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APPLICATION NUMBER:
21-299

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA # 21-299
Sponsor: Synthron Pharmaceuticals Ltd.
User Fee Due Date: May 26, 2001

Drug Name

Generic Name: Paroxetine mesylate
Trade Name: (Not Available)

Drug Categorization

Pharmacological Class: Selective serotonin reuptake inhibitor
Indication: Depression, OCD, Panic Disorder
NDA Classification: S2
Dosage Forms: 10, 20, 30, and 40mg Tablets
Route: Oral

Reviewer Information

Clinical Reviewer: Gregory M. Dubitsky, M.D.
Completion Date: March 21, 2001

**NDA 21-299:
PAROXETINE MESYLATE
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1.0 Materials Utilized for Review

1.1 Materials from the NDA/IND

This review entailed an examination of the following items:

NDA VOLUMES	SUBMISSION DATE	MATERIAL
1.1	7-26-00	Cover Letter Financial Disclosure Certificate Master Index Application Summary
1.46	"	Clinical Expert Report Literature References Safety Summary Draft Labeling
1.47	"	Case Report Forms
2.1	10-31-00	Response to FDA Request for Information
2.1	12-8-00	Revision of Impurity Specifications

No Computer Assisted New Drug Application (CANDA) was provided with this supplement.

The following Case Report Forms (CRF's) were examined by the undersigned as part of the safety review of this NDA:

<u>Study</u>	<u>Subject#</u>	<u>Study</u>	<u>Subject#</u>
009/65/98	19	982413	46
009/65/98	24	982413	50
009/65/98	33	982413	60
982413	8	982413	61
982413	16	982413	87
982413	30	982413	91
982413	38	CPR PA5	8
982413	39	CPR PA5	12
982413	44	CPR PA5	24

1.2 Related Reviews and Consultations

Iftekhar Mahmood, Ph.D., of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB), reviewed the pharmacokinetic data from the four submitted human studies.

The Division of Scientific Investigations (DSI) was consulted to inspect study 982413. Data from this study were found to be acceptable.

2.0 Background

2.1 Indications

Paroxetine hydrochloride is currently approved and marketed by GlaxoSmithKline (GSK) in the U.S. for the treatment of depression, panic disorder, obsessive-compulsive disorder, and social anxiety disorder. This NDA provides for the use of paroxetine mesylate in the first three indications; the sponsor is not seeking approval for social anxiety disorder since this indication is the subject of a new indication exclusivity for Paxil, the hydrochloride salt of paroxetine.

2.2 Administrative History

Synthon Pharmaceuticals submitted IND 57,407 for the development of the mesylate salt of paroxetine on December 2, 1998. At that time, the sponsor indicated their intention to file an NDA under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the "Act") for paroxetine mesylate based on safety and efficacy data for the hydrochloride salt, which is marketed in the U.S. as Paxil, and a demonstration of comparable bioavailability between Paxil and their product. The original submission contained a protocol for such a bioavailability study using a single 40mg dose. In a December 18, 1998, meeting of the review team, it was decided to allow the sponsor to proceed.

A patent for this compound was assigned to Synthon B.V. on 2-23-99 (Patent # US 5,874,447).

A pre-NDA meeting was held with the sponsor on October 21, 1999. During this meeting, OCPB communicated to Synthon the need for a study of the multiple dose pharmacokinetics of paroxetine mesylate. A head-to-head comparison with the marketed paroxetine hydrochloride would not be required; a

historical comparison with PK data for Paxil would be acceptable. Major points of that meeting were reiterated in a December 10, 1999, letter to the sponsor.

On July 26, 2000, Synthon submitted NDA 21-299 under section 505(b)(2) for paroxetine mesylate tablets. A Refuse To File meeting was held on September 14, 2000. The biopharmaceutics staff felt that sufficient information had been submitted to bridge the hydrochloride and mesylate salts and the pharmacology staff indicated that there were — impurities in the final commercial product that required qualification by additional animal toxicology studies or a modification of their specifications for the commercial drug product. The application was judged to be fileable, with a User Fee due date of May 26, 2001 (10-month clock).

In an October 16, 2000, telephone conference with the sponsor, the Division communicated the requirement for additional preclinical studies or modified specifications due to the — unqualified impurities. Synthon indicated that they would internally discuss these two options and decide on a plan to address this issue. In a December 8, 2000, submission, Synthon communicated their intention to reduce the specifications of these impurities to the maximum levels required by the Agency.

On November 17, 2000, the OCPB review team, up to the Division Director level, convened to discuss this application, in particular the failure of study 982413 to demonstrate bioequivalence of the 10mg Synthon tablet to the 10mg Paxil tablet. This issue was further discussed in a March 21, 2001, meeting between the clinical review team, up to the Division Director level, and the OCPB reviewer and Team Leader. This topic is covered in more detail in section 6.0 below.

On November 22, 2000, SmithKline Beecham Corporation (now GlaxoSmithKline) filed a lawsuit against Synthon for patent infringement on their marketed paroxetine hydrochloride product, Paxil. Therefore, we cannot approve this drug until one of the following: 1) adjudication of the lawsuit OR 2) April 9, 2003.

2.3 Financial Disclosure

Susan W. Harts, Vice President of Regulatory Affairs for Synthon Pharmaceuticals, has certified that the principal investigators for the four human studies (Drs. Serfaty, Clark, Williams, and Ulc) did not participate in any financial arrangement with the sponsor whereby compensation could be affected by the study outcome, had no proprietary interest in this product or significant equity interest in the sponsor, and were not the recipients of significant payments of other sorts (as defined in 21 CFR 54.2).

2.4 Proposed Labeling

It is expected that the labeling for paroxetine mesylate will be essentially identical to that for paroxetine hydrochloride with the exception of the product description, some pharmacokinetic data, and absence of the social anxiety disorder indication.

2.5 Foreign Marketing

Paroxetine is not marketed as the mesylate salt in any country. Paroxetine hydrochloride tablets are marketed in several foreign countries, to include the U.K., France, and Germany.

3.0 Chemistry

— impurities were detected in the "to-be-marketed" drug substance or product which exceed the threshold for preclinical qualification: _____ Please see Section 4.0 below for further details.

The sponsor intends to market the 10, 20, 30, and 40mg tablet strengths of paroxetine mesylate. It is notable that all tablet strengths will be _____ filmcoated, modified-oval tablets distinguished only by an inscription on one side of the tablet (e.g., "POT 10" on the 10mg tablets). It is questionable whether this is adequate to permit easy distinction between the tablets and whether the otherwise identical appearance of the strengths will contribute to medical errors. This concern was conveyed by the undersigned to the chemistry reviewer and Team Leader on November 17, 2000.

4.0 Preclinical Pharmacology

The Division had requested two preclinical studies to "bridge" the mesylate and hydrochloride salts of paroxetine: an Ames test and a 30 day general toxicology study in one species.² Studies which were conducted prior to this NDA submission included acute toxicity studies in mice and rats, 14 day and 4 week studies in rats, in vitro mutagenicity testing, an ADME study in rats, and an AD study in pregnant rats. These investigations directly compared paroxetine mesylate with paroxetine hydrochloride hemihydrate and reportedly found no significant differences in toxicity, mutagenicity, or pharmacokinetics between the two salts.

There were _____ impurities in the "to be marketed" drug substance or product which exceeded thresholds for preclinical qualification (_____ for the drug substance and > _____ for the drug product). These impurities had been designated as _____

The _____ that is present in much higher amounts in animals than humans and does not require qualification.

The _____ was present in sufficient quantities in the preclinical batch used in the above completed studies to be partially qualified (i.e., the Ames test and 28 day toxicology study in rats).

The _____ was "not reported" using an initial HPLC method on the preclinical samples but it was quantified using an adapted method for the "to be marketed" drug substance and product and found to be above specified levels for qualification. Since it is not known whether sufficient amounts of this entity were present in the studies conducted prior to the NDA submission, _____ required full qualification.

In lieu of conducting preclinical studies to fully qualify the _____ impurities, Synthon has decided to lower specifications for these entities in the marketed drug substance and product to the maximum levels required by the Agency.

² This information was obtained from Linda Fossom, Ph.D., the Pharmacology Reviewer for this NDA.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

In support of this application, the sponsor has conducted four pharmacokinetic studies in humans:

- Study 982413: a two-part bioavailability study comparing Synthron BV paroxetine mesylate to the GlaxoSmithKline (GSK) paroxetine hydrochloride (Paxil) at doses of 10mg and 40mg.
- Study 009/65/98: a bioavailability study comparing Synthron CZ paroxetine mesylate to the GSK hydrochloride salt marketed in Germany (Seroxat) at a dose of 20mg.
- Study 013/78/99: a bioavailability study comparing Synthron CZ paroxetine mesylate to the GSK hydrochloride salt marketed in Australia (Aropax) at a dose of 20mg.
- Study CPR PA5: a study of the single and multiple dose pharmacokinetics of the Synthron 30mg paroxetine mesylate tablets compared to historical data for Paxil. The study designs will be described in more detail under Sections 8.1.1 through 8.1.4 below.

Safety data from the four human pharmacokinetic studies consisted of Case Report Forms (CRF's) for subjects who dropped out due to adverse experiences and listings of adverse events reported in each study. (There were no deaths in any of the four clinical studies.)

All CRF's submitted in the original submission as well as five additional CRF's were examined by the undersigned and pertinent data were incorporated into this review. Three of the additional CRF's were for patients who experienced "collapse" in study 009/65/98 (subjects 19, 24, and 33). These were requested from the sponsor to better assess the nature of these adverse experiences. Two of the additional CRF's were for patients who reportedly dropped out for reasons other than adverse experiences (subjects 8 and 24 in study CPR PA5). These were examined to verify that these subjects did not dropout due to adverse events.

5.2 Secondary Sources of Clinical Data

5.2.1 "Clinical Expert Report"

A "Clinical Expert Report," which summarizes previous human experience with paroxetine hydrochloride, was provided in this NDA submission. The compilation of information and

drafting of this report was done by Astrid Engbersen, M.Sc., Manager of Clinical Research for Synthon BV, The Netherlands. The final document review and authorization was performed by _____ an independent Medical Specialist in Psychiatry and Neurology.

Data regarding the following areas were summarized: pharmacokinetics, pharmacodynamics, clinical efficacy, interactions, and safety.

5.2.2 Literature Abstracts

A listing of abstracts of clinical literature pertaining to paroxetine was provided in this submission. All databases offered by _____ which include MEDLINE, were searched for publications that cite the compound paroxetine. Searches have been updated on a biweekly basis. Over 100 articles were critically reviewed under the supervision of Ms. Astrid Engbersen and _____ (see above). Articles were selected based on scientific soundness, important safety information, pharmacokinetic or pharmacodynamic data, or information that could lead to new indications.

6.0 Human Pharmacokinetics

Study 982413 demonstrated that the Synthon 40mg paroxetine mesylate tablets are bioequivalent to the marketed GSK Paxil (paroxetine hydrochloride) 40mg tablets.

The 10mg tablets meet bioequivalence criteria for Cmax but not for AUC (90% confidence interval for the log transformed AUC(0-∞) ratio was 112.9-138.5).

The need to perform another study with the 10mg strength was discussed by both the OCPB and clinical review teams in a March 21, 2001, meeting.³ All present agreed that such a study was not needed due to the following considerations.

1) Current biopharmaceutical guidance does not require a demonstration of bioequivalence (BE) at submaximal dose strengths. Even for drugs with non-linear pharmacokinetics, bioequivalence at the highest strength, along with equivalent dissolution and compositional

³ Meeting participants were Drs. Russell Katz, Thomas Laughren, Gregory Dubitsky, Raman Baweja, and ~~Pr~~tekhhar Mahmood.

proportionality at lower strengths, is sufficient to waive BE for lower strengths.⁴

2) The failure to show BE for the 10mg strength in study 982413 was felt to be largely attributable to the very high intersubject variability for AUC seen with both the Synthron and standard GSK 10mg formulations (coefficient of variation greater than 100%). It was opined by OCPB that simply conducting another study using a larger sample size will likely produce a finding of bioequivalence for both parameters.

Hence, it was deemed reasonable to approve all strengths.

Study CPR PA5 showed that after multiple dosing with paroxetine mesylate, the C_{max}, C_{min}, AUC(0-24), and half-life were 1.3, 1.4, 1.5, and 1.6 times higher than for paroxetine hydrochloride, respectively. However, these results may be an artifact of the historical comparison in this study and, thus, they are difficult to interpret.

7.0 Efficacy Findings

No new efficacy data were provided in this application. Efficacy for paroxetine mesylate is based on the established efficacy for paroxetine hydrochloride in accordance with Section 505(b)(2) of the "Act."

8.0 Review of Clinical Safety

8.1 Safety Findings from Pharmacokinetic Studies

Safety information for the four human studies was not integrated in this submission. Hence, the safety data are summarized separately by study below.

8.1.1 Study 982413

8.1.1.1 Study Design

The first part of this study was an open label, randomized, single-dose, 2-way crossover study in 46 healthy volunteers (23 males and 23 females) to compare the bioavailability of the Synthron 40mg paroxetine mesylate tablets with the GSK 40mg paroxetine hydrochloride tablets (Paxil) under fasting

⁴ BE study of the 10mg strength was performed by the sponsor to meet Australian regulatory requirements, not U.S. requirements.

conditions. Treatment periods were separated by a 21 day washout.

The second part of the study was an open label, randomized, single-dose, 2-way crossover study in 46 healthy volunteers (23 males and 23 females) to compare the bioavailability of the Synthron 10mg paroxetine mesylate tablets with the GSK 10mg paroxetine hydrochloride tablets (Paxil) under fasting conditions. Doses were given as two 10mg tablets (20mg). Treatment periods were separated by a 21 day washout.

8.1.1.2 Safety Findings

In the first part of this study, a total of 39 subjects completed both treatment periods. Seven subjects dropped out after the first dose of paroxetine due to vomiting (three received the mesylate salt and four the marketed Paxil). Although this is a higher proportion of subjects with significant vomiting compared to experience from clinical trials (see Paxil labeling), this may be explained on the basis of the high initial dose (40mg) and the fact that these subjects were normal volunteers. A review of other adverse experiences from this trial revealed none that were considered clinically important and unexpected.

In the second part of the trial, a total of 40 subjects completed both treatment periods. Five subjects dropped out due to adverse experiences, generally nausea, dizziness, anxiety, and loose stools. Three had received the mesylate salt of paroxetine and two had received the marketed Paxil. None of these dropouts were due to events deemed by me to be unexpected and possibly attributable to paroxetine. A sixth subject dropped out due to "personal reasons." An examination of all reported adverse events revealed only one event of note: one patient who had received Paxil reported "visual hallucinations" consisting of "seeing colors and geometric shapes" when she closed her eyes.

8.1.2 Study 009/65/98

8.1.2.1 Study Design

This was an open label, randomized, single-dose, 2-way crossover study conducted in 48 healthy volunteers (25 males and 23 females) to compare the bioavailability of the Synthron 20mg paroxetine mesylate tablets to the GSK 20mg

paroxetine hydrochloride tablets under fasting conditions. The crossover periods were separated by a 21 day washout.

Synthon tablets were from the Czech Republic but from a batch manufactured using the same processes and at the same facility as batches described under this IND and used in U.S. studies. GSK tablets were Seroxat tablets currently marketed in Europe.

8.1.2.2 Safety Findings

One subject withdrew for "serious family reasons" near the end of the second dosing period. No subjects withdrew due to adverse events.

A review of all reported adverse events revealed that three patients had experienced adverse experiences translated from Czech as "collapse" (one after the mesylate salt and two after the marketed Seroxat). These events were transient and intervention in all three cases consisted of assuming the supine position. These events are summarized below:

- Subject 19 experienced dizziness with orthostatic hypotension (BP=105/60, HR=60 bpm; baseline 116/80, HR=66) after receiving the mesylate salt of paroxetine. This lasted for 5 minutes.
- Subject 24 reported dizziness with a blood pressure of 100/60 and heartrate of 89 after receiving Seroxat (baseline BP=126/74, HR=68). This event had a duration of 10 minutes with a subsequent blood pressure of 115/75 and heartrate of 66.
- Subject 33 reported dizziness and fainted (i.e., a "few second" loss of consciousness) after receiving Seroxat. Serial vital signs were as follows: Time 0, BP=90/60 & HR=90; Time +10 minutes, BP=105/60 & HR=84; Time +40 minutes, BP=105/70, HR=89) (baseline:BP=105/74,HR=80).

The sponsor did not consider any of these events as clinically significant and no consultations or ECG tracings were obtained.

8.1.3 Study 013/78/99

8.1.3.1 Study Design

This was an open label, randomized, single-dose, 2-way crossover study conducted in 48 healthy volunteers (24 males and 24 females) to compare the bioavailability of the Synthron 20mg paroxetine mesylate tablets to the GSK 20mg paroxetine hydrochloride tablets under fasting conditions. The crossover periods were separated by a 21 day washout. Synthron tablets were from the Czech Republic but from a batch manufactured using the same processes and at the same facility as batches described under this IND and used in U.S. studies. GSK tablets were Aropax tablets currently marketed in Australia.

8.1.3.2 Safety Findings

All 48 subjects completed the trial. There were no remarkable adverse events reported in this study.

8.1.4 Study CPR PA5

8.1.4.1 Study Design

This was an open label, single period, multiple dose study to evaluate the pharmacokinetics of Synthron 30mg paroxetine mesylate tablets after a single 30mg dose and at steady state after 24 days of dosing with 30 mg/day, both under fasting conditions. Subjects were 25 healthy, non-smoking, male adults.

8.1.4.2 Safety Findings

A total of 22 subjects completed the study. No subject dropped out due to an adverse event. Three subjects dropped out for "personal reasons."

Among the adverse events reported in this trial, only one was notable: subject 12, a 42 y.o. white male, reported dizziness with a 5 minute syncopal episode and headache and nausea, all occurring 176 hours (1 week) after receiving the final dose of study drug and following a "combative episode" with his wife. The subject was transported by EMS to the local emergency room, where a medical work-up, to include a CT scan of the head, was performed. An ECG was remarkable only for a prolonged PR interval (212 msec)

consistent with first-degree AV block; this finding was not evident on a pre-treatment ECG. Nevertheless, this work-up was not felt to reveal any cause for the adverse events. An evaluation by the study physician the following day likewise revealed no etiology.

In the conduct of this trial, vital sign and laboratory data were evaluated by first considering whether any values met criteria for being "abnormal" (see Exhibit 1 in the sponsor's October 5, 2000, submission for a listing of these criteria). If so, the study physician made an assessment of whether the finding was "clinically significant" by considering the following factors:

- 1) other laboratory or vital sign data.
- 2) medical history.
- 3) presence of symptoms.
- 4) physical examination.
- 5) any additional tests or procedures.

Based on the above process, the sponsor states that there were no clinically significant changes in vital sign or laboratory values in this study.

8.2 Safety Findings from Secondary Sources

The "Clinical Expert Report" was reviewed by the undersigned and no important new clinical data was discovered.

Synthon has warranted that the summarized literature articles in this submission contain no information averse to previous conclusions about the safety of paroxetine.

Article titles and, where deemed appropriate, article abstracts were examined by the undersigned. No important new clinical information about paroxetine was found.

8.3 Adequacy of Patient Exposure and Safety Assessments

The paroxetine mesylate safety database alone is incapable of providing adequate information to support the safety of this compound. However, considering that: 1) the mesylate salt is instantly converted to the hydrochloride upon entering the stomach, 2) the mesylate moiety is generally felt to be safe, and 3) the safety of paroxetine hydrochloride is well established based on a wealth of

safety experience, it seems reasonable to conclude that paroxetine mesylate is safe.

8.4 Assessment of Data Quality and Completeness

No laboratory test or vital sign data were provided beyond the sponsor's statement that, in study CPR PA5, no significant changes were found. Given that this study, as well as the other trials, cannot provide the basis for any definitive conclusions about the human safety of paroxetine mesylate, this deficiency has little impact on the approvability of this NDA.

8.5 Summary of Safety Results

A review of the submitted clinical safety data revealed no previously unrecognized hazards associated with paroxetine when administered as the mesylate salt.

9.0 Labeling

Synthon's proposed labeling for paroxetine mesylate is similar to the GlaxoSmithKline (GSK) labeling for Paxil, with the following major exceptions: product description, deletion of references to the Social Anxiety Disorder indication, and replacement of the hydrochloride multiple dose PK data with the data from the multiple dose study using the mesylate salt.

The proposed labeling is acceptable.

10.0 Conclusions

This review revealed no safety findings that would preclude approval of paroxetine mesylate and it seems reasonable to extrapolate clinical efficacy and safety from paroxetine hydrochloride to paroxetine mesylate based on bioequivalence at the 40mg strength and, for lower strengths, dissolution equivalence and compositional proportionality. However, it is felt that more prominent differences in the physical appearance of the four tablet strengths would facilitate visual discrimination and reduce the risk of medication errors.

11.0 Recommendations

From a clinical perspective, this application may be approved. Of course, as noted in section 2.2, we cannot legally approve this drug until one of the following: 1) adjudication of the lawsuit filed by the sponsor of Paxil OR 2) April 9, 2003.

It is recommended that we suggest that the sponsor attempt to render the four tablet strengths more easily distinguishable to reduce the probability of a medication error.

Gregory M. Dubitsky, M.D.
Medical Officer

cc: NDA #21-299
HFD-120 (Div. File)
HFD-120/GDubitsky
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Greg Dubitsky
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Thomas Laughren
5/6/01 11:14:05 AM
MEDICAL OFFICER

I agree that this application is approvable. See memo to file for more detailed comments.--TPL

Review and Evaluation of Clinical Data
NDA #21-299

Sponsor: Synthon Pharmaceuticals, Ltd.
Drug: Paroxetine Mesylate
Indications: Depression, Panic Disorder, OCD
Material Submitted: Response to 5-25-01 Approvable Letter
Correspondence Date: September 19, 2001
Date Received: September 20, 2001

I. Background

Paroxetine, a selective serotonin reuptake inhibitor, is currently approved and marketed by GlaxoSmithKline (GSK) in the U.S. as the hydrochloride salt, Paxil, for the treatment of depression, panic disorder, obsessive-compulsive disorder, social anxiety disorder, and generalized anxiety disorder.

This NDA, a 505(b)(2) application, provides for the use of a mesylate salt of paroxetine in depression, panic disorder, and obsessive-compulsive disorder. Social anxiety disorder and generalized anxiety disorder are protected by market exclusivity regulations for Paxil and these indications cannot be approved for the mesylate salt at this time.

An approvable letter for this NDA was issued on 5-25-01. That letter communicated that final approval was contingent on the following:

- 1) Agreement to labeling revisions as described in the approvable letter and attachment.
- 2) Stipulation of a single color for each of the four strengths of paroxetine mesylate tablets (10, 20, 30, and 40mg) to reduce the likelihood of medication errors.
- 3) Resolution of chemistry, manufacturing, and controls deficiencies.
- 4) Agreement to dissolution method and specifications as requested by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

D. Dissolution Methods and Specifications

The dissolution method and specification have been adopted in accordance with the approvable letter request. This will be verified by the OCPB review team and will not be further addressed here.

III. Conclusions and Recommendations

The sponsor's final printed labeling was examined line-by-line by this reviewer. Revisions to the DESCRIPTION and HOW SUPPLIED sections will be evaluated by the chemistry review team and will not be addressed here.

Changes to the "Other Events.." listing under ADVERSE REACTIONS was compared to the corresponding listing in the approved labeling for supplement S-026 to NDA 20-031. This listing is acceptable except for the following:

- 1) Under Body as a Whole, the term " _____ " should be removed a rare event since it is already listed as an infrequent event, the correct categorization.
- 2) Under Nervous System, the term "delirium" was inadvertently omitted as an _____ event and should be inserted.
- 3) Also under Nervous System, the infrequent event _____ should read "hypokinesia."
- 4) Under Skin and Appendages, the rare event " _____ " should read "sweating decreased."

It was also noted that the introductory paragraph under ADVERSE REACTIONS/Commonly Observed Adverse Events/Incidence in Controlled Clinical Trials is misworded. This text should be revised for consistency with the corresponding language in Paxil labeling.

The sponsor's proposal of a distinct color for each tablet strength of the mesylate product adequately addresses the medication error concern from a clinical perspective.

The Office of Postmarketing Drug Risk Assessment (OPDRA) was consulted on 9-24-01 to evaluate the acceptability of the sponsor's proposed tradenames.

From a clinical standpoint, approval is contingent on Synthon's agreement with the above labeling changes and OPDRA's acceptance of one of the proposed tradenames.

Gregory M. Dubitsky, M.D.
September 26, 2001

cc: NDA #21-299
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