reviewer: Phelicia B. Bush).

The firm repeated the dissolution testing according to the Agency recommendation and submitted the data on August 16, 2005 to the Agency for review as an amendment. The dissolution testing data are presented below:

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times					Study Report Location
					Mean % Dissolved (Range)					
					5 min	10 min	15 min	20 min	30 min	
Test Product	GL6385	10 mg/5 mL	Apparatus: USP #2 Speed of Rotation: 100 rpm Medium: SGF (w/o pepsin) Volume: 900 mL Temperature: 37°C	12	83	96	100	101	101	N/A
Reference Product	X10 3P15	10 mg/5 mL		12	47	69	81	98	94	N/A

Note: Above dissolution table was provided by the firm and it is not possible to modify that table. For that reason, the additional information is given below.

Product	5 min (Range) CV% (of 12 units)	10 min (Range) CV% (of 12 units)	15 min (Range) CV% (of 12 units)	20 min (Range) CV% (of 12 units)	30 min (Range) CV% (of 12 units)
Test	(b) (4)				
	6.0	3.3	2.7	2.3	1.9
Reference	(b) (4)				
	3.4	5.7	5.2	3.4	1.7

Comments: The data meet the specification of NLT (b) (4) (Q) in 30 minutes at S1 level. However, it is not clear if each unit was taken from separate bottles.

C. Consult Reviews

None

D. SAS Output

STUDY	DATA		SAS PROGRAM	SAS OUTPUT
Fasting Study	 Conc. TXT	 Pk. TXT	 FAST77395BE02dp1. Txt	 Fast77395STAT.1st. Txt
Fed Study	 FED77395\Conc.Txt	 FED77395\Pk.Txt	 FED77395BE02dp1.T xt	 FED77395STAT.1st. TXT

E. Additional Attachments

None

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-395

APPLICANT: Apotex Inc.

DRUG PRODUCT: Paroxetine Oral Suspension, 10 mg/5 mL

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

1. We acknowledge that you have accepted the following dissolution method:

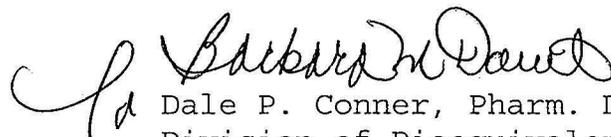
The dissolution testing should be conducted in 900 mL of Simulated Gastric Fluid without pepsin at 37°C using USP Apparatus 2 (paddle) at 100 rpm. The test product should meet the following specification: Not less than (b) (4) (Q) of the labeled amount dissolved in 30 minutes.

2. Your dissolution testing is incomplete. It is not clear from the data submitted if each dosage unit used for dissolution testing was taken from the same bottle or from different bottles. Please note that 12 dosage units should be from 12 separate bottles. If the dosage units were not taken from separate bottles, please conduct and submit dissolution testing on the test and reference products taking each dosage unit from separate bottles. In your response, please also acknowledge your acceptance of the FDA-recommended dissolution specification.

3. Please provide potency and content uniformity of the test and potency of the reference listed drug used in the bioequivalence studies. Please also provide the bio-batch size and the production batch size of the test product.

4. From the Tables of Reanalysis of Study (both fasting and fed) Samples you provided, it is not clear if those reanalyzed values were used in the statistical analysis. Please clarify.

Sincerely yours,



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

CC: ANDA 77-395
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

HFD-650 / Bio Drug File
HFD-650 / Reviewer: S. Pradhan

Endorsements: (Final with Dates)

HFD-650/ S. Pradhan *SP*
HFD-650/ Y. Huang *WT 3/15/2006*
HFD-650/ D. Conner *BM 3/17/02*
HFD-650/ Fritsch

In

V:\FIRMSAM\Apotex\ltrs&rev\77395N0205.doc
Printed in final on

BIOEQUIVALENCE - Incomplete

Submission date:

- 1. FASTING STUDY (STF) *o/c* Strength: 10 mg/5 mL
Outcome: IC
Clinical: Apotex, Inc.
465 Garyray Drive, Toronto, Ontario, Canada
Analytical: Apotex, Inc.
 Biomedical Division
 440 Garyray Drive, Toronto, Ontario, Canada

- 2. FED STUDY (STP) *o/c* Strength: 10 mg/5 mL
Outcome: IC
Clinical: Apotex, Inc.
465 Garyray Drive, Toronto, Ontario, Canada
Analytical: Apotex, Inc.
 Biomedical Division
 440 Garyray Drive, Toronto, Ontario, Canada

- 3. STUDY Amendment (STA) *o/c* Strength: 10 mg/5 mL
Outcome: IC
 (Dissolution Amendment)

OUTCOME DECISIONS: IC: Incomplete

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-395
Drug Product Name	Paroxetine Hydrochloride Suspension
Strength	10 mg/5 mL
Applicant Name	Apotex Inc.
Submission Date(s)	November 18, 2004
First Generic	Yes
Reviewer	Phelicia B. Bush
File Location	V:\firmsam\apotex\ltrs&rev\77395D1104.doc
Clinical Site	Apotex Inc. Biomedical Division 465 Garyray Drive Toronto, Ontario Canada M9L 1P9
Analytical Site	Apotex Inc. Biomedical Division 440 Garyray Drive Toronto, Ontario Canada M9L 1P7

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 firm conducted dissolution testing with a non-FDA-recommended method. The firm should conduct dissolution testing with the FDA-recommended method.

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

FDA METHOD

Medium Simulated gastric fluid without pepsin
Volume 900 mL
Temperature 37°C
Apparatus II(paddle)
Rotational Speed 100 rpm
Specification NLT (b) (4) (Q) in 30 minutes

Source of Method: NDA 20-710, OCPB Review, submission date 4/12/1996, review date 1/24/1997 (method) and NDA 20-710/S-014, submission date 8/3/2004, review date 2/2/05 (specification).

Table 1. Summary of In Vitro Dissolution Data

Study Ref. No.	Product ID/ Batch No.	Strength	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)					Study Report Location
					5 min	10 min	15 min	20 min	30 min	
Not provided	Apotex GL6385	10 mg/5 mL	Dissolution: Apparatus 2 (USP) Speed of Rotation (b) rpm Medium: SGF, (b) (4)	12	93	93	94	95	95 (b) (4)	V 2.1 p. 12 (Blue jacket)
Not provided	Paxil® G-X103P15	10 mg/5 mL	(b) Volume: 900 mL Temperature: 37°C Specification: NLT (b) (4) (Q) in (b) minutes	12	65	94	97	98	99 (b) (4)	V 2.1 p. 11 (Blue jacket)

Table 2. SAS Transport Files

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

COMMENTS:

- The firm's proposed dissolution method (900 mL of Simulated Gastric Fluid (b) (4) using apparatus 2 (paddle) at (b) (4) rpm differs from the FDA-recommended method (innovator's method).
- The DBE currently recommends the following RLD method for dissolution testing:

Medium: Simulated Gastric Fluid **without pepsin**
 Volume: 900 mL
 Apparatus: II (Paddles)
 Rotational speed: 100 rpm
 Specifications: NLT (b) (4) (Q) of labeled amount of drug is dissolved in 30 minutes

- The firm should repeat the dissolution testing using the FDA method.

DEFICIENCY COMMENTS:

1. The *in vitro* dissolution testing conducted on the test and reference products is incomplete. The firm is advised to perform dissolution testing using the FDA recommended method, as stated above.
2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data summary, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

RECOMMENDATIONS:

The firm should conduct dissolution testing using twelve units of each test and reference product using the following method:

Medium: Simulated Gastric Fluid **without pepsin**
 Volume: 900 mL
 USP Apparatus: II (Paddles)
 Rotational speed: 100 rpm
 Sampling times: 5, 15, 20, 30 and 45 minutes and until at least (b) (4) of the labeled amount is dissolved

Phelicia B. Bush

5/18/05

Phelicia B. Bush, Pharm. D., Reviewer, Team # V
Division of Bioequivalence
Office of Generic Drugs

Moheb H. Makary

5/20/05

Moheb H. Makary, Ph.D., Team Leader, Team # V
Division of Bioequivalence
Office of Generic Drugs

Barbara M. Savitt

5/25/05

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

PC

ANDA 77-395

Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL

Apotex Inc.

V:\firmsam\apotex\ltrs&rev\77395D1104.doc

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-395

APPLICANT: Apotex Inc.

DRUG PRODUCT: Paroxetine Hydrochloride Oral Suspension,
10 mg/5 mL

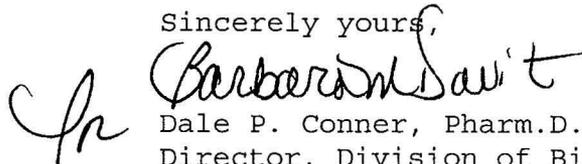
The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. The dissolution testing is not acceptable. Please conduct dissolution testing using 12 dosage units of each test and reference product using the following method:

USP Apparatus	2 (paddle)
Speed	100 rpm
Medium	Simulated Gastric Fluid without pepsin
Volume	900 mL
Sampling times:	5, 10, 15, 20, and 30 minutes and until at least (b) (4) of the labeled content is dissolved.

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

Sincerely yours,



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

CC: ANDA 77-395
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ P. Bush
HFD/650/ B. Fabian-Fritsch

V:\firmsam\ivax\ltrs&rev\77395D1104

Endorsements: (Final with Dates)

HFD-650/P. Bush *Revised 5/18/05*

HFD-650/M. Makary *MHM 5/20/05*

HFD-650/D.P. Conner *BAD 5/25/05*

fr

BIOEQUIVALENCE - INCOMPLETE

Submission date: November 19, 2004

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

1. DISSOLUTION (Dissolution Data)

Strength: 10 mg/5 mL

Outcome: IC

Outcome Decisions: IC – Incomplete

WinBio Comments: IC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-395

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-395 Applicant Apotex
Drug Paroxetine Hydrochloride Oral Suspension Strength(s) 10 mg/5 mL

APPROVAL [X] TENTATIVE APPROVAL [X] SUPPLEMENTAL APPROVAL (NEW STRENGTH) [] OTHER []

REVIEWER: DRAFT Package FINAL Package

1. Martin Shimer
Chief, Reg. Support Branch
Date 26 Sept 2006
Initials MAS
Contains GDEA certification: Yes [X] No []
Determ. of Involvement? Yes [] No []
Patent/Exclusivity Certification: Yes [X] No []
Date of latest Labeling Review/Approval Summary 2 August 2006

Comments: PIV to all listed patents -> not sure
Apotex is eligible for 180 Day exclusivity for this product } eligible for Full AP

2. Project Manager, Cheryl Wiseman Team8
Review Support Branch
Date 09-25-06
Initials CW
Original Rec'd date November 18, 2004
EER Status Pending [] Acceptable [X] OAI []
Date Acceptable for Filing February 10, 2005
Date of EER Status July 6, 2006
Patent Certification (type) IV
Date of Office Bio Review July 31, 2006
Date Patent/Exclus. expires
Date of Labeling Approv. Sum August 2, 2006
Citizens' Petition/Legal Case Yes [] No [X]
Labeling Acceptable Email Rec'd Yes [] No []
Labeling Acceptable Email filed Yes [] No []
First Generic (for Oral Suspension) Yes [X] No []
Date of Sterility Assur. App.
Priority Approval Yes [] No []
Methods Val. Samples Pending Yes [] No [X]
MV Commitment Rcd. from Firm Yes [X] No []
Acceptable Bio reviews tabbed Yes [X] No []
Modified-release dosage form: Yes [] No [X]
Suitability Petition/Pediatric Waiver 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

3. David Read (PP IVs Only) Pre-MMA Language included []
OGD Regulatory Counsel, Post-MMA Language Included [X]
Date 10/12/06
Initials DR
Comments: see revised version.

4. Div. Dir./Deputy Dir.
Chemistry Div. I [X] OR III
Date 10/25/06
Initials RCA
Comments: cnc ok
see attached spreadsheet

REVIEWER:

FINAL ACTION

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

For
Frank

Date 12/4/06
Initials FK

eme is adequate Radhika Rajajapalan 12/4/06

6. Vacant
Deputy Dir., DLPS

Date _____
Initials _____

7. Peter Rickman
Director, DLPS

Date 12/4/2006
Initials PR

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

*PTV to all listed patents - not suel-eligible for 180 day exclusivity
No exclusivity*

OR
*Labeling acceptable 10/2/2006 per DFS
Bio acceptable 7/31/2006 (Fasting & Fed BE studies) NO DSI inspec needed
EER acceptable 7/6/2006*

8. Robert L. West
Deputy Director, OGD

Date _____
Initials _____

Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Press Release Acceptable
Comments:

9. Gary Buehler
Director, OGD
Comments:

Date 12/4/06
Initials GB

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

10. Project Manager, Team Cheryl Wiseman
Review Support Branch

Date 12-5-06
Initials CW

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

11/20 Time notified of approval by phone 11/23 Time approval letter faxed
FDA Notification:

12-5-06 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

12-5-06 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou11.doc (08/25/2006)

September 29, 2006

ORIG AMENDMENT

NIAF

Ms. Michelle Dillahunt
Division of Labeling and Program Support
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Dillahunt:

Re: GRATUITOUS LABELING AMENDMENT
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL; ANDA No. 77-395

Further to your telephone conversation with Robin Windover on September 11, 2006, we are pleased to provide you with our revised package insert (prescribing information and medication guide) as per the recent change to the Reference Listed Drug (FDA Approved 08/22/2006). The Gratuitous Labeling Amendment has been provided in duplicate (Archival and Review copies). An Application Form FDA 356h has been prepared and is enclosed as Attachment 1.

Copies of the final printed package insert (prescribing information and medication guide) have been provided electronically (appended to the cover letter in the Review copy only). In addition, a side-by-side comparison of Apotex Inc.'s final printed package insert (prescribing information and medication guide) and the Reference Listed Drug labeling (provided electronically from Michelle Dillahunt of FDA on September 11, 2006), has been provided in Attachment 2.

In the event that there are additional approved changes for the reference listed drug labeling, Apotex Inc. shall further revise our labeling accordingly.

Please note that the enclosed electronic CD has been confirmed to be virus free using McAfee VirusScan Enterprise 7.1.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 508-2359.

Yours sincerely,



for Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

RECEIVED

OCT 02 2006

CGD / CDER





September 11, 2006

Mr. Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

**RE: ANDA # 77-395
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL
- Change in Point Of Contact Information**

This letter is to notify FDA (Office of Generic Drugs) that we have hired a US Director of Regulatory affairs and thus, Mr. John Lay will be the primary point of contact, effective September 11, 2006 in relation to the above-mentioned ANDA application.

The new contact information is as follows:

John G. Lay, B.Sc., RAC
Director, Regulatory Affairs
Apotex Corp.
2400 N. Commerce Parkway Suite 400
Weston, FL 33326

Telephone: (954) 384-3987
Fax: (954) 349-4233

Should you have any questions, please do not hesitate to me at the information above.

Sincerely,

Tammy McIntire

Tammy McIntire, M.S., R.Ph.
President

RECEIVED
SEP 14 2006
CGD / CDER

August 08, 2006

Me

Ms. Cheryl Wiseman
Project Manager
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Wiseman:

Re: TELEPHONE AMENDMENT
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL; ANDA No. 77-395

Further to our Telephone Amendment dated August 04, 2006 and as per your request in your Minor Amendment letter dated July 26, 2006, we are pleased to provide you with one (1) bottle of Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL for your reference. An Application Form FDA 356h for this response has been prepared and is enclosed.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 508-2359.

Yours sincerely,



fr: Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:sf

Encl.

RECEIVED
AUG 09 2006
OGD / CDER



August 04, 2006

Ms. Cheryl Wiseman
Project Manager
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N-AM

Dear Ms. Wiseman:

Re: **TELEPHONE AMENDMENT**
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL; ANDA No. 77-395

Further to your Minor Amendment letter dated July 26, 2006, we are pleased to provide you with our responses in triplicate (Archival, Field and Review copies). For ease of review, we have enclosed a copy of your letter as Attachment 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment 2. A signed Field Copy Certification can be found in Attachment 3. Please note that based on the nature of the questions in the letter and our ability to provide responses within ten calendar days, we feel this amendment can be re-categorized to a telephone amendment and therefore have submitted it as such.

A. *Chemistry Deficiencies:*



(b) (4)

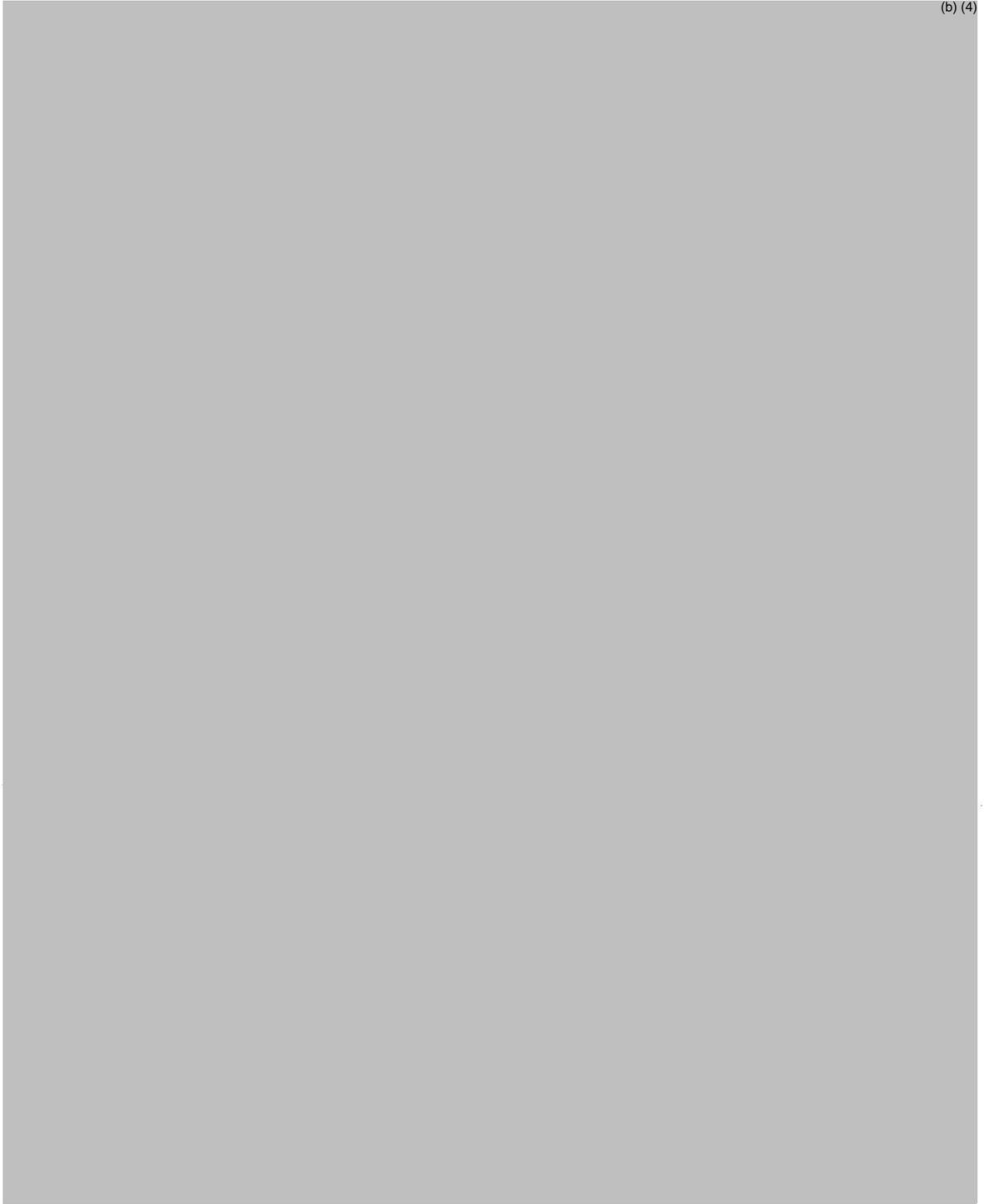
RECEIVED

AUG 07 2006

OGD / CDER



(b) (4)



.../cont'd



(b) (4)

APOTEX INC.

TELEPHONE
AMENDMENT

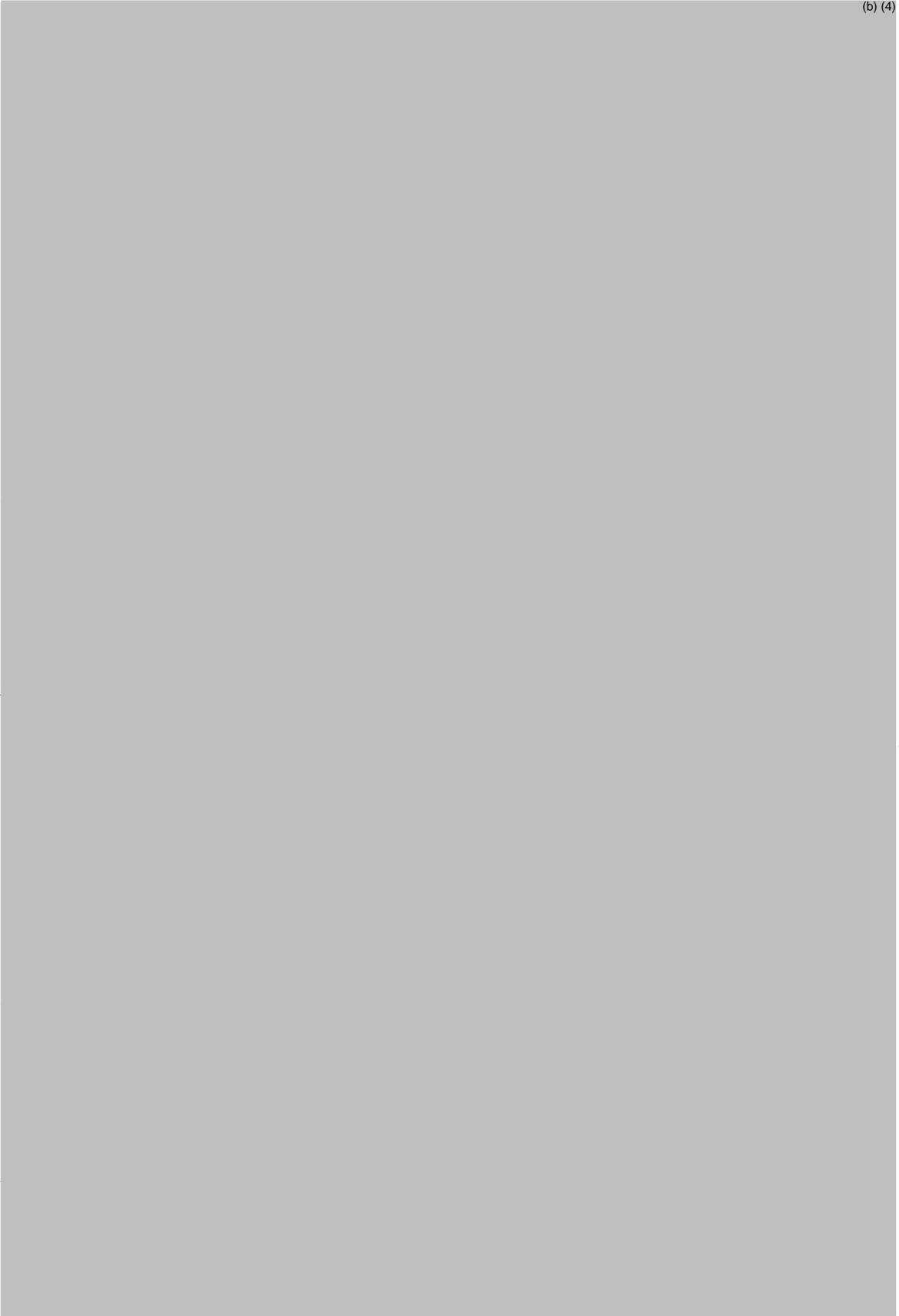
Paroxetine HCl Oral Suspension

10 mg/5 mL, ANDA No. 77-395

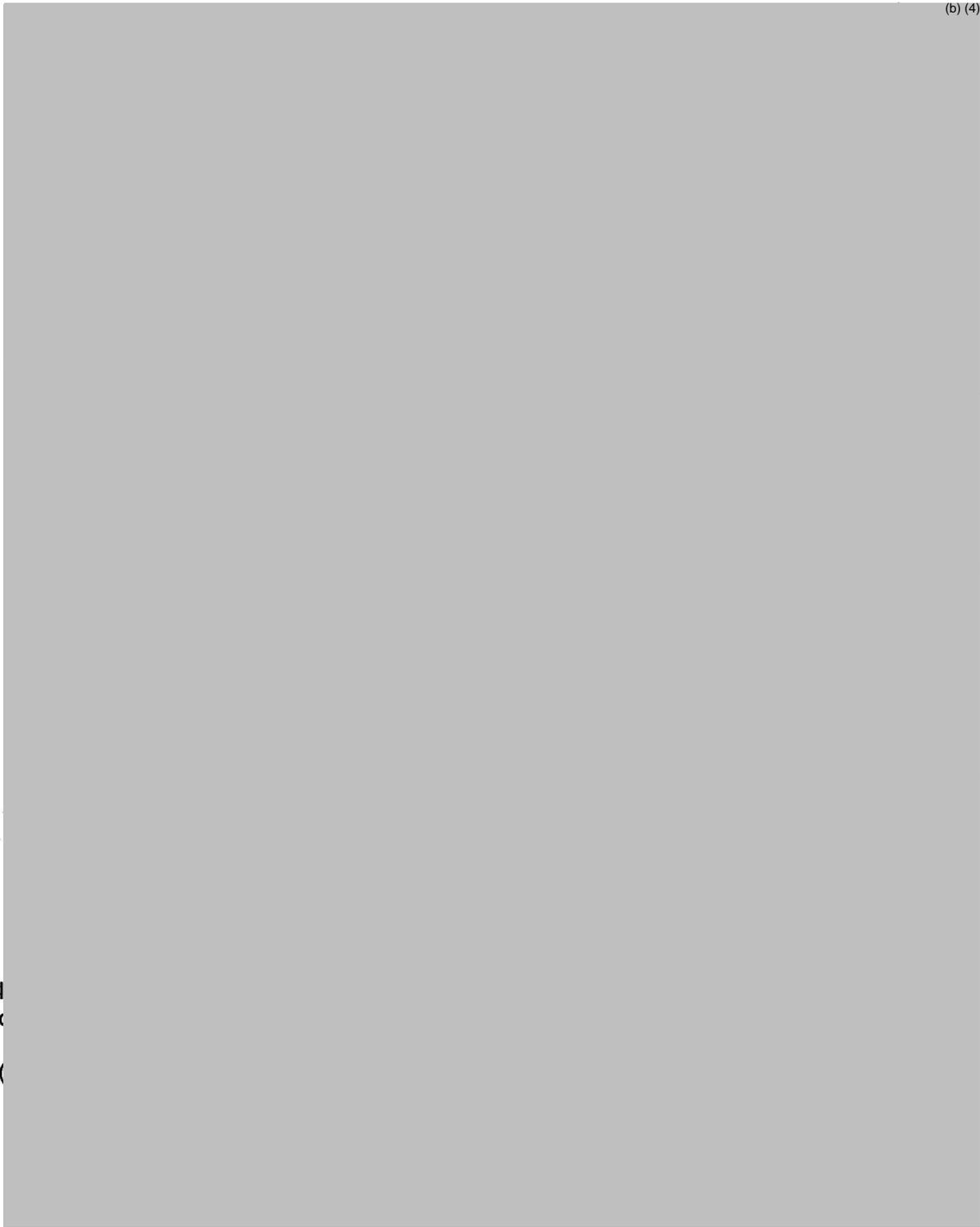
August 04, 2006

- 4 -

(b) (4)



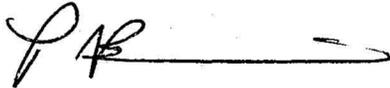
.../cont'd



(b) (4)

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 508-2359.

Yours sincerely,



Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:cd

Encl.

.../cont'd

MINOR AMENDMENT

ANDA 77-395

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)



JUL 26 2006

APPLICANT: Apotex Corp.

TEL: (954) 349-4217

ATTN: Tammy McIntire

FAX: (905) 508-2359

FROM: Cheryl Wiseman

PROJECT MANAGER: (301) 827-5806

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated November 18, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Paroxetine Hydrochloride Oral Suspension, 10 mg/mL.

Reference is also made to your amendment dated December 23, 2005 and June 13, 2006.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

CW

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

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

2 pages are withheld after this page as b4 (CCI/TS)

ORIGINAL

ORIG AMENDMENT

N / AF

July 07, 2006

Ms. Michelle Dillahunt
Division of Labeling and Program Support
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Dillahunt:

Re: **LABELING AMENDMENT**
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL; ANDA No. 77-395

Further to your Labeling Amendment letter dated June 05, 2006, we are pleased to provide you with our response in duplicate (Archival and Review copies). For ease of review, we have enclosed a copy of your letter as Attachment 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment 2.

Labeling Deficiencies:

INSERT

Due to revisions to the current insert labeling for Paxil Tablets (combined insert with Paxil Suspension), approved May 3, 2006, please make the following changes:

1. **PRECAUTIONS**

- a. *Add the following paragraph to appear after the "Discontinuation of Treatment with Paroxetine" subsection;*
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.*

RECEIVED

JUL 10 2006

OGD / CDER

.../cont'd



- b. Add the following paragraph to appear after the "Abnormal Bleeding" subsection;
Serotonin Syndrome: The development of a serotonin syndrome may occur in association with treatment with paroxetine, particularly with concomitant use of serotonergic drugs and with drugs which may have impaired metabolism of paroxetine. Symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia, and tremor. The concomitant use of paroxetine with serotonin precursors (such as tryptophan) is not recommended (see WARNINGS, Potential for Interaction with Monoamine Oxidase Inhibitors and PRECAUTIONS, Drug Interactions).
- c. Drug interactions, Tryptophan, add the following to follow the last sentence: "(see Serotonin Syndrome)".
- d. Add the following paragraph to appear after the "Pimozide" subsection;
Serotonergic Drugs: Based on the mechanism of action of paroxetine and the potential for serotonin syndrome, caution is advised when PAXIL is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see Serotonin Syndrome).
- e. Triptans, add the following to follow the last sentence; "(see Serotonin Syndrome)".
- f. Pediatric Use, add the following as the second and third paragraphs;
In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with paroxetine 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 paroxetine in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received paroxetine 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 Discontinuation of Treatment With Paroxetine).

Response: As requested, the above changes have been incorporated into the Apotex Inc. prescribing information.

2. HOW SUPPLIED

- a. *Add the established name to precede the description of your product.*
- b. *Include the flavor of your product to be in accordance with the reference listed drug.*

Response: As requested, the How Supplied section has been amended to include the established name of the Apotex Inc. product and the flavor of the product has been added to be in accordance with the reference listed drug.

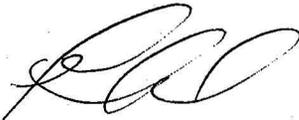
Copies of the final printed package insert (prescribing information and medication guide) have been provided electronically (appended to the cover letter in the Review copy only). In addition an annotated side-by-side labeling comparison for the package insert has been included in Attachment 3.

In the event that there are additional approved changes for the reference listed drug labeling, Apotex Inc. shall further revise our labeling accordingly.

Please note that the enclosed electronic CD has been confirmed to be virus free using McAfee Virus 7.1

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 508-2359.

Yours sincerely,



Dr. Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

ORIG AMENDMENT

N-000-AB

June 14, 2006

Ms. Keri Suh, Pharm. D.
Project Manager, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Suh:

Re: BIOEQUIVALENCY AMENDMENT
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL; ANDA No. 77-395

Further to your Bioequivalency Amendment letter dated March 27, 2006, we are pleased to provide you with our response in duplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of your letter as Attachment 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h and a Field Copy Certification for this response have been prepared and are enclosed in Attachments 2 and 3 respectively.

The following deficiencies have been identified:

1. *We acknowledge that you have accepted the following dissolution method:*

The dissolution testing should be conducted in 900 mL of Simulated Gastric Fluid without pepsin at 37°C using USP Apparatus 2 (paddle) at 100 rpm. The test product should meet the following specification: Not less than (b) (4) (Q) of the labeled amount dissolved in 30 minutes.

Response: The dissolution testing will be conducted as per the dissolution method outlined above.

2. *Your dissolution testing is incomplete. It is not clear from the data submitted if each dosage unit used for dissolution testing was taken from the same bottle or from different bottles. Please note that 12 dosage units should be from 12 separate bottles. If the dosage units were not taken from separate bottles, please conduct and submit dissolution testing on the test and reference products taking each dosage unit from separate bottles. In your response, please also acknowledge your acceptance of the FDA-recommended dissolution specification.*

RECEIVED
JUN 15 2006
OGD / CDER

.../cont'd

Response: As requested, the dissolution testing has been conducted on 12 dosage units from 12 separate bottles for both the test and reference products. A copy of the comparative dissolution data is provided in Attachment 4.

Apotex Inc. hereby acknowledges acceptance of the FDA-recommended dissolution specification. The finished product specification has been updated accordingly and a copy is included in Attachment 5. A copy of the revised test method TM-1939 is also included in Attachment 6.

3. *Please provide potency and content uniformity of the test and potency of the reference listed drug used in the bioequivalence studies. Please also provide the bio-batch size and production batch size of the test product.*

Response: As requested, the potency and content uniformity of the test product and potency of the reference listed drug product used in the bioequivalence studies have been provided in the tables below. The assay and content uniformity were analyzed using test method TM-1485.

Paroxetine HCl Oral Suspension (Apotex Inc.) Batch No. GL6385			
Assay	Content Uniformity (% Label Claim)		
98.6%	1	(b) (4)	
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
	Mean:	98.8	
	% RSD:	0.4	
	Min:	97.8	
Max:	99.1		

Paxil (GlaxoSmithKline) Lot No. X103P15 (Expiry: 12/2006)	
Assay	99.4%

The batch size of the bio-batch and the production batch (Bulk Batch No. GL6384/
 Finished Product Batch No. GL6385) is (b) (4)

4. *From the Tables of Reanalysis of Study (both fasting and fed) Samples you provided, it is not clear if those reanalyzed values were used in the statistical analysis. Please clarify.*

Response: All samples referred to in Table 8 "Reanalysis of Study Samples" in the studies (PARO-IMSU-01NB01-2FA, Internal Study Code: PX1543 and PARO-IMSU-01NB02-2FE Internal Study Code: PX1720) were reanalyzed because there was no acceptable original value. In these studies the reanalysis generated the only reportable value that there is no recalculation value to consider. Therefore, in all cases the reanalyzed sample values were used in the statistical analysis.

Apotex Inc.'s interpretation of the right hand column in this table is that it is only used where there was more than one valid value.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,



for: Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

ORIG AMENDMENT

N/A

June 13, 2006

Office of Generic Drugs – HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

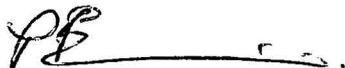
Re: GRATUITOUS CHEMISTRY AMENDMENT
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL; ANDA No. 77-395

In accordance with 21 CFR 314.96(a)(1), we are submitting a Gratuitous Amendment to our unapproved application for Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL. This Gratuitous Amendment has been provided in triplicate (Archival, Review and Field copies). A signed Application Form FDA 356h has been prepared and can be found as Attachment 1, and a Field Copy Certification can be found as Attachment 2.

We would like to inform the Agency of a change to the Cap Removal Torque range (an In-Process check parameter) used during the filling/packaging process for Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL. The removal torque range is being changed from [REDACTED] (b) (4). The supporting data (Study Protocol # PPD-PK-06-03) for this change is provided in Attachment 3.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 508-2359.

Yours sincerely,



Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:sf

Encl.

RECEIVED
JUN 14 2006
OGD / CDER

ORIG AMENDMENT
N/AF

May 03, 2006

Ms. Michelle Dillahunt
Division of Labeling and Program Support
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Dillahunt:

Re: LABELING AMENDMENT
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL; ANDA No. 77-395

Further to your Labeling Amendment letter dated September 08, 2005, we are pleased to provide you with our response in duplicate (Archival and Review copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

Labeling Deficiencies:

1. CONTAINER – 250 mL

Include a statement; "PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE" on the principal display panel.

Response: As requested, the statement has been added to the container label.

2. CARTON – 250 mL

See comment under CONTAINER.

Response: As requested, the statement has been added to the carton.

RECEIVED
MAY 05 2006
OGD / CDER

.../cont'd



3. *INSERT*a. *GENERAL*

Revise your insert labeling to be in accord with the reference listed drug, Paxil® Oral Suspension, approved 7-13-05. You should address all patents and exclusivities listed in the "Approved Drug Products with Therapeutic Equivalence Evaluation" (the Orange Book) and revise your labeling accordingly.

Response: The package insert (prescribing information and medication guide) has been updated according to the Reference Listed Drug labeling (dated 2005) provided electronically by Michelle Dillahunt of FDA, on February 13, 2006.

All patents and exclusivities listed in the "Approved Drug Products with Therapeutic Equivalence Evaluation" have been addressed. Please refer to the Paragraph IV Patent Certification and Exclusivity Statements.

Copies of the final printed labeling (container label, carton and package insert) have been provided electronically (appended to the cover letter in the Review copy only). In addition an annotated side-by-side labeling comparison for the container label, carton and package insert (prescribing information and medication guide) have been included in Attachment No. 3.

In the event that there are additional approved changes for the reference listed drug labeling, Apotex Inc. shall further revise our labeling accordingly.

Please note that the enclosed electronic CD has been confirmed to be virus free using McAfee Virus 7.1

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 508-2359.

Yours sincerely,



Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

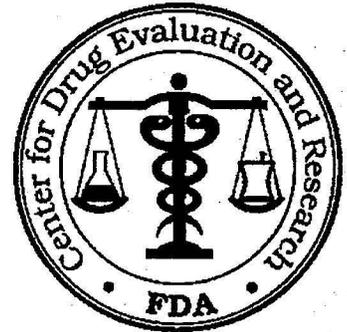
Encl.

BIOEQUIVALENCY AMENDMENT

ANDA 77-395

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)

MAR 27 2006



APPLICANT: Apotex Corp.
U.S. Agent for Apotex Inc.

TEL: 954-349-4200

FAX: 954-349-4233

ATTN: Tammy McIntire

FROM: Keri Suh 

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on February 9, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL.

Reference is also made to your amendment dated August 16, 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:

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

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

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-395

APPLICANT: Apotex Inc.

DRUG PRODUCT: Paroxetine Oral Suspension, 10 mg/5 mL

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

1. We acknowledge that you have accepted the following dissolution method:

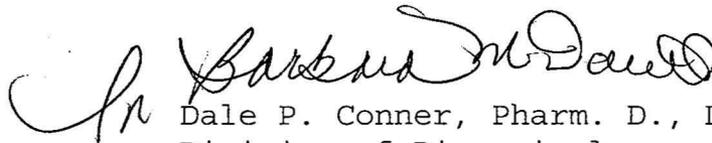
The dissolution testing should be conducted in 900 mL of Simulated Gastric Fluid without pepsin at 37°C using USP Apparatus 2 (paddle) at 100 rpm. The test product should meet the following specification: Not less than (b)(4)(Q) of the labeled amount dissolved in 30 minutes.

2. Your dissolution testing is incomplete. It is not clear from the data submitted if each dosage unit used for dissolution testing was taken from the same bottle or from different bottles. Please note that 12 dosage units should be from 12 separate bottles. If the dosage units were not taken from separate bottles, please conduct and submit dissolution testing on the test and reference products taking each dosage unit from separate bottles. In your response, please also acknowledge your acceptance of the FDA-recommended dissolution specification.

3. Please provide potency and content uniformity of the test and potency of the reference listed drug used in the bioequivalence studies. Please also provide the bio-batch size and the production batch size of the test product.

4. From the Tables of Reanalysis of Study (both fasting and fed) Samples you provided, it is not clear if those reanalyzed values were used in the statistical analysis. Please clarify.

Sincerely yours,



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

December 23, 2005

Ms. Cheryl Wiseman
Project Manager, Division of Chemistry II
Office of Generic Drugs (HFD-640)
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

n/a

Dear Ms. Wiseman:

Re: MINOR AMENDMENT
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL; ANDA No. 77-395

Further to your Minor Amendment letter dated August 18, 2005, we are pleased to provide you with our response in triplicate (Archival, Field and Review Copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in question-and-answer format. An Application Form 356h has been prepared and enclosed in Attachment No. 2 and a signed Field Copy Certification can be found in Attachment No. 3.

A. Chemistry Deficiencies:



(b) (4)

DEC 27 2005

.../cont'd

OGD/CDER

(b) (4)

(b) (4)

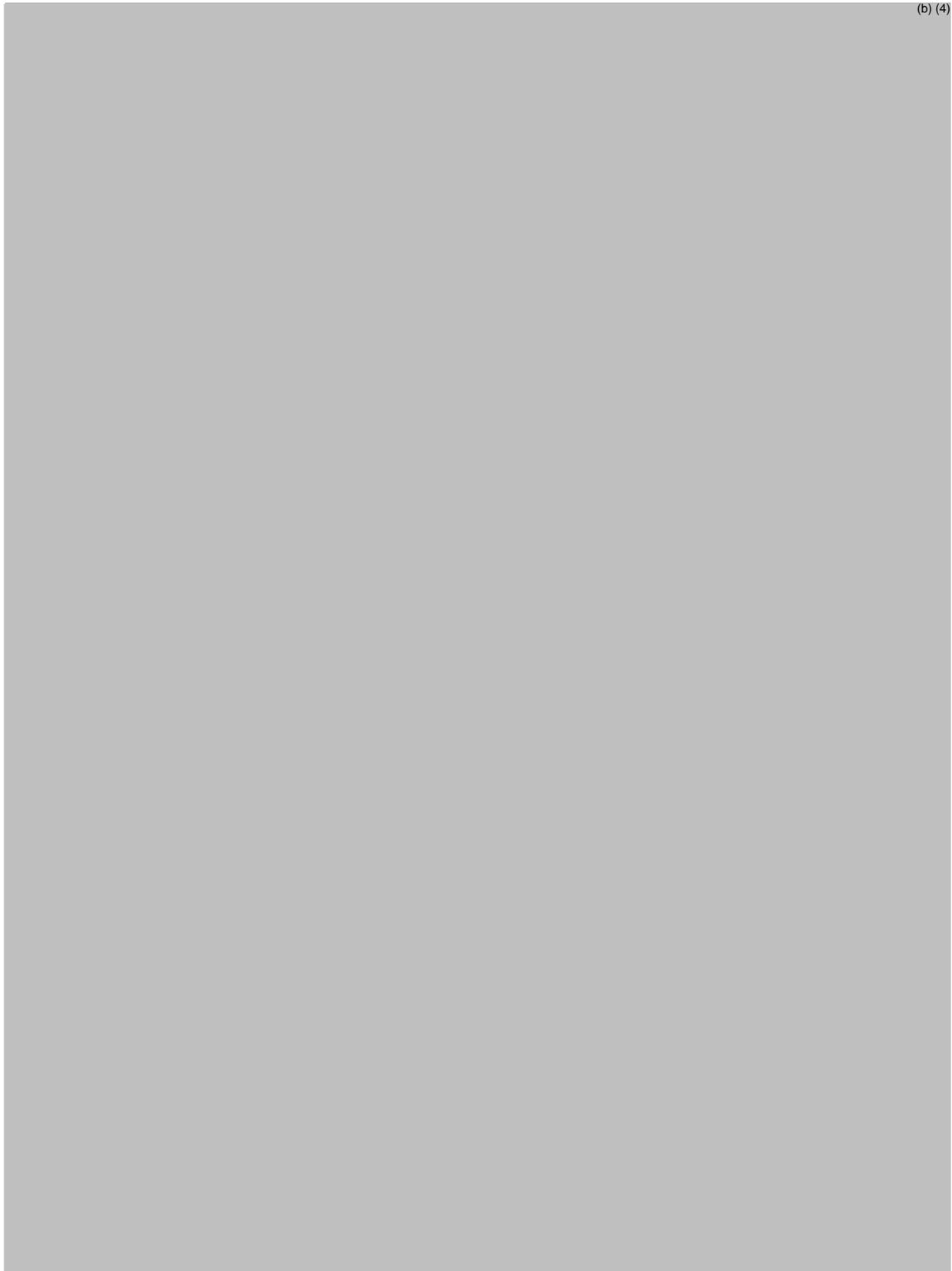
(b) (4)

.../cont'd

(b) (4)



.../cont'd



(b) (4)

.../cont'd

(b) (4)



b.

.../cont'd

(b) (4)



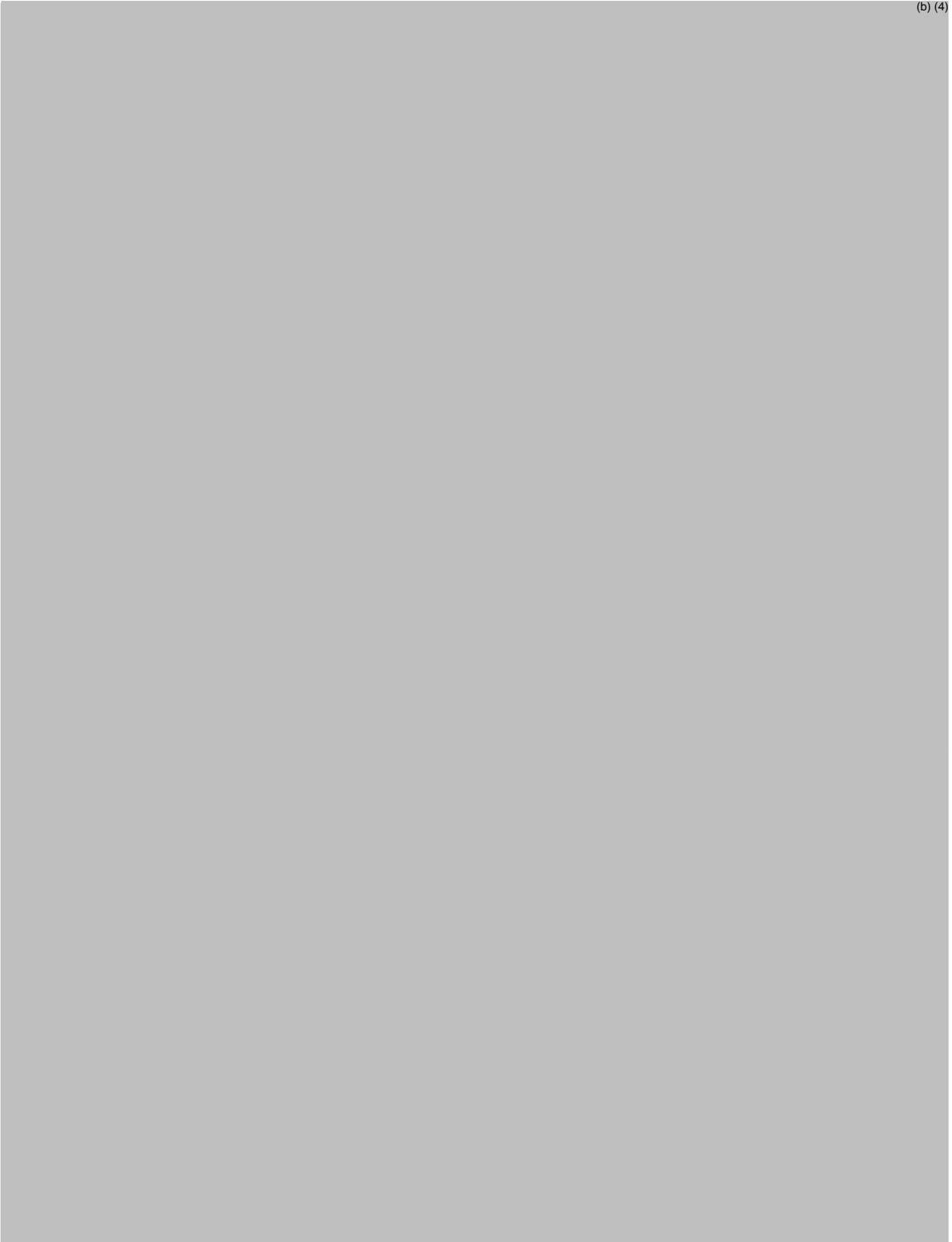
.../cont'd



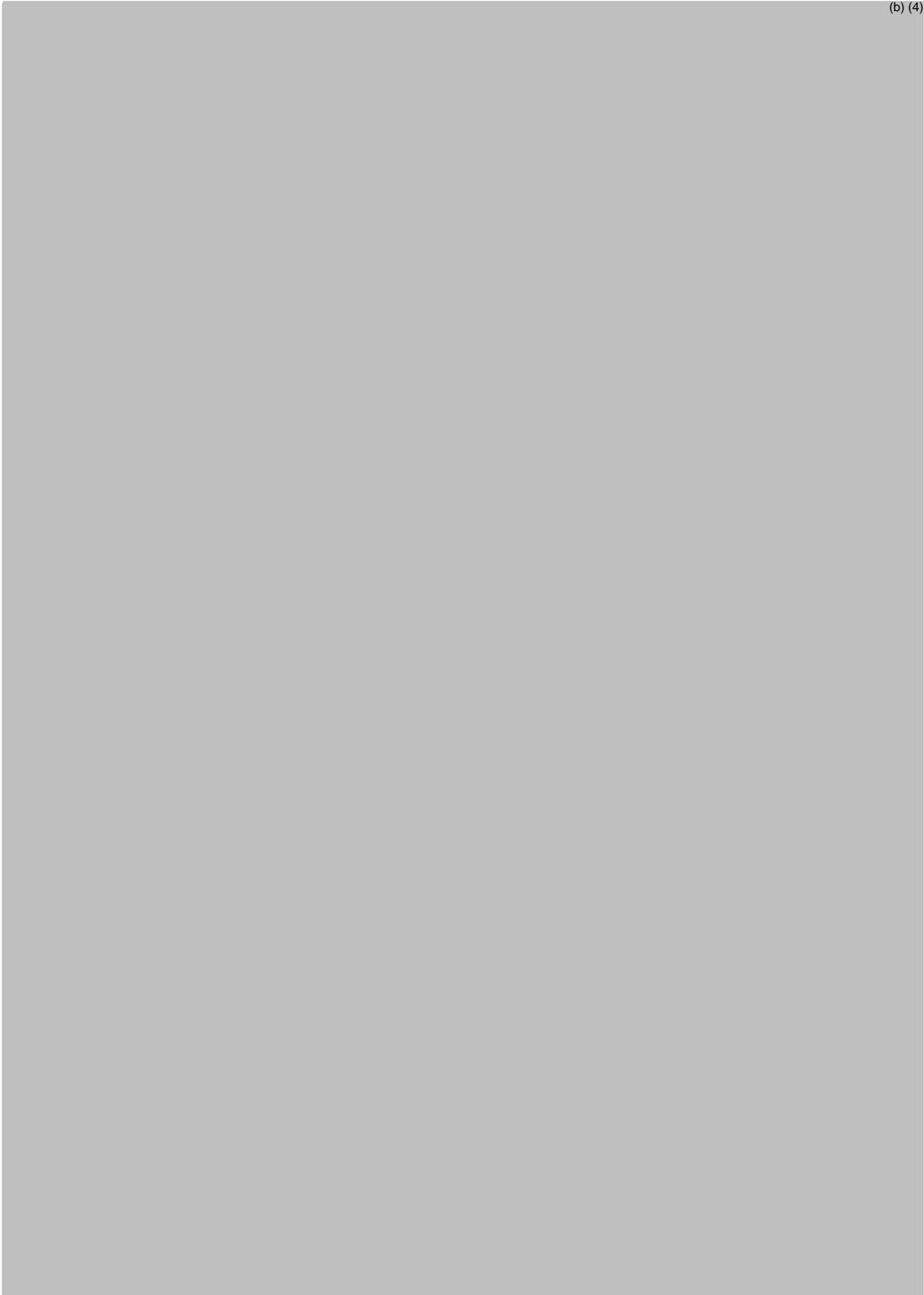
(b) (4)

.../cont'd

(b) (4)



.../cont'd



(b) (4)

5.

.../cont'd

(b) (4)



.../cont'd

(b) (4)



.../cont'd

[Redacted] (b) (4)

[Redacted]

[Redacted]

[Redacted]

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 884-0357.

Yours sincerely,



Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

ORIG AMENDMENT
N/AB

August 16, 2005

Ms. Christina Thompson
Project Manager, Division of Bioequivalence
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Thompson:

Re: BIOEQUIVALENCY AMENDMENT
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL; ANDA No. 77-395

Further to your Bioequivalency Amendment letter dated May 31, 2005, we are pleased to provide you with our response in duplicate (Archival and Review copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

The following deficiencies have been identified:

- 1. The dissolution testing is not acceptable. Please conduct dissolution testing using 12 dosage units of each test and reference product using the following method:*

<i>USP Apparatus</i>	<i>2 (paddle)</i>
<i>Speed</i>	<i>100 rpm</i>
<i>Medium</i>	<i>Simulated Gastric Fluid without pepsin</i>
<i>Volume</i>	<i>900 mL</i>
<i>Sampling times:</i>	<i>5, 10, 15, 20, and 30 minutes and until at least (b) (4) of the labeled content is dissolved.</i>

Response: As requested, the dissolution testing has been conducted as outlined above. The results are included in Attachment No. 3.

.../cont'd

RECEIVED

AUG 17 2005

OGD/CDER

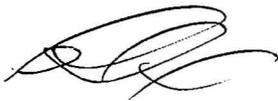


2. *In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.*

Response: As requested, the *in vivo* study data, dissolution data and formulation data are provided in accordance with the template provided (see Attachment No. 4). In addition, an electronic file of the study summaries is also included in Attachment No. 4 (of the Review copy only).

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 884-0357.

Yours sincerely,



for: Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:mt

Encl.

XP

NAI
Not sued on
'436, '423, '132, '44
'289 & '291.
CMB
7/20/05

June 10, 2005

Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

Re: PATENT AMENDMENT
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL, ANDA No. 77-395

Further to our Abbreviated New Drug Application dated November 18, 2004, and our Patent Amendment dated April 04, 2005, we would like to inform you that no litigation has been filed against Apotex Inc. to date, by the NDA holder/Patent owner of Patent Nos. 4,721,723; 5,811,436; 5,900,423; 5,872,132; 5,789,449; 6,133,289 and 6,121,291. A signed Application Form FDA 356h is included.

Please note that as previously stated in the Patent Amendment dated April 20, 2005, the notification of certification of invalidity or non-infringement to Mr. Michael Norden, one of the patent owners, was sent to at the address indicated in the US Patent and Trademark Office as required by CFR 314.95(a)(1); however, the notice letter was returned as undeliverable. Apotex Inc. made several additional attempts to notify Mr. Michael Norden but was unsuccessful. As per Mr. Martin Shimer's advice on a telephone call with Ms. Robin Windover on April 28, 2005, please find enclosed a copy of the receipt for the undeliverable notice letter as a proof of patent notification to Mr. Michael Norden. In addition, the FedEx tracking log and a copy of the cover letter on the FedEx package have also been included for review.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 884-0357.

Yours sincerely,



Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:sf

Encl.

cc: William A. Rakoczy, Counsel for Apotex

RECEIVED

JUN 13 2005

OGD / CDER

BIOEQUIVALENCY AMENDMENT

2.1

ANDA 77-395

MAY 31 2005

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



APPLICANT: Apotex Corp.
U.S. Agent for Apotex Inc.

TEL: 847-279-7740

ATTN: Marcy Macdonald

FAX: 847-353-2982

FROM: Christina Thompson U

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on November 18, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL.

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

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

SPECIAL INSTRUCTIONS:

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

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

MAY 31 2005

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-395

APPLICANT: Apotex Inc.

DRUG PRODUCT: Paroxetine Hydrochloride Oral Suspension,
10 mg/5 mL

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

1. The dissolution testing is not acceptable. Please conduct dissolution testing using 12 dosage units of each test and reference product using the following method:

USP Apparatus	2 (paddle)
Speed	100 rpm
Medium	Simulated Gastric Fluid without pepsin
Volume	900 mL
Sampling times:	5, 10, 15, 20, and 30 minutes and until at least (b) (4) of the labeled content is dissolved.

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

Sincerely yours,



Barbara M. Davis

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

Table 1. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters (+/-SD)						Study Report Location
					C _{max} (units/mL)	T _{max} (hr)	AUC _{0-t} (units)	AUC _∞ (units)	T _{1/2} (hr)	K _{e1} (hr ⁻¹)	
Study #	Fasting study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #
Study #	Fed study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean y (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #

Table 2. Statistical Summary of the Comparative Bioavailability Data

Drug Dose (# x mg) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	Ratio	90% C.I.
AUC _{0-t}				
AUC _∞				
C _{max}				
Fed Bioequivalence Study				
Parameter	Test	Reference	100*Ratio	90% C.I.
AUC _{0-t}				
AUC _∞				
C _{max}				

Table 3. Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	Provide the name(s) of the analyte(s)
Internal standard (IS)	Identify the internal standard used
Method description	Brief description of extraction method; analytical method
Limit of quantitation	LOQ, units
Average recovery of drug (%)	%
Average recovery of IS (%)	%
Standard curve concentrations (units/mL)	Standard curve range and appropriate concentration units
QC concentrations (units/mL)	List all the concentrations used
QC Intraday precision range (%)	Range or per QC
QC Intraday accuracy range (%)	Range or per QC
QC Interday precision range (%)	Range or per QC
QC Interday accuracy range (%)	Range or per QC
Bench-top stability (hrs)	hours @ room temperature
Stock stability (days)	days @ 4°C
Processed stability (hrs)	hours @ room temperature; hours @ 4°C
Freeze-thaw stability (cycles)	# cycles
Long-term storage stability (days)	17 days @ -20°C (or other)
Dilution integrity	Concentration diluted X-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 4. Summary of In Vitro Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)				Study Report Location
					min	min	min	min	
Diss. study report #	Test prod name/ #	mg Tab./Cap./Susp.	Dissolution: Apparatus Speed of Rotation: rpm Medium: Volume: mL Temperature: °C	12					
Diss. study report #	Ref prod name/ #	mg Tab./Cap./Susp.		12					

Table 5. Formulation Data

Ingredient	Amount (mg) / Tablet		Amount (%) Tablet	
	Lower strength	Higher strength	Lower strength	Higher strength
Cores				
Coating				
Total			100.00	100.0

Table 6. Demographic Profile of Subjects Completing the Bioequivalence Study

	Study No.	
	Treatment Groups	
	Test Product N =	Reference Product N =
Age (years)		
Mean ± SD	50 ± 15	
Range	20-85	
Groups		
< 18	N(%)	N(%)
18 – 40	N(%)	N(%)
40 – 64	N(%)	N(%)
65 – 75	N(%)	N(%)
> 75	N(%)	N(%)
Sex		
Female	N(%)	N(%)
Male	N(%)	N(%)
Race		
Asian	N(%)	N(%)
Black	N(%)	N(%)
Caucasian	N(%)	N(%)
Hispanic	N(%)	N(%)
Other	N(%)	N(%)
Other Factors		

Table 8. Reanalysis of Study Samples

Study No.								
Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹								
Reason A (e.g. below LOQ)								
Reason B								
Reason C								
Etc.								
Total								

¹ If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

Cindy
Thelmer
PAI
5/2/05

April 20, 2005

616 HEATHROW DRIVE • LINCOLNSHIRE • ILLINOIS 60069 • TEL: (847) 821-8005 • FAX: (847) 821-1001

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

N/XP

PATENT AMENDMENT

RE: Paroxetine Hydrochloride Oral Suspension,
10 mg/5 mL,
ANDA No. 77-395
U.S. Patent No.'s: 4,721,723; 5,811,436; 5,900,423; 5,872,132; 5,789,449; 6,133,289 and
6,121,291.

To Whom It May Concern:

Apotex Corp., is submitting proof of patent notification to the patent holders regarding the above referenced product and patent numbers.

Apotex sent out notification letters dated March 30, 2005; all six notices are identical and have original signatures. Unfortunately, the notification letter to Mr. Michael Norden, Seattle, Washington was returned as undeliverable, although Apotex sent notice of its certification to Mr. Norden at the address he has on record at the U.S. Patent and Trademark Office, as required under 21 C.F.R. 314.95(a)(1). Several attempts were made to find a correct address to forward notification to Mr. Norden with no success to date.

As Apotex's responsibility is only to provide notice to the patentee at the address listed with the Patent and Trademark Office, Apotex considers this requirement to be fulfilled in light of their due diligence in attempting to contact this individual.

If you have any further questions, please do not hesitate to contact me at 847-279-7740.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs

RECEIVED
APR 21 2005
OGD / CDER

G. Meher
NAI
4/21/05

PATENT AMENDMENT

N/x P

April 04, 2005

Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

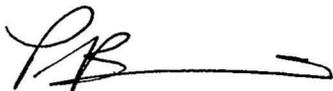
Dear Sir/Madam:

Re: Patent Amendment
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL, ANDA No. 77-395

Further to our Abbreviated New Drug Application dated November 18, 2004, and in accordance with 21 CFR 314.95, please find enclosed a Statement indicating that the required Notice of Certification of Invalidity, Unenforceability or Non-Infringement has been given to the approved NDA holder and the patent owners. The Statement also indicates that said Notice meets the requirements of 21 CFR 314.95(a) and 21 CFR 314.95(c). Documentation of receipt of notice will be provided as required by 21 CFR 314.95(e). In addition, a Form FDA 356h, a Field Copy Certification and a copy of the Notice of Certification of Invalidity, Unenforceability or Non-Infringement are provided.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 884-0357.

Yours sincerely,



Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

cc: Apotex Corp.

RECEIVED
APR 06 2005
OGD/CDER

ANDA 77-395

Apotex Corp.
U.S. Agent for Apotex Inc.
Attention: Marcy Macdonald
616 Heathrow Drive
Lincolnshire, IL 60069
|||||

MAR 18 2005

Dear Madam:

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

Reference is made to the "Refuse to Receive" letter dated January 14, 2005 and your amendment dated February 9, 2005.

NAME OF DRUG: Paroxetine Hydrochloride Oral Suspension,
10 mg/5 mL

DATE OF APPLICATION: November 18, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 10, 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 court order or judgement, or a settlement agreement, 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)827-5862.

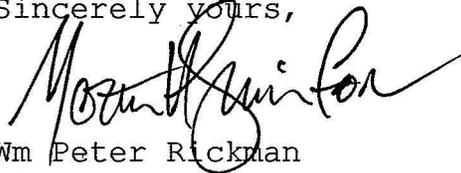
We will correspond with you further after we have had the opportunity to review the application.

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

Should you have questions concerning this application, contact:

Thomas Hinchliffe
Project Manager
(301) 827-5849

Sincerely yours,



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

ANDA 77-395

cc: DUP/Jackets

HFD-600/Division File

Field Copy

HFD-610

HFD-92

Endorsement:

HFD-615/MShimer, Chief, RSB *Monty R...* date 16 March 05

HFD-615/ETHakur, CSO *...* date

Word File V:\Firmsam\apotex\ltrs&rev\77395.ack

FT/ETT03/15/05

ANDA Acknowledgment Letter!

ANDA 77-395 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
- NDA 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. Phxi (Susp.
- 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. I-315 exp 12/14/04 → ped 6/14/05 PIV → '732, '436, '132, '423, '41
'289, '291
- 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. [Signature]

date

16 March 2005

ORIG AMENDMENT

February 09, 2005

Ms. Emily Thakur
Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/A
505167 (A)
Mortimer
16 March 2005

Dear Ms. Thakur:

Re: RESPONSE TO REFUSAL TO FILE
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL; ANDA No. 77-395

Further to your Refusal to File letter dated January 14, 2005, we are pleased to provide you with our response in triplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2. A signed Field copy certification has been included as Attachment No. 3.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

You have failed to submit in vitro comparative dissolution profiles comparing your proposed drug product against the reference listed drug. A complete dissolution report should contain the individual data for twelve dosage units (for both the proposed product and the reference listed product), including means, range and relative standard deviation (RSD) at each time point, a description of the methodology being used, and the lot numbers being tested.

Response: As requested, a complete dissolution report with individual data for twelve dosage units (for both the proposed product and the reference listed product) has been prepared and included in Attachment No. 4. In addition, a copy of test method TM-1939 has been included in Attachment No. 5.

RECEIVED

FEB 10 2005

.../cont'd

OGD / CDER



In addition, please provide a revised exclusivity statement that clarifies your intent upon approval of your ANDA or upon expiration of the exclusivity.

Response: As requested, Apotex Inc. has revised the exclusivity statement to indicate that our product will not be marketed until after expiration of the exclusivities. The revised Exclusivity Statement is included in Attachment No. 6.

You have omitted claims from your proposed labeling related to the treatment of Posttraumatic Stress Disorder. We note that Apotex has provided a Paragraph IV certification to the 6,121,291 patent associated with U-431. Please explain this incongruous relationship between your labeling and your patent certification.

Response: The 'Usage and Indication' section of the prescribing information has been revised to include Posttraumatic Stress Disorder.

A copy of the current labeling has been provided electronically (appended to the cover letter in the review copy only). In addition, an annotated side-by-side labeling comparison has been included in Attachment No. 7.

Please provide a sample statement – a statement of availability and identification of the drug substance and finished drug product.

Response: A copy of the Sample Commitment can be located in the original submission under Section 3.2.R.3.P 'Methods Validation Package'. A reference to the Sample Commitment was also included in the Table of Contents.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 884-0357.

Yours sincerely,



Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:cd

Encl.

ANDA 77395 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.
- CR 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)
- 5) Check address and contact person on letter vs. 356h.
- NIA 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. Paxil Susp
- 12) Check for MOU patents (must include PTSD)
- 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.
- 14) Review Basis for Submission. Paxil 20-710
- 15) Review Patent Certifications and Exclusivity Statement. (If an PIV cert to '723, '436, '132, '423, '449
'289 & '291
I-345+ ped exp 6/14/2005 expiration of an exclusivity has occurred make a note to the Labeling reviewer.)
- 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. Why is PTSD removed from Label '291 U-431
- CR 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 A. Suman date 15 Jan 2005

JAN 14 2005

Apotex Corp.
U.S. Agent for Apotex Inc.
Attention: Marcy Macdonald
616 Heathrow Drive
Lincolnshire, IL 60069
|||||

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated November 18, 2004, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d) (3) for the following reasons:

You have failed to submit *in vitro* comparative dissolution profiles comparing your proposed drug product against the reference listed drug. A complete dissolution report should contain the individual data for twelve dosage units (for both the proposed product and the reference listed product) including means, range and relative standard deviation (RSD) at each time point, a description of the methodology being used, and the lot numbers being tested.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, please provide a revised exclusivity statement that clarifies your intent upon approval of your ANDA or upon expiration of the exclusivity.

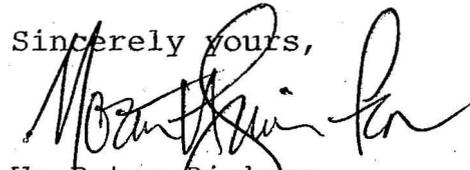
You have omitted claims from your proposed labeling related to the treatment of Posttraumatic Stress Disorder. We note that Apotex has provided a Paragraph IV certification to the 6,121,291 patent associated with U-431. Please explain this incongruous relationship between your labeling and your patent certification.

Please provide a sample statement - a statement of availability and identification of the drug substance and finished drug product.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Emily Thakur
Project Manager
(301) 827-5862

Sincerely yours,



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

ANDA 77-395

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/
HFD-92

Endorsement:

HFD-615/MShimer, Chief, RSB  date MAY 2005

HFD-615/ETHakur, CSO Anthony Rickman 11/14/05 date

Word Document V:\Firmsam\apotex\ltrs&rev\77395.rtf

F/T ETT01/14/05

ANDA Refuse to File!

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-395 FIRM NAME: APOTEX INC.

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: PAROXETINE HYDROCHLORIDE

DOSAGE FORM: ORAL SUSPENSION, 10 MG/5 ML

Bio Assignments:		<input type="checkbox"/> Micro Review
<input checked="" type="checkbox"/> BPH	<input type="checkbox"/> BCE	
<input type="checkbox"/> BST	<input checked="" type="checkbox"/> BDI	

Random Queue: 10

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

Letter Date: NOVEMBER 19, 2004	Received Date: NOVEMBER 22, 2004
Comments: EC-1 YES On Cards: YES	
Therapeutic Code: 2020100 ANTIDEPRESSANTS	
Archival Format: PAPER Sections I (356H Sections per EDR Email)	<i>Scanned 12-14-04</i>
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) NO (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	Recommendation:
Date	<input type="checkbox"/> FILE <input checked="" type="checkbox"/> REFUSE to RECEIVE
Supervisory Concurrence/Date: <i>[Signature]</i>	Date: 14 JAN 2005
ADDITIONAL COMMENTS REGARDING THE ANDA: • <i>Check EDR</i> • <i>check OB</i> • <i>copy financial disclosure - revise exclusivity statement - verify condition of use in comparison</i> • <i>need list of addresses for marketing</i> • <i>sample statement</i> • <i>where is dissolution?</i>	
Top 200 Drug Product:	

lot # ~~626385~~ 626385
(b) (4)



Sec. I	Signed and Completed Application Form (356h) YES (Statement regarding Rx/OTC Status) RX YES <i>marcy macdonald (847) 279-7740</i>	<input checked="" type="checkbox"/>
Sec. II	Basis for Submission NDA# : 20-710 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. <p style="text-align: right;">Wavier Granted:</p>	<input checked="" type="checkbox"/>
Sec. III	Patent Certification 1. Paragraph: IV 2. Expiration of Patent: 9-17-2017 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? Exclusivity Statement: YES	<input type="checkbox"/>
Sec. IV	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use <i>PTSD removed</i> 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓	<input type="checkbox"/>
Sec. V	Labeling (Mult Copies N/A for E-Submissions) 1. X copies of draft (each strength and container) or 12 copies of FPL 1 ✓ 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? (If yes, send email to Labeling Rvwr indicating such.)	<input type="checkbox"/>
Sec. VI	Bioavailability/Bioequivalence 1. Financial Certification (Form FDA 3454) and Disclosure Statement (Form 3455) YES ✓ 2. Request for Waiver of In-Vivo Study(ies): NA 3. Formulation data same? (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) <i>U/A</i> 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)	<input checked="" type="checkbox"/>
Study Type	IN-VIVO PK STUDY(IES) (i.e., fasting/fed/sprinkle) FASTING AND FED ON 10 MG/5 ML a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) <i>fast - vol 1.4 pg 10 ✓</i> b. EDR Email: Data Files Submitted: YES SENT TO EDR <i>fed - vol 1.7 pg 10 ✓</i> c. In-Vitro Dissolution: YES	<input type="checkbox"/>

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

<p>Sec. VIII</p>	<p>Raw Materials Controls</p> <p>1. Active Ingredients</p> <p>a. Addresses of bulk manufacturers ✓</p> <p>b. Type II DMF authorization letters or synthesis ✓ 12770</p> <p>c. COA(s) specifications and test results from drug substance mfr(s) ✓</p> <p>d. Applicant certificate of analysis ✓</p> <p>e. Testing specifications and data from drug product manufacturer(s) ✓</p> <p>f. Spectra and chromatograms for reference standards and test samples ✓</p> <p>g. CFN numbers</p> <p>2. Inactive Ingredients</p> <p>a. Source of inactive ingredients identified ✓</p> <p>b. Testing specifications (including identification and characterization) ✓</p> <p>c. Suppliers' COA (specifications and test results) ✓</p> <p>d. Applicant certificate of analysis ✓</p>	<p>☒</p>
<p>Sec. IX</p>	<p>Description of Manufacturing Facility</p> <p>1. Full Address(es) of the Facility(ies) ✓</p> <p>2. CGMP Certification: YES ✓</p> <p>3. CFN numbers</p>	<p>☒</p>
<p>Sec. X</p>	<p>Outside Firms Including Contract Testing Laboratories</p> <p>1. Full Address ✓</p> <p>2. Functions ✓</p> <p>3. CGMP Certification/GLP ✓</p> <p>4. CFN numbers</p>	<p>☒</p>
<p>Sec. XI</p>	<p>Manufacturing and Processing Instructions</p> <p>1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) ✓</p> <p>2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified ✓</p> <p>3. If sterile product: Aseptic fill / Terminal sterilization (b) (4) ✓</p> <p>4. Filter validation (if aseptic fill) (b) (4) ✓</p> <p>5. Reprocessing Statement ✓</p>	<p>☒</p>
<p>Sec. XII</p>	<p>In-Process Controls</p> <p>1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ✓</p> <p>2. In-process Controls - Specifications and data ✓</p>	<p>☒</p>
<p>Sec. XIII</p>	<p>Container</p> <p>1. Summary of Container/Closure System (if new resin, provide data) ✓</p> <p>2. Components Specification and Test Data (Type III DMF References) ✓</p> <p>3. Packaging Configuration and Sizes ✓</p> <p>4. Container/Closure Testing ✓</p> <p>5. Source of supply and suppliers address ✓</p>	<p>☒</p>

Sec. XIV	Controls for the Finished Dosage Form 1. Testing Specifications and Data ✓ 2. Certificate of Analysis for Finished Dosage Form ✓	<input checked="" type="checkbox"/>
Sec. XV	Stability of Finished Dosage Form 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 4. Stability Data Submitted a. 3 month accelerated stability data ✓ b. Batch numbers on stability records the same as the test batch ✓	<input checked="" type="checkbox"/>
Sec. XVI	Samples - Statement of Availability and Identification of: 1. Drug Substance 2. Finished Dosage Form 3. Same lot numbers	<input type="checkbox"/>
Sec. XVII	Environmental Impact Analysis Statement ✓	<input checked="" type="checkbox"/>
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 3. List of Convictions statement (original signature) ✓	<input checked="" type="checkbox"/>

(FYI)

MEMORANDUM

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

DATE : December 10, 2004
TO : Director
Division of Bioequivalence (HFD-650)
FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)



Handwritten signature and date: "11 Dec 2004"

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 77-395 for Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Apotex Inc. has submitted ANDA 77-395 for Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also 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 Apotex Inc. on November 18, 2004 for its Paroxetine Hydrochloride 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 Application Completeness of First Generic ANDA

ANDA# 77-395 **FIRM NAME** Apotex Inc.

DRUG NAME Paroxetine Hydrochloride

DOSAGE FORM 10 mg/5 ml oral suspension

SUBJ: Request for examination of bioequivalence study

Summary of Findings by Division of Bioequivalence	
<input type="checkbox"/>	Study meets statutory requirements
<input checked="" type="checkbox"/>	Study does NOT meet statutory requirements
	Reason: dissolution testing is not included
<input type="checkbox"/>	Waiver meets statutory requirements
<input type="checkbox"/>	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION:

The firm is requested to submit the dissolution testing results in the application.

Reviewed by:

Bing Li
Reviewer



Date:

01/11/05

S. Nerurkar
Team Leader



Date:

Item Verified:	YES	NO	Fasting study	Fed study
Protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, 1.1, p117	Section 16, p118
Assay Methodology	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Clinical: Section 3, p8 Analytical: Section 16, p 463 & 481	Clinical: Section 3, p8 Analytical: Section 16, p452
Procedure SOP	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, p490	Section 16, p 472
Methods Validation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16.6, p982	Section 16, p1010
Study Results Ln/Lin	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, p 319 & 356	Section 16, p 247 & 308
Adverse Events	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 12, p40, Section 14, p76, Section 16, p 393& 395	Section 12, p40 Section 14, p76
IRB Approval	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16.1.3, p 185	Section 16, p178
Dissolution Data	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not included	
Pre-screening of Patients	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 10, p32	Section 10, p32
Chromatograms	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16.5.12, p 561	Section 16, p527
Consent Forms	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, p143 (sample form only. It was mentioned (Section 5, p 19) that the consent forms were signed by the patients but the actual patient signed forms was not included)	Section 16, p142 (sample form only. It was mentioned (Section 5, p 19) that the consent forms were signed by the patients but the actual patient signed forms was not included)
Composition	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3.2.P.2.2.1 (red jacket, chemistry section)	3.2.P.2.2.1 (red jacket, chemistry section)
Summary of Study	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 13.1, p44	Section 13, p44
Individual Data & Graphs, Linear & Ln	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16.2.6, p283	Section 16, p274 & 308

PK/PD Data Disk Submitted)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Mentioned in cover letter Data can be found in EDR	
Randomization Schedule	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16.1.7, p228	Section 16, p217
Protocol Deviations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 10, p32	Section 16.2.2, p267 Section 14, p85
Clinical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 6, p20 Section 2, p8	Section 2, p8 Section 6, p20
Analytical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 2, p8 Section 6, p20	Section 2, p8 Section 6, p20
Medical Records	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 14, p47 Section 16, p395	Section 14, p47 & 95
Clinical Raw Data	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, p396	Section 16, p383
Test Article Inventory	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 9, p 27 Not a complete inventory, the amount of drug product used was not included	
BIO Batch Size	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3.2.p.3.2 (red jacket, chemistry section)	3.2.p.3.2 (red jacket, chemistry section)
Assay of Active Content Drug	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3.2.p.5.2 (red jacket, chemistry section)	3.2.p.5.2 (red jacket, chemistry section)
Content Uniformity	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable	Not applicable
Date of Manufacture	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 1, p1	Section 1, p1
Exp. Date of RLD	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 1, p1	Section 1, p1
BioStudy Lot Numbers	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 1, p1	Section 1, p1
Statistics	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, p240	Section 16, p227

Summary results provided by the firm indicate studies pass BE criteria	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 3, p10 Section 11, p38 Section 13, p44	Section 3, p10 Section 11, p38 Section 13, p44
Waiver requests for other strengths / supporting data	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable	

Deficiency:

The firm did not submit any data on the dissolution test of its product. In NDA 20-710, the dissolution testing was conducted in 900 ml of SGF (without enzyme) with USP apparatus 2 (paddle) at 100 rpm. The specification set for Paxil® Oral Suspension was "NLT ^{(b) (4)} (Q) in 30 min". The dissolution testing data were submitted for ANDAs of the similar dosage form (acyclovir, carbamazepine, ibuprofen, megestrol acetate, phenytoin oral suspension).

Additional Comments regarding the ANDA:

1. The test product is Paroxetine Hydrochloride 10 mg/5 ml oral suspension intended for the treatment of major depressive disorder, obsessions and compulsions in patients with obsessive compulsive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder. It is a first generic.
2. The RLD is GlaxoSmithKline's Paxil® (Paroxetine HCl) Oral Suspension, 10mg/5ml (NDA 20710, approved date Jun 25, 1997).
3. The firm has submitted two bioequivalent study results (one fast and one fed) demonstrating the bioequivalence of the test product to the RLD.
4. The pharmaceutical equivalence of the test product to the RLD was demonstrated by the following tests: pH, viscosity, density, water content.
5. The Orange Jackets volumes 1.2 to 1.4 contain the fasting study report and the Orange Jackets volumes 1.5 to 1.7 contain the fed study report. The Red Jackets volumes 1.1 to 1.3 contain the chemistry report.

BIOEQUIVALENCE CHECKLIST
for Application Completeness of First Generic ANDA

ANDA# 77-395 FIRM NAME Apotex Inc.

DRUG NAME Paroxetine Hydrochloride

DOSAGE FORM 10 mg/5 ml oral suspension

SUBJ: Request for examination of bioequivalence study

Summary of Findings by Division of Bioequivalence	
<input type="checkbox"/>	Study meets statutory requirements
<input checked="" type="checkbox"/>	Study does NOT meet statutory requirements
	Reason: dissolution testing is not included
<input type="checkbox"/>	Waiver meets statutory requirements
<input type="checkbox"/>	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION:

The firm is requested to submit the dissolution testing results in the application.

Reviewed by:

Bing Li
Reviewer *Bing Li*

Date: 01/11/05

S. Nerurkar
Team Leader

[Signature]
Date:

Item Verified:	YES	NO	Fasting study	Fed study
Protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, 1:1, p117	Section 16, p118
Assay Methodology	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Clinical: Section 3, p8 Analytical: Section 16, p 463 & 481	Clinical: Section 3, p8 Analytical: Section 16, p452
Procedure SOP	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, p490	Section 16, p 472
Methods Validation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16.6, p982	Section 16, p1010
Study Results Ln/Lin	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, p 319 & 356	Section 16, p 247 & 308
Adverse Events	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 12, p40, Section 14, p76, Section 16, p 393& 395	Section 12, p40 Section 14, p76
IRB Approval	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16.1.3, p 185	Section 16, p178
Dissolution Data	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not included	
Pre-screening of Patients	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 10, p32	Section 10, p32
Chromatograms	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16.5.12, p 561	Section 16, p527
Consent Forms	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, p143 (sample form only. It was mentioned (Section 5, p 19) that the consent forms were signed by the patients but the actual patient signed forms was not included)	Section 16, p142 (sample form only. It was mentioned (Section 5, p 19) that the consent forms were signed by the patients but the actual patient signed forms was not included)
Composition	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3.2.P.2.2.1 (red jacket, chemistry section)	3.2.P.2.2.1 (red jacket, chemistry section)
Summary of Study	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 13.1, p44	Section 13, p44
Individual Data & Graphs, Linear & Ln	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16.2.6, p283	Section 16, p274 & 308

PK/PD Data Disk Submitted)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Mentioned in cover letter Data can be found in EDR	
Randomization Schedule	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16.1.7, p228	Section 16, p217
Protocol Deviations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 10, p32	Section 16.2.2, p267 Section 14, p85
Clinical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 6, p20 Section 2, p8	Section 2, p8 Section 6, p20
Analytical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 2, p8 Section 6, p20	Section 2, p8 Section 6, p20
Medical Records	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 14, p47 Section 16, p395	Section 14, p47 & 95
Clinical Raw Data	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, p396	Section 16, p383
Test Article Inventory	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 9, p 27 Not a complete inventory, the amount of drug product used was not included	
BIO Batch Size	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3.2.p.3.2 (red jacket, chemistry section)	3.2.p.3.2 (red jacket, chemistry section)
Assay of Active Content Drug	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3.2.p.5.2 (red jacket, chemistry section)	3.2.p.5.2 (red jacket, chemistry section)
Content Uniformity	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable	Not applicable
Date of Manufacture	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 1, p1	Section 1, p1
Exp. Date of RLD	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 1, p1	Section 1, p1
BioStudy Lot Numbers	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 1, p1	Section 1, p1
Statistics	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 16, p240	Section 16, p227

Summary results provided by the firm indicate studies pass BE criteria	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Section 3, p10 Section 11, p38 Section 13, p44	Section 3, p10 Section 11, p38 Section 13, p44
Waiver requests for other strengths / supporting data	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable	

Deficiency:

The firm did not submit any data on the dissolution test of its product. In NDA 20-710, the dissolution testing was conducted in 900 ml of SGF (without enzyme) with USP apparatus 2 (paddle) at 100 rpm. The specification set for Paxil® Oral Suspension was "NLT (b) (4) (Q) in 30 min". The dissolution testing data were submitted for ANDAs of the similar dosage form (acyclovir, carbamazepine, ibuprofen, megestrol acetate, phenytoin oral suspension).

Additional Comments regarding the ANDA:

1. The test product is Paroxetine Hydrochloride 10 mg/5 ml oral suspension intended for the treatment of major depressive disorder, obsessions and compulsions in patients with obsessive compulsive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder. It is a first generic.
2. The RLD is GlaxoSmithKline's Paxil® (Paroxetine HCl) Oral Suspension, 10mg/5ml (NDA 20710, approved date Jun 25, 1997).
3. The firm has submitted two bioequivalent study results (one fast and one fed) demonstrating the bioequivalence of the test product to the RLD.
4. The pharmaceutical equivalence of the test product to the RLD was demonstrated by the following tests: pH, viscosity, density, water content.
5. The Orange Jackets volumes 1.2 to 1.4 contain the fasting study report and the Orange Jackets volumes 1.5 to 1.7 contain the fed study report. The Red Jackets volumes 1.1 to 1.3 contain the chemistry report.

November 18, 2004

77-395

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**RE: Original Abbreviated New Drug Application
Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL**

To Whom It May Concern:

Pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act, as amended September 8, 1992, the following is submitted as an Abbreviated New Drug Application in CTD (Common Technical Document) format for Paroxetine Hydrochloride Oral Suspension, 10 mg/5 mL. The drug product described herein is equivalent to Paxil® (Paroxetine HCl) Oral Suspension, 10 mg/5 mL, marketed by GlaxoSmithKline.

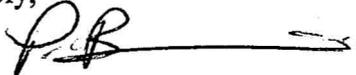
Enclosed are the following copies:

- Archival Copy (blue cover) - Modules 1, 2, 3 and 5
- Review Copy (red cover) - Modules 1, 2, and 3
- Pharmacokinetic Copy (orange cover) - Modules 1 and 5
- Field Copy (burgundy cover) - Modules 1, 2, and 3

Please note that an electronic (compact disc) copy of the label and bioequivalence studies is provided in Module 5 at the front of each review copy. An electronic diskette copy has been provided in the review copy only. The pharmacokinetic and bioequivalence studies are provided in Module 5 at the front of each review copy.

Please direct any communications regarding the application to Ms. Marcy Macdonald at Apotex Corp., the authorized US agent for Apotex Inc., at telephone: (847) 279-7740 or fax: (847) 353-2982 or for any concerns related to the submission of the CTD format, please do not hesitate to contact me directly at telephone: (905) 508-2396 or fax: (905) 884-0357.

Sincerely,



Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:mt

cc: Apotex Corp.

RECEIVED

NOV 22 2004

OGD / CDER

