Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 14, 2002

NDA NUMBER: 21-299

NAME OF DRUG: Asimia (Paroxetine mesylate tablets)
10 mg, 20 mg, 30 mg, 40 mg

NDA HOLDER: Synthon Pharmaceuticals, Ltd.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120), for assessment of the tradename "Asimia", regarding potential name confusion with other proprietary/generic drug names. The Division notes that the NDA for Asimia (paroxetine mesylate) is identical to the approved NDA for Paxil (paroxetine hydrochloride) except for the salt form (mesylate vs. hydrochloride).

PRODUCT INFORMATION

Asimia is the proposed proprietary name for paroxetine mesylate tablets. Asimia is indicated for the treatment of depression, obsessive compulsive disorder, and panic disorder. Asimia will be supplied as 10 mg, 20 mg, 30 mg, and 40 mg oral tablets. The recommended dosage in treating depression is 20 mg/day up to a maximum of 50 mg/day as a single daily dose. The usual dosage in the treatment of obsessive compulsive disorder is 40 mg daily, not to exceed 60 mg/day as a single daily dose. The daily dosage in treating panic disorder is 40 mg/day up to a maximum of 60 mg/day as a single daily dose. Elderly patients and/or patients with severe renal or hepatic impairment should begin with 10 mg/day (maximum 40 mg/day). The use of Asimia is contraindicated in patients concomitantly taking either monoamine oxidase inhibitors (MAOIs) or thioridazine.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names that sound alike or look alike to "Asimia" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system[4] (TESS) was conducted.
The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Asimia". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Asimia. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have concerns about the name with regard to promotional claims.

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[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.
[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, New Drug Approvals 98-02, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess.uspto.gov/bin/gate.exe?f=searchss&state=nvpshm.1.1
[5] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Asimia	Paroxetine mesylate tablets 10 mg, 20 mg, 30 mg, 40 mg	Depression: 20 mg/day (max: 50 mg/day) Obsessive Compulsive Disorder: 40 mg/day (max: 60 mg/day) Panic Disorder: 40 mg/day (max: 60 mg/day)	
Asmalix	Theophylline elixir, 80 mg/15mL	Not currently being made by Century Pharmaceuticals	L/A, S/A
Aromasin	Exemestane tablets, 25 mg	25 mg once daily after a meal	L/A, S/A
Aredia	Pamidronate disodium powder for injection, 30 mg, 90 mg vials	Hypercalcemia: 60 mg as a single dose intravenous infusion over 4 hours or 90 mg as a single dose intravenous infusion given over 24 hours Paget's Disease: 30 mg daily as a single 4 hour infusion for 3 days for a total dose of 90 mg	S/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three studies were conducted by DMETS and involved 113 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Asimia with other drug names due to similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of marketed and unapproved drug products and a prescription for Asimia (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretation and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

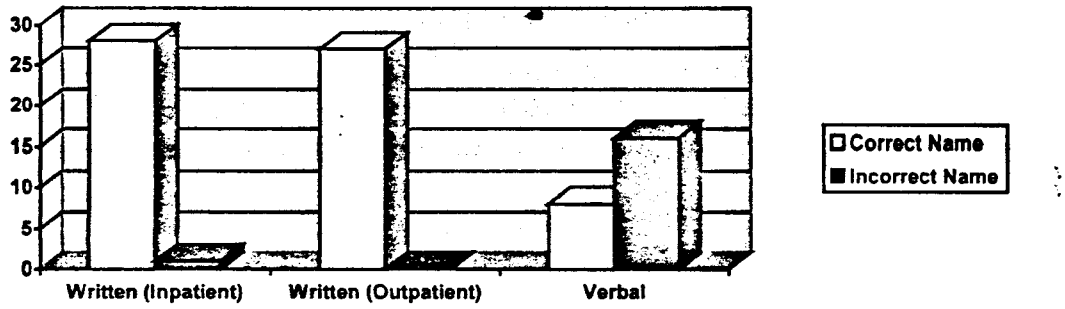
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient RX: Asimia 30 mg Sig: 1 po qd #30	Asimia 30 mg Take one tablet daily. Dispense 30 with no refills.
Inpatient RX: Asimia 30 mg po daily #30	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted Asimia	Incorrectly Interpreted
Written: Inpatient	40	29 (73%)	28 (97%)	1 (3%)
Outpatient	39	27 (69%)	27 (100%)	0 (0%)
Verbal: Outpatient	34	24 (71%)	8 (33%)	16 (67%)
Total	113	80 (71%)	63 (79%)	17 (21%)



Among the verbal outpatient Asimia prescriptions, 8 of 24 (33%) respondents interpreted the name correctly. Many of the incorrect name interpretations were misspelled variations of "Asimia". Interpretations included Assimia, Asemia, Afenia, Asimian, Afinia, Isimia, Athemia, Assymia, Afemia, and Asemeda.

When examining the interpretations from the written inpatient prescriptions, 28 of 29 (97%) respondents interpreted the name correctly. In addition, all of the respondents (100%) from the written outpatient prescriptions interpreted the name correctly. The one incorrect response from the written inpatient study was "Asinia".

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Asimia", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Asimia were Asmalix, Aromasin, and Aredia.

Asmalix (theophylline) is a bronchodilator used in the treatment of reversible airway obstruction due to asthma, chronic bronchitis, and emphysema. Asmalix is available as an 80 mg per 15 mL oral elixir and is available only by prescription. Asmalix is manufactured by Century Pharmaceuticals in gallon quantities. Century Pharmaceuticals was contacted (2/14/02) and is currently not distributing Asmalix. However, the company can still manufacture the product if a contract is placed through the office and a quantity of 50 gallons or more is ordered. Saegis[6]

Although Asmalix can sound-alike and look-alike to Asimia,

[6] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

there are differences between the two that help to limit the risk for confusion. Asmalix is available as an elixir, and Asimia is available as oral tablets. Asimia is available in four different strengths and therefore would likely be prescribed with an accompanying strength. However, Asmalix is only available in one strength (80 mg/15 mL) and does not require a designating strength to be prescribed. Both Asmalix and Asimia belong to different pharmacologic classes and have completely different indications for use. In addition, a prescription for Asmalix would most likely include the use of the word "teaspoon/tablespoon" or "mL/cc" in order to provide dosing instructions or total amount dispensed, thus adding another checkpoint for errors. Due to the differences in dosage form, strength, dosing instructions, indication, and pharmacologic class, the risk of a product mix-up between Asmalix and Asimia is minimal.

Aromasin (exemestane) is an antineoplastic indicated in the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy. The recommended dose of Aromasin is 25 mg once a day following a meal. Aromasin is supplied as 25 mg tablets. The name Aromasin looks and sounds slightly similar to Asimia. The two drug names contain a beginning upstroke "A" with no upstroke or downstroke letters to follow, and each have four syllables. Yet, when scripted, the difference in length (8 letters in Aromasin vs. 6 letters in Asimia) of the drug names helps to distinguish one from the other. Asimia is available in four different strengths and therefore must be prescribed with an accompanying strength. However, Aromasin is only available as one strength (25 mg) and does not require a designating strength to be prescribed. The two drugs have different strengths, indications for use, and prescriber populations (general practitioner vs. specialist). The risk of a product mix-up due to name confusion between Aromasin and Asimia appears to be minimal.

Aredia (pamidronate disodium) is a bisphosphonate derivative used in the treatment of hypercalcemia associated with malignancy and Paget's disease. The usual adult dose is 60 mg given as a single dose intravenous infusion over four hours or 90 mg over 24 hours for the treatment of hypercalcemia. Aredia is available as 30 mg and 90 mg vials containing a powder for injection. Aredia and Asimia can sound alike because each name begins with the letter "A" and ends in the stem "ia". Although Aredia and Asimia sound slightly similar, the two drugs have many factors that help to distinguish one from the other. Both drugs have different indications for use and are available in different dosage forms (tablet vs. intravenous injection). Asimia is prescribed as a once daily oral dose while Aredia is given as a single dose intravenous infusion over four or 24 hours. Similarly, Aredia must be reconstituted from a powder form before use, requiring the addition of a health care provider as a check point before administration to a patient. Thus, due to the differences in indication, dosage form, route of administration, and dispensing the risk of confusion between these two products is low.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the container labels and insert labeling of Asimia, DMETS has attempted to focus on the safety issues relating to possible medication errors. DMETS has reviewed the current container labels and insert labeling and has identified several areas of possible improvement, which might minimize potential user error. Carton labeling was not provided for review at this time.

A. GENERAL COMMENTS

In accordance with the Poison Prevention Act, drugs packaged in "unit of use" bottles and dispensed on an outpatient basis, such as the 30 capsule bottles, should include Child Resistant Closures (CRC). Please ensure the bottles utilize such a closure.

B. CONTAINER LABEL (10 mg, 20 mg, 30 mg, 40 mg – 30 tablets;
20 mg – 100 tablets, 20mg – 500 mg)

1. We believe that the strength of the product is not clear and legible as shown with the [redacted] We recommend [redacted]

2. We note the product strength is expressed [redacted]
Revise the established name and strength so the strength is expressed as one of the following:

[redacted]

3. Revise the " [redacted] statement accordingly:

For example, ' [redacted]

4. We recommend relocating the [redacted] statement to appear on the principal display panel.

5. We recommend revising the [redacted] statement to read:

[redacted]

C. CARTON LABELING

Not provided for review.

D. INSERT LABELING

The print size of the insert appears blurry and is difficult to read. Ensure the font size is a minimum of four-point type.

IV. RECOMMENDATIONS:

DMETS has no objections to the use of the proprietary name, Asimia.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names from this date forward.

DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Carol Holquist
2/15/02 10:45:14 AM
PHARMACIST

Jerry Phillips
2/19/02 10:17:43 AM
DIRECTOR

2 Page(s) Withheld

MEMORANDUM

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

DATE: March 31, 2003
TO: NDA File
FROM: Lorenzo A. Rocca, Ph.D. and Thomas F. Oliver, Ph.D.
SUBJECT: Recommendation for CMC approval action for NDA 21-299, paroxetine mesylate tablets 10 mg, 20 mg, 30 mg and 40 mg, for the treatment of major depressive disorder, obsessive compulsive disorder, and panic disorder.

NDA 21-299 is a 505(b)(2) application, sponsored by Synthon Pharmaceuticals, Ltd. NDA 21-299 is eligible for final NDA approval on April 9, 2003. A tentative approval (TA) letter was issued on March 11, 2002. At that time NDA 21-299 was recommended for approval from the CMC standpoint. However, it was noted in the TA letter that further labeling changes might be needed prior to final approval.

Synthon has concurred with all changes to the labeling that the FDA has proposed with the exception that Synthon has requested the chemical name, (-)-trans-4R-(4'-fluorophenyl)-3S-[3',4'-methylenedioxyphenoxy)methyl] piperidine mesylate. The CMC team had initially recommended the chemical name, [redacted] However, Paxil® contains the same active ingredient [different salt form, hydrochloride hemihydrate] and utilizes the "trans" name. As a result, the "trans" name will be granted since the division would like to keep the labeling of Paxil® and paroxetine mesylate similar as to avoid possible dual dosing.

In response to a FDA request, Synthon has applied for a USAN name for paroxetine mesylate on March 14, 2003, and received acknowledgement receipt from the USAN Council on March 24, 2003. Synthon anticipates receiving final approval of the name from the USAN Council within the next 2 to 6 months.

Synthon's container labels have been reviewed (see NDA 21-299 Amendment 024, January 8, 2003) and found compliant with the CFR for labeling (i.e., 21CFR 201.10(g)(2).

On January 22, 2003 a consultation was requested with the Division of Medication Errors and Technical Support (DMETS)/HFD-420 for a re-evaluation of Synthon's proposed trade name ASIMIA™ prior to final approval. On March 28, 2003 DMETS completed their reassessment and recommended against the use of the ASIMA™ tradename. It is the decision of FDA to inform the sponsor that submission of a new tradename for their paroxetine mesylate drug product can be done post-approval.

Synthon Pharmaceuticals has committed (see NDA 21-299 Amendment 024, January 8, 2003) to provide the FDA with a current Methods Validation Package and introductory promotional material in the near future.

NDA 21-299 is recommended for approval from the CMC standpoint. The approval recommendation is based on the following:

- Synthon Pharmaceuticals Ltd. has responded adequately to all CMC deficiencies.
- All facilities involved in the manufacture and control of the drug substance and drug product have been found to have acceptable cGMP
- Synthon Pharmaceuticals Ltd. proposed container/carton labeling and package insert for their paroxetine mesylate tablets 10 mg, 20 mg, 30 mg and 40 mg is acceptable for CMC.
- Synthon Pharmaceuticals Ltd. proposed tradename (i.e., ASIMA™) for paroxetine mesylate tablets has been rejected by DMETS (HFD-420), but the sponsor will be allowed to submit a new trade name post-approval.

Reviewer Name

Lorenzo Rocca, Ph.D.

Team Leader Name

Thomas F. Oliver, Ph.D.

cc: Orig. NDA 21-299
HFD-120/Div. File
HFD-120/TLaughren
HFD-120/PDavid
HFD-120/TOliver
HFD-120/LRocca

File: C:Data\LR\NDA\Nda21299\N21299REVIEW_5.doc

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/s/

Lorenzo Rocca
3/31/03 11:42:30 AM
CHEMIST
NDA 21-299 is a 505(b)(2) application eligible for final approval on 4/9/03. A tentative approval letter was issued on 3/11/02. DMETS (HFD-420) on 3/28/03 against the use of the ASIMA tradename. FDA agrees to evaluate a new tradename post-approval.

Thomas Oliver
3/31/03 12:35:26 PM
CHEMIST

Table of Contents
Tentative Approval Package
Paroxetine Mesylate
10 mg, 20 mg, 30 mg, and 40 mg Tablets
NDA 21-299

MEMORANDUM

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

DATE: March 8, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Tentative Approval Action for
Asimia (paroxetine mesylate tablets in strengths of 10, 20, 30, and 40 mg, for the treatment of major depressive disorder, obsessive compulsive disorder, and panic disorder

TO: File NDA 21-299
[**Note:** This overview should be filed with the 9-19-01 response, to our approvable letter, which constituted a complete response to our 5-25-01 approvable letter.]

Paroxetine hydrochloride is a selective serotonin reuptake inhibitor currently approved and marketed for depression, OCD, panic disorder, social anxiety disorder, generalized anxiety disorder, and PTSD, in an immediate release tablet, i.e., Paxil (NDA 20-031. This NDA provides date in support of a claim for 4 tablet strengths (10, 20, 30, and 40 mg) of a new salt of paroxetine, i.e., paroxetine mesylate, for three of the currently approved claims: depression, OCD, and panic disorder. This was a 505(b)(2) application based on (1) knowledge of the efficacy and safety of paroxetine hydrochloride for the above 3 claimed indications, and (2) a demonstration of bioavailability for the hydrochloride and mesylate formulations.

The NDA was submitted on 7-26-00, and we issued an approvable letter on 5-25-01, with 4 requirements for final approval:
-Agreement on final labeling.
-Stipulation of a separate color for each of the 4 strengths, to avoid medication errors.
-Resolution of CMC deficiencies.
-Agreement with our proposed dissolution specifications.

Final Labeling
-Labeling agreement has been reached as of 3-6-02, including both CMC changes and clinical changes. The label now is identical regarding clinical issues to the Paxil labeling approved in December, 2001,

except, of course, without any references to the 3 indications to which this product is not entitled, i.e., social anxiety disorder, GAD, and PTSD.

Separate Color for Each of the 4 Strengths
-The sponsor has agreed to separate colors for each of the 4 strengths.

Resolution of CMC Deficiencies
-One issue was the proposed name, Asimia, and, as of 2-19-02, DMET/ODS has recommended that we accept this name.
-The sponsor has agreed to certain packaging changes proposed by OPDRA regarding the expression of product strength, i.e., active moiety vs salt.
-All other CMC issues have been satisfactorily resolved.

Dissolution Specifications
-The sponsor accepted our proposed dissolution specifications

Patent Issue
-Of course, the litigation regarding patent infringement is pending, thus, this action can only be a tentative approval.

I recommend that we issue the attached tentative approval letter, along with the agreed upon final labeling.

cc:
Orig NDA 21-299
HFD-120
HFD-120/TLaughren/RKatz/GDubitsky/PDavid

DOC: MEMPXMES.AP1

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/s/

Thomas Laughren
3/8/02 02:49:55 PM
MEDICAL OFFICER

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21299/000 Priority: 2S Org Code: 120

Stamp: 26-JUL-2000 Regulatory Due: 26-MAY-2001 Action Goal: District Goal: 27-MAR-2001

Applicant: SYNTHON PHARMS
6300 QUADRANGLE DR STE 305
CHAPEL HILL, NC 27514

Brand Name: PAROXETINE MESYLATE 10/20/30/40MG TABLET

Established Name:

Generic Name: PAROXETINE MESYLATE 10/20/30/40MG TABLET

Dosage Form: TAB (TABLET)

Strength: 10, 20, 30, 40 MG

FDA Contacts:			
	P. DAVID	(HFD-120)	301-594-2850 , Project Manager
	L. ROCCA	(HFD-810)	301-594-5357 , Review Chemist
	R. SEEVERS	(HFD-120)	301-594-2850 , Team Leader

Overall Recommendation:

ACCEPTABLE on 26-JAN-2001 by M. GARCIA (HFD-322) 301-594-0095

Establishment: [redacted]

DMF No:

AADA No:

Profile: CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-JAN-2001

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:

AADA No:

Profile: CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-NOV-2000

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]

Profile: TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-NOV-2000

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: [redacted]

DMF No:

AADA No:

FDA CDER ES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

[redacted]

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-SEP-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: [redacted]

Establishment: 9614550
SYNTHON BV

6545 CM NIJMEGEN, , NL

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-JAN-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

REGULATORY PROJECT MANAGER
LABELING REVIEW
NDA 21-299

Date of Review:	March 4, 2002
NDA:	21-299
Type of NDA:	505(b)(2)
DRUG/NDA #:	Asimia (paroxetine mesylate) 10 mg, 20 mg, 30 mg and 40 mg Tablets; NDA 21-299
Referenced Listed Drug:	Paxil (paroxetine HCl) 10 mg, 20 mg, 30 mg and 40 mg Tablets; NDA 20-031
Sponsor [505(b)(2)]:	Synthon Pharmaceuticals
Indication [505(b)(2)]:	Major Depressive Disorder/OCD/Panic Disorder

Notes of interest:

- Asimia (paroxetine mesylate), NDA 21-299, was submitted under 505(b)(2) with a paragraph IV patent certification claiming that the application does not infringe on any of the patents held by the referenced listed drug (RLD), Paxil (paroxetine HCl), for the indications being sought under this application (Major Depressive Disorder/OCD/Panic Disorder).
- The Agency issued an AE action for this 505(b)(2) application in a letter dated 5-25-01.
- Synthon submitted a Type 2 complete response in a submission dated 9-19-01. The submitted labeling was identical to the labeling contained in the Agency AE letter dated 5-25-01 except that Synthon also incorporated safety related changes made to the Paxil labeling in 20-031/SE1-026 (AP letter dated April 13, 2001 providing for a new indication of generalized anxiety disorder). The new indication of GAD was not included with these changes.
- The Agency has subsequently approved Paxil for PTSD (NDA 20-031/SE1-029) in an AP action dated 12-14-01. The labeling changes made to the Paxil labeling, with the approval of this supplement, also incorporated several safety related revisions.
- The sponsor e-mailed me revised labeling (attached) to incorporate safety related Paxil labeling changes approved under 20-031/S-029. The new indication of PTSD was not included with these changes.

NDA 21-299
Label Code: N/A
Type of Submission: Draft Labeling Pre-Tentative Approval Action
Reviewed by Medical Officer: No

The labeling attached to my review is [redacted]

[redacted]

CONCLUSIONS

1. With concurrence by the medical officer, I recommend that the labeling attached to this review be used as the labeling enclosure in the tentative approval Agency action.
2. At the time of final approval of this 505(b)(2) application, the labeling will need to be updated to reflect any revisions made to the RLD, Paxil, labeling.

Paul David. RPh
Regulatory Project Manager

Robbin Nighswander, R.Ph., Supervisory Regulatory Health Officer

20 Draft Labeling Page(s) Withheld

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/s/

Paul David
3/4/02 01:42:17 PM
CSO

Robbin Nighswander
3/4/02 02:23:38 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Synthon Pharmaceuticals Ltd.
6330 Quadrangle Dr. Suite 305
Chapel Hill, NC 27514

2. TELEPHONE NUMBER *(Include Area Code)*

(919) 493-6006

3. PRODUCT NAME

Paroxetine (as mesylate) tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? NO
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☒ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Susan M. Harte	Vice President of Regulatory Aff.	July 25, 2000

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☒ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Susan W. Harts	Vice President of Regulatory Affairs
FIRM/ORGANIZATION: Synthon Pharmaceuticals Ltd.	
SIGNATURE: Susan W. Harts	DATE: July 25, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

LIST OF CLINICAL INVESTIGATORS

Samuel Serfaty, M.D.
Phoenix International Life Sciences Inc.
2350 Cohen Street
St-Laurent, Quebec H4R 2N6
Canada

Thomas S. Clark, M.D.
Clinical and Pharmacological Research, Inc.
763 Chestnut Ridge Road
Morgantown, WV 26504

Dorian Williams, M.D.
Clinical and Pharmacological Research, Inc.
763 Chestnut Ridge Road
Morgantown, WV 26504

MUDr. Ivan Ulc, CSc.
CEPHA s.r.o.
Masarykova 62
312 12 Pilsen
Czech Republic

LIST OF CLINICAL INVESTIGATORS FOR EACH STUDY CONTAINED WITHIN NDA 21-299

STUDY	INVESTIGATOR(S)
982413A and B 10 and 40 mg Comparative Bioavailability Study	Samuel Serfaty, M.D. Phoenix International Life Sciences Inc. 2350 Cohen Street St-Laurent, Quebec H4R 2N6 Canada
CPR-PA5 Single Dose and Multiple Dose Pharmacokinetic Study	Thomas S. Clark, M.D. Clinical and Pharmacological Research, Inc. 763 Chestnut Ridge Road Morgantown, WV 26504 Dorian Williams, M.D. Clinical and Pharmacological Research, Inc. 763 Chestnut Ridge Road Morgantown, WV 26504
009/65/98 20 mg Comparative Bioavailability Study (European)	MUDr. Ivan Ulc, CSc. CEPHA s.r.o. Masarykova 62 312 12 Pilsen Czech Republic
013/78/99 20 mg Comparative Bioavailability Study (Australian)	MUDr. Ivan Ulc, CSc. CEPHA s.r.o. Masarykova 62 312 12 Pilsen Czech Republic

47 Draft Labeling Page(s) Withheld

Table 9 Biopharmaceutics Study Summary

Study Number	Route	Dosage Form/ Study Design	Dose	Batch No./ Plant/ Date of Manufacture	No. of Subjects Enrolled	Related IND No.	Submission Date of IND	Applicant conclusion	Agency correspondence and date
982413	Oral	Tablet 2 way crossover comparative bioavailability	40 mg	Test Product: Batch# 98G15/3 7/98 Reference Product: Lot # 9378B13	N=46		12/2/98	Proved comparative bioavailability to reference product Paxil®	Pre-NDA meeting Oct. 21, 1999 Required for submission. Use as basis for biowaiver request.
CPR - PA5	Oral	Tablet Single dose and multiple dose pharmacokinetic study	30 mg	Test Product: Batch# 98G14/1 7/98 Reference Product: Lot # NA	N=25		12/1/99 12/22/99	Similar to historical data of reference product Paxil®	Pre-NDA meeting Oct. 21, 1999 Required for submission. Compare to historical data for Paxil®
982413B	Oral	Tablet 2 way crossover comparative bioavailability	20 mg (2X10)	Test Product: Batch# 98G14/2 7/98 Reference Product: Lot # 248B10	N=46		1/20/99	Comparable to reference product Paxil® in relation to extent of absorption	12/30/99, Agency requests in addition to 40 mg study. Pre-NDA meeting Oct. 21, 1999, Agency requests to include in application
009/65/98	Oral	Tablet 2 way crossover comparative bioavailability	20 mg	Test Product: Batch# 98E25 5/98 Reference Product 828	N=48	NA	NA	Proved comparative bioavailability to reference product Seroxat®	Pre-NDA meeting Oct. 21, 1999 Agency requests to include in application
013/78/99	Oral	Tablet 2 way crossover comparative bioavailability	20 mg	Test Product: Batch# 98G14/1 7/98 Reference Product: Lot# 53767	N=48	NA	NA	Proved comparative bioavailability to reference product Aropax™	Pre-NDA meeting Oct. 21, 1999 Agency request to include in application

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Meeting Minutes

Date: October 16, 2000
Time: 10:00-10:30 AM, EST
Location: WOC II – Conference Room E
Drug: Paroxetine Mesylate Tablets
NDA: 21-299
Indication: Depression

Sponsor:	Synthon Pharmaceuticals
Type of Meeting:	Conference Call
Meeting Chair:	Russell Katz, M.D., Division Director, Division of Neuropharmacological Drug Products (DNDP; HFD-120)
Meeting Recorder:	Paul David, R.Ph., Senior Regulatory Manager

FDA Attendees:
Paul David, R.Ph. – Senior Regulatory Manager, DNDP (HFD-120)
Russell Katz, M.D. – Division Director, DNDP (HFD-120)
Thomas Laughren, M.D.– Psychopharm Team Leader DNDP (HFD-120)
Glenna Fitzgerald, Ph.D. – Pharm/Tox Team Leader, DNDP (HFD-120)
Linda Fossom, Ph.D. – Pharm/Tox Reviewer, DNDP (HFD-120)
Gregory Dubitsky, M.D. – Clinical Reviewer, DNDP (HFD-120)

External Participants:
Susan Harts, Regulatory Affairs, Synthon
Sherrron Weichert, Regulatory Affairs, Synthon
Dr. Theo Peters, Senior Scientist, Synthon
Dr. Frans van Delen, VP Pharmaceutical R&D, Synthon
Dr. Carla Mol, Toxicologist, Synthon
Dr. Jan Henk Brinkman, Head of QC, Synthon
Gary Yingling, McKenna & Cuneo

Meeting Objective:
The Agency requested the conference call with Synthon to discuss — impurities, —, present in the final commercial product that require qualification.

Discussion:
- Synthon's NDA contains an Ames test and a 28-day toxicology test in 1 species. However, there are — impurities, — present in the final commercial product that require qualification, i.e., additional animal toxicology data.
- Synthon will need to submit an *in vitro* chromosomal aberration test, and a Segment II reproduction study in order to qualify these — impurities.
- Alternatively, in lieu of conducting these additional toxicology studies, Synthon can lower the specifications of these impurities to not greater than — of drug product and not greater than — of drug substance.

Summary
- Synthon will determine whether it is feasible to lower the impurity level of these new impurities. If they cannot lower the level, they agreed to conduct the additional toxicology studies.

Action Items:

- Synthon will inform the Agency within the next couple of weeks regarding the course of action they will take in order to address the Agency's concerns.

Minutes Preparer **Concurrence, Chair**

cc:
NDA 21-299
HFD-120/Div File
HFD-120/R.Katz/T.Laughren/P.David
HFD-120/G.Fitzgerald/L.Fossom
HFD-120//R.Seevers/L.Rocca
drafted: 11/1/00 pd,
concurrence:
final:

MEETING MINUTES

5 Page(s) Withheld

FAX'd 9/20/00 DMA

MEMORANDUM

TO: Susan W. Harts
Vice President of Regulatory Affairs
Synthon Pharmaceuticals Ltd.
6330 Quadrangle Drive
Suite 305
Chapel Hill, NC 27514

FROM: Food and Drug Administration
Center for Drug Evaluation and Research/ORM/ODEI
Division of Neuropharmacological Drug Products
HFD-120
Psychiatric Drug Products Group
5600 Fishers Lane
Rockville, MD 20857

DATE: September 20, 2000

SUBJECT: NDA 21-299 (Paroxetine Mesylate Tablets)
Request for Clinical Information

We request that you provide us with the following items to facilitate our clinical review of your New Drug Application for paroxetine mesylate tablets:

1) On page 3 of the Safety Summary (volume 1.46), you have indicated that there were no clinically significant changes in vital signs or laboratory values in the multiple dose study CPR PA5. Kindly provide a description of your methods for examining these data, to include your criteria for a clinically significant change.

2) On page 5 of the Safety Summary, we note that one subject in study CPR PA5 experienced dizziness with syncope. Please submit the Case Report Form, along with any other information (e.g., consultations, ECG tracings) for this patient so that we may better assess this adverse event.

3) Likewise, please provide the Case Report Forms and any additional information for the three patients who experienced "collapse" and who are mentioned on page 9 of the Safety Summary.

4) Regarding the Clinical Expert Report (volume 1.46), please provide information on the author of this document, to include credentials and relationship to Synthon Pharmaceuticals.

5) With respect to the Abstracts of Supporting Clinical Literature References (volume 1.46), please submit a description of the methodology for performing the literature search and examining these data, information on the person(s) involved in this search and examination, and your warrant that the articles contain no information averse to previous conclusions about the safety of paroxetine.

6) As an audit of subjects who dropped out for reasons other than adverse events, we would like to examine Case Report Forms and any other pertinent data for the following two subjects:

Study CPR PA5, Subject #8
Study CPR PA5, Subject #24

We would greatly appreciate your prompt attention to this request. If you have any questions, please contact Dr. Dubitsky at 301-594-5543. Thank you.

/S/

Gregory M. Dubitsky, M.D.
Medical Reviewer
Psychiatric Drug Products Group

/S/

Thomas P. Laughren, M.D.
Group Leader
Psychiatric Drug Products Group

Cc: HFD-120/GDubitsky
TLaughren
PDavid

MEETING MINUTES
IND 57,407

Date: October 21, 1999; 1:00 PM
Location: Conference Room E; WOC2
Firm: Synthon Pharmaceuticals
Type: Face-to-Face
Drug: Paroxetine mesylate 10 mg, 20 mg, 30 mg, and 40 mg

Participants:
FDA:
Drs. Thomas Laughren, Gregory Dubitsky, Ray Baweja, Thomas Parmelee, Robert Seevers, Ms. Khyati Roberts, Ms. Virginia Beakes, Ms. Kim Dettelbach, and Mr. Paul David

Synthon:

Dr. Jacques Lemmens	President, Synthon B.V.
Susan Harts	VP of Regulatory Affairs; Synthon Pharmaceuticals
Dr. Frans van Dalen	Head of Pharmaceutical R&D, Synthon, BV
Dr. Theodorus Peters	Senior Scientist, Synthon, BV
[redacted]	
Dr. William J. Taylor	President, Synthon Pharmaceuticals
Gary Yingling	Regulatory Counsel for Synthon, McKenna & Cuneo, L.L.P.

PURPOSE

Synthon requested a Type B Pre-NDA meeting to discuss the CMC and biopharmaceutics portions of this new salt formulation of paroxetine, viz., paroxetine mesylate. The meeting request along with the briefing document were submitted to their paroxetine mesylate IND in a submission dated September 13, 1999.

DISCUSSION

- Synthon acknowledged understanding that they would not be AB rated in the Orange Book. They additionally stated that they are [redacted]

- The Agency requested that, prior to filing of the NDA, and in accordance with 21 CRF 320.25(e), Synthon conduct a single dose and steady state pharmacokinetic study to characterize the pharmacokinetic parameters with single and multiple dose paroxetine mesylate. This data would need to be submitted at the time of the 505(b)(2) NDA submission, and it is needed to show clinically comparable profiles between the mesylate and the hydrochloride. This test only needs to be conducted on the mesylate, since the sponsor could refer to the hydrochloride NDA for the comparability data.

- The Agency requested that all comparative bioavailability study data (10, 20, and 40 mg Paroxetine Mesylate tablets) be submitted in the application.

- FDA agreed that Synthon could use its 40 mg comparative bioavailability study and proportional formulation data to request a biowaiver request for the lower strengths, i.e., 10, 20, and 30 mg tablet strengths. The biowaiver request should be based on: (1) proportional similarity in its active and inactive ingredients of all strengths; and (2) all strengths meeting an appropriate in vitro dissolution test (comparative in vitro dissolution between 40 mg versus 30 mg, 40 mg versus 20 mg, and 40 mg versus 10 mg Synthon Paroxetine Mesylate tablets).

- FDA will not require a food study.

- FDA will review the application as a 505(b)(2) NDA, and acknowledges that the clinical and preclinical data will be referenced to the innovator NDA, Paxil (paroxetine HCl) tablets.

- FDA noted that the [redacted] speed used to conduct the dissolution studies is too excessive, and is not a discerning test. During the discussion of the problem of the tablet sticking to the [redacted]. FDA recommended that Synthon review the FDA guidance on dissolution studies which allows for the use of alternative methods, including adding surfactants, in order to develop a method using a lower [redacted] speed. FDA requested that dissolution studies with a lower [redacted] speed be conducted using three different dissolution media (in accordance with applicable FDA guidances). FDA also stated that Synthon, after evaluating the results, should suggest one medium to be used for future testing. Synthon should also provide F1 and F2 calculations at the time of submission.

- FDA stated that they expect at least [redacted] of real time stability data and [redacted] of accelerated stability data to be submitted with the filing. The photostability studies were considered by FDA to be adequate.

- FDA requested that a pH solubility profile for the active substance be prepared and submitted in the application.

- FDA stated that impurities differing from SB's drug product should be followed carefully during the stability studies. The limits for these impurities in the specifications should be accounted from both a toxicological and chemical perspective.

- FDA sought clarification on Synthon's understanding that a 505(b)(2) application requires a Paragraph 4 patent certification and notification of non-infringement to SmithKline Beecham once the application is accepted for filing by the FDA. Synthon acknowledged understanding of these requirements.

Conclusions

- Synthon will submit their 505(b)(2) application for paroxetine mesylate once their single dose and steady state pharmacokinetic study in humans is completed.

Minutes Preparer: /S/
Paul A. David , R.Ph.
Regulatory Project Manager, DNDP

Chair Concurrence: /S/
(or designated signatory)

IND:ORIG
IND:DIV FILE
HFD-120/RKatz/TLaughren/GDubitsky
HFD-120/GFitzgerald
HFD-120/RSeevers/RLostritto
HFD-120/PDavid
HFD-860/RBaweja/TParmelee
11/19/99pd
Doc #IND\I57407\PRE-NDA MEETING MINUTES LETTER 10-21-99.DOC
GENERAL CORRESPONDENCE

4 Page(s) Withheld

Synthon
Pharmaceuticals Ltd.

6330 Quadrangle Dr. Suite 205
Chapel Hill, NC 27517
USA

Tel: +1-919-493-6006
Fax: +1-919-493-6104
Email: sharts@synthon-usa.com

To: **Paul David**

Fax No: 301-594-2859
From: Susan W. Harts, RN, RAC
Vice President of Regulatory Affairs

Date: March 6, 2002

Number of Pages (including this page): 3

Regarding: Paroxetine (as mesylate) Tablets NDA 21-299

Synthon
Pharmaceuticals Ltd.

March 6, 2002

VIA FACSIMILE

Mr. Paul David
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852-1420

Re: **Paroxetine (as mesylate) Tablets**
NDA 21-299

Dear Mr. David:

This letter is to confirm that Synthon agrees to incorporate the following labeling revisions that the FDA has requested in its fax correspondence dated March 6, 2002.

1. Synthon has incorporated the most recent revisions to the Paxil prescriber labeling into the paroxetine mesylate labeling. We agree that the prescriber labeling will use a minimum four-point type font size.
2. In regard to the container/carton labeling, Synthon agrees on the following issues:
   a. On the container and carton label, the proposed [redacted] statement "[redacted]" will be replaced by the following statement: '[redacted]'
   b. In accordance with the Poison Prevention Act, drugs packaged in "unit of use" bottles and dispensed on an outpatient basis, such as the 30 capsule bottles, will include Child Resistant Closures (CRC).
   c. The strength of the product will be relocated so that it appears [redacted] Also, the number, i.e., strength, will be [redacted]
   d. The container labeling dosage statement will be revised to read: [redacted]
   e. The '[redacted]' statement will be relocated to appear on the principal display panel.

6330 Quadrangle Drive Suite 205 Chapel Hill North Carolina 27517
Tel +1 (919) 493-6006 Fax +1 (919) 493-6104

These revisions will be submitted in the final printed labeling.

Should you have any additional questions, please do not hesitate to contact me at (919) 493-6006.

Sincerely,

Susan W. Harts, RN, RAC
Vice President of Regulatory Affairs

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: MARCH 6, 2002

To: Attention: **Susan Harts, Drug Regulatory Affairs**	**From:** Paul David
Company: Synthon	Division of Division of Neuropharmacological Drug Products
Fax number: 919-493-6104	**Fax number:** 301-594-2859
Phone number: 919-493-6006	**Phone number:** 301-594-5530

Subject: Prescriber/Container Labeling Agreement; Paroxetine mesylate; NDA 21-299

Total no. of pages including cover: 22

Comments: Susan, The Agency would like to secure labeling agreement with Synthon for this NDA. Please see attached.

Document to be mailed: ☐ YES ☑ NO

Attachment

1. We note that Synthon has incorporated the most revisions to the Paxil prescriber labeling into the paroxetine mesylate labeling. This labeling is attached. We additionally wish to secure agreement that the prescriber labeling will use a minimum four-point type font size.
2. In regard to the container/carton labeling, the Agency wishes to secure agreement on the following issues:
   a) On the container and carton label, the proposed [redacted] statement ' [redacted] should be replaced by the following statement: ' [redacted]
   b) In accordance with the Poison Prevention Act, drugs packaged in "unit of use" bottles and dispensed on an outpatient basis, such as the 30 capsule bottles, should include Child Resistant Closures (CRC). Please commit to using bottles that utilize such a closure.
   c) We believe that the strength of the product is not clear and legible as shown with the [redacted] We are requesting that you relocate the strength so it appears [redacted]. Also, the number, i.e., strength, must be accompanied by [redacted]
   d) Please revise the container labeling dosage statement to read: " [redacted]
   e) Please relocate the [redacted] ' statement to appear on the principal display panel.

80 Draft Labeling Page(s) Withheld

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: August 28, 2001

To: Attention: **Susan Harts, Drug Regulatory Affairs**	**From:** Paul David
Company: Synthon	Division of Division of Neuropharmacological Drug Products
Fax number: 919-493-6104	**Fax number:** 301-594-2859
Phone number: 919-493-6006	**Phone number:** 301-594-5530

Subject: CMC Clarification; Paroxetine mesylate; NDA 21-299

Total no. of pages including cover: 2

Comments: Susan, the chemist reviewed Synthon's questions regarding the Agency's discipline review letter dated July 17, 2001. I have attached the response. Please contact me if you have any questions. Thanks, Paul

Document to be mailed: ☐ YES ☑ NO

Attachment

Synthon's proposal to recalculate the RRF values for the impurities in [redacted] in Paroxetine mesylate ds & in Paroxetine (as mesylate) tablets is acceptable. However, Synthon's proposal to analyze samples needs to include analysis of three lots of each proposed strength of dp (i.e., 10 mg, 20 mg, 30 mg & 40 mg). In addition, Synthon needs to address the following:

1. Please provide the FDA with Synthon's commitment to immediately implement the revised methods for calculating the impurities in [redacted], in Paroxetine mesylate drug substance and in Paroxetine (as mesylate) tablets. Snynthon should immediately update the drug substance and drug product stability protocols to reflect the fact that impurities will be calculated by new analytical methods.

2. Please provide the FDA with a copy of the validated methods for testing [redacted] Paroxetine mesylate drug substance and Paroxetine (as mesylate) tablets, which reflect the revised methods for calculating impurities.

3. As requested in the FDA's July 17, 2001 Discipline Review Letter please provide the FDA with a copy of the validated methods for testing the enantiomeric purity of Paroxetine (as mesylate) Tablets 10 mg, 20 mg, 30 mg, 40 mg.

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

/s/

Paul David
8/28/01 03:34:22 PM
CSO