

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-299

CHEMISTRY REVIEW(S)

**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS**

NDA 21-299

CHEM REVIEW: #1

REVIEW DATE: 4/3/01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	ACTION
ORIGINAL	07/26/00	07/27/00	08/10/00	Approvable
AMENDMENT	12/8/00	12/11/00	12/13/00	NAI

NAME AND ADDRESS OF APPLICANT

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

DRUG PRODUCT NAME

Proprietary:	NA
Non proprietary/USAN:	Paroxetine mesylate
Code Name/Number:	POT.mes
Chem. Type/Ther. Class:	2S

PHARMACOLOGICAL CATEGORY/INDICATION: Antidepressant/Depression, Obsessive Compulsive Disorder, Panic Disorder

DOSAGE FORM: Tablet

STRENGTHS: 10 mg, 20 mg, 30 mg, 40 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

SPECIAL PRODUCTS: Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

CA Name: (3S,4R)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-piperidine methane sulphonic acid

USAN Name: Paroxetine mesylate

Chemical Formula: $C_{19}H_{20}FNO_3 \cdot CH_3SO_3H$

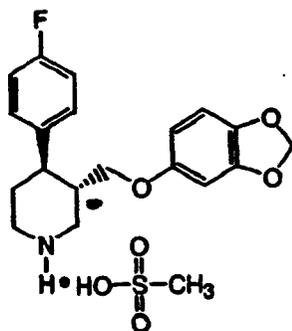
Molecular Weight: — (as mesylate), 329.37 (free base)

CAS Registry Number: 217797-14-3 [as mesylate], 61869-08-7 [free base]

Laboratory Code: 500

Synonyms: NA

Chemical Structure:



Paroxetine mesylate

SUPPORTING DOCUMENTS:

TYPE/No.	SUBJECT	HOLDER/SPONSOR	STATUS	REVIEW DATE	LETTER DATE
IND 57,407	Paroxetine Mesylate Tablets	Synthon Pharmaceuticals Ltd	CMC reviews up to date	Not Applicable	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Lorenzo Rocca (HFD-120) on 3/13/01	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Don Klein (HFD-120) on 9/28/00	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Sharon Kelly (HFD-510) on 9/26/00	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by David Cummings (HFD-120) on 11/09/98	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Thomas F. Oliver (HFD-120) on 5/19/99	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate; sufficient data provided by Applicant	Not Applicable	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Kevin A. Swiss (HFD-570) on 2/16/00	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate; sufficient data provided by Applicant	Not Applicable	Not Applicable
DMF (Type IV)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Lorenzo Rocca (HFD-120) on 3/13/01	Not Applicable

CONCLUSIONS & RECOMMENDATIONS: Concerning the chemistry, manufacturing, and controls (CMC), NDA 22-299 is approvable. The Applicant must address the CMC deficiencies before the NDA can be approved for CMC. See draft deficiency letter (not attached to this review).

The Applicant has proposed a _____ expiration date for Paroxetine (as mesylate) tablets, 10 mg, 20 mg, 30 mg, 40 mg when stored at room temperature in the market container (i.e., _____ bottle) or in bulk packaging (i.e., _____ bag packaged in _____ container with desiccant bag). The currently available stability date (i.e., _____ room temperature and _____, accelerated) supports a two-year (24-month) expiration period for Paroxetine (as mesylate) tablets, 10 mg, 20 mg, 30 mg, 40 mg.

The applicant's proposed dissolution method (i.e., _____) is acceptable. The FDA requests that the applicant revise the regulatory dissolution specification for Paroxetine (as mesylate) Tablets from NLT Q= _____ in 30 minutes to NLT Q= _____ in 30 minutes.

Lorenzo A. Rocca, Ph.D., Review Chemist

Robert H. Seevers, Ph.D., Chemistry Team Leader

cc:
Orig. NDA 21-299
HFD-120/Division File
HFD-120/PDavid
HFD-120/LRocca
HFD-120/RSeevers

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/s/

Lorenzo Rocca

4/3/01 09:47:44 AM
CHEMIST

Robert H. Seevers

4/3/01 10:05:22 AM
CHEMIST

**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS**

NDA 21-299

CHEM REVIEW: #2

REVIEW DATE: 7/09/01

SUBMISSION TYPE	DOCUMENT	CDER	ASSIGNED	ACTION
ORIGINAL	07/26/00	07/27/00	08/10/00	Approvable 5/25/01, Discipline Review Letter, 4/3/01
AMEND(N-BZ)	12/08/00	12/11/00	12/13/00	NAI 12/20/00
AMEND(N-BC)	01/26/01	01/29/01	01/29/01	NAI 4/12/01
AMEND(N-BC)	06/07/01	06/08/01	06/11/01	Approvable 7/09/01 Deficiency Letter, 7/09/01

NAME AND ADDRESS OF APPLICANT

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

DRUG PRODUCT NAME

Proprietary:	NA
Non proprietary/USAN:	Paroxetine mesylate
Code Name/Number:	POT.mes
Chem. Type/Ther. Class:	2S

PHARMACOLOGICAL CATEGORY/INDICATION: Antidepressant/Depression, Obsessive Compulsive Disorder, Panic Disorder

DOSAGE FORM: Tablet

STRENGTHS: 10 mg, 20 mg, 30 mg, 40 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

SPECIAL PRODUCTS: Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

CA Name: (3S,4R)-3-[(1,3-benzodioxol-5-yloxy-)methyl]-4-(4-fluorophenyl)-piperidine methane sulphonic acid

USAN Name: Paroxetine mesylate

Chemical Formula: $C_{19}H_{20}FNO_3 \cdot CH_3SO_3H$

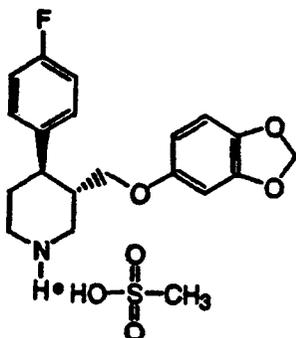
Molecular Weight: ~~329.37~~ (as mesylate), 329.37 (free base)

CAS Registry Number: 217797-14-3 [as mesylate], 61869-08-7 [free base]

Laboratory Code: 500

Synonyms: NA

Chemical Structure:



Paroxetine mesylate

SUPPORTING DOCUMENTS:

TYPE/No.	SUBJECT	HOLDER/SPONSOR	STATUS	REVIEW DATE	LETTER DATE
IND 57,407	Paroxetine Mesylate Tablets	Synthon Pharmaceuticals Ltd	CMC reviews up to date	Not Applicable	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Lorenzo Rocca (HFD-120) on 3/13/01	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Don Klein (HFD-120) on 9/28/00	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Sharon Kelly (HFD-510) on 9/26/00	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by David Cummings (HFD-120) on 11/09/98	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Thomas F. Oliver (HFD-120) on 5/19/99	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate; sufficient data provided by Applicant	Not Applicable	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Kevin A. Swiss (HFD-570) on 2/16/00	Not Applicable
DMF (Type III)	[REDACTED]	[REDACTED]	Adequate; sufficient data provided by Applicant	Not Applicable	Not Applicable
DMF (Type IV)	[REDACTED]	[REDACTED]	Adequate	Reviewed by Lorenzo Rocca (HFD-120) on 3/13/01	Not Applicable

RELATED DOCUMENTS: NDA 20-031 Paxil® Tablets (GlaxoSmithKline)

CONSULTS: None

OTHER REQUESTS:

Request	Status	Status of Request
Establishment Evaluation	4 sites found acceptable	Submitted on 9/1/00: CFN _____ Acceptable on 11/21/00 (district recommendation) CFN _____ Acceptable on 9/5/00 (based on profile) CFN _____ Acceptable on 10/26/00 (inspection, no FD-483) Submitted on 9/8/00: CFN _____ Acceptable on 11/3/00 (inspection, no FD-483)
Methods Validation	Pending	Will be submitted after all the CMC deficiencies have been addressed.

RELATED REVIEWS:

Pharmacology and Toxicology; Primary Reviewer, Linda Fossom, Ph.D. (HFD-120), completed 5/7/01. Team Leader concurrence 5/8/01.	From a pharmacology/toxicology perspective there are no objections to the approval of this NDA.
Clinical Pharmacology and Biopharmaceutics Review; Primary Reviewer, Iftekhar Mahmood, Ph.D. (HFD-860), completed 5/3/01. Team Leader, Raman Baweja, Ph.D. (HFD-860), concurrence, 5/3/01.	The 40 mg paroxetine mesylate tablets are bioequivalent to the 40 mg paroxetine hydrochloride tablets. The 20 and 30 mg paroxetine mesylate tablets fulfill the requirements of biowaver. Therefore, the Sponsor can market 20, 30, and 40 mg paroxetine mesylate tablets. The 10-mg paroxetine mesylate tablets (dosed as 2x10 mg) failed to meet the bioequivalence criteria. Though the mean C_{max} and AUC of 10 mg paroxetine mesylate tablets are comparable to the mean C_{max} and AUC of 10 mg paroxetine HCl tablets, the failure of AUC to meet the bioequivalence criteria may be due to very high intersubject variability (approximately 200% for both test and reference), small sample size and lack of power. Inclusion of more subjects ($n \geq 50$) in the study may have demonstrated bioequivalence between the test and the reference. Furthermore, paroxetine mesylate tablets are compositionally proportional from 10 to 40 mg and they have similar dissolution profiles for all tablet strengths. Since the 10 mg paroxetine mesylate tablets are bioequivalent to the 10 mg paroxetine hydrochloride tablets, the approval of this strength should be based on clinical consideration. Comments to the Sponsor: The FDA's dissolution method and specification for all strengths of paroxetine mesylate tablets is: _____ Specification: Q= _____ in 30 minutes.

REMARKS/COMMENTS:

None

CONCLUSIONS & RECOMMENDATIONS: Concerning the chemistry, manufacturing, and controls (CMC), NDA 22-299 is approvable. The Applicant must address the CMC deficiencies before the NDA can be approved for CMC. See draft deficiency letter.

Lorenzo A. Rocca, Ph.D., Review Chemist

Robert H. SeEVERS, Ph.D., Chemistry Team Leader

cc:

Orig. NDA 21-299
HFD-120/Division File
HFD-120/PDavid
HFD-120/LRocca
HFD-120/RSeEVERS

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/s/

Lorenzo Rocca
7/9/01 11:33:54 AM
CHEMIST

Robert H. Seevers
7/10/01 02:54:03 PM
CHEMIST

NDA 21-299

Paroxetine (as mesylate) Tablet

Synthon Pharmaceuticals Ltd.

**Lorenzo Rocca, Ph.D.
HFD-120**

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Chemistry Review Data Sheet

1. NDA 21-299
2. REVIEW #:3
3. REVIEW DATE: 3/05/02
4. REVIEWER: Lorenzo Rocca, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
ORIGINAL	7/26/00
Amendment 7(N-BZ)	12/8/00
Amendment 9(N-BC)	1/26/01
Amendment 11(N-BC)	3/9/01
Discipline Review Letter	4/3/01
Approvable Letter	5/25/01
Amendment 13(N-BC)	6/7/01
Amendment 18(N-BC)	6/15/01
Discipline Review Letter	7/17/01
Letter (NC)	8/7/01
NDA Telecon: Fax to Synthon	8/28/01
Amendment 20(N-AZ)	9/19/01
Amendment 21(N-BC)	12/13/01
Amendment 22(N-C)	12/20/01

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 21(N-BC)	12/13/01

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Synthon Pharmaceuticals Ltd.
Address: 6330 Quadrangle Drive, Suite 305
Chapel Hill, NC 27514
Representative: Susan W. Harts, RN, RAC
Vice President of Regulatory Affairs
Telephone: 919-493-6006

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Asimia™
- b) Non-Proprietary Name (USAN): Paroxetine mesylate (USAN)
- c) Code Name/# (ONDC only): POT.mes
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 2
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505(b)(2) submission

Paxil® (paroxetine hydrochloride) Tablets 10 mg, 20 mg, 30 mg and 40 mg
GlaxoSmithKline
NDA 20-031 (approved 12/29/92)

10. PHARMACOL. CATEGORY: Depression, Obsessive Compulsive Disorder, Panic Disorder

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10 mg, 20 mg, 30 mg, 40 mg

13. ROUTE OF ADMINISTRATION: Oral

CHEMISTRY REVIEW

Chemistry Review Data Sheet

14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note22]:

 SPOTS product – Form Completed

 X Not a SPOTS product

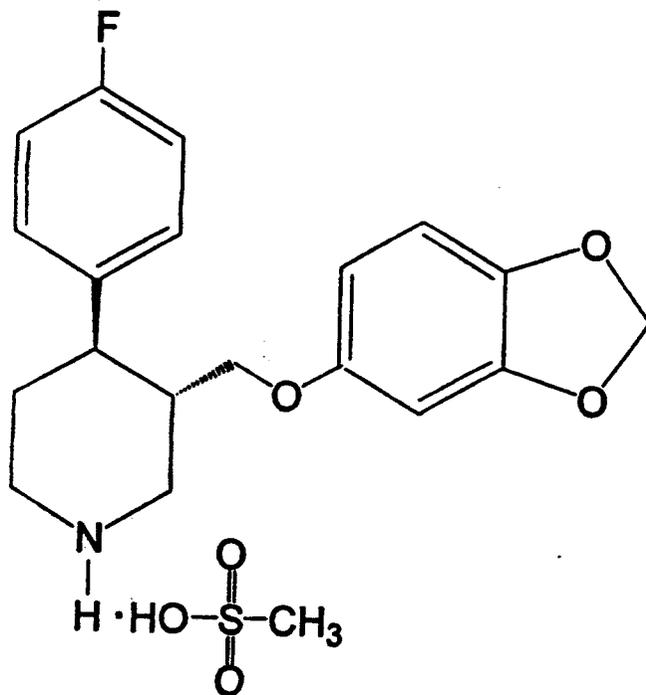
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: (3S,4R)-3-[(1,3-benzodioxol-5-yloxy-)methyl]-4-(4-fluorophenyl)-piperidine methane sulphonic acid

Chemical Formula: $C_{19}H_{20}FNO_3 \cdot CH_3SO_3H$

Molecular Weight: --- (as mesylate), 329.37 (free base)

Chemical Structure:



Paroxetine mesylate

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
1	III	[REDACTED]	[REDACTED]	1	Adequate	3/13/01	N/A
2	III	[REDACTED]	[REDACTED]	1	Adequate	9/28/00	N/A
3	III	[REDACTED]	[REDACTED]	1	Adequate	9/26/00	N/A
4	III	[REDACTED]	[REDACTED]	1	Adequate	11/09/98	N/A
5	III	[REDACTED]	[REDACTED]	1	Adequate	5/19/99	N/A
6	III	[REDACTED]	[REDACTED]	4	Adequate	N/A	N/A
7	III	[REDACTED]	[REDACTED]	1	Adequate	2/16/00	N/A
8	III	[REDACTED]	[REDACTED]	4	Adequate	N/A	N/A
9	IV	[REDACTED]	[REDACTED]	1	Adequate	3/13/01	N/A

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)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57,407	Original

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	1/4/01	Office of Compliance
Pharm/Tox	Approval Recommended	5/8/01	Linda Fossum, Ph. D.
Biopharm	Approval Recommended	10/2/01	Iftekha Mahmood, Ph.D.
LNC	USAN Available	N/A	N/A
Methods Validation	Pending	N/A	N/A
OPDRA	Proprietary Name "Asimia" Acceptable	2/14/02	Nora Roselle, Pharm. D.
EA	Categorical Exclusion Granted	4/3/01	Lorenzo Rocca, Ph.D.
Microbiology	N/A	N/A	N/A

The Chemistry Review for A/NDA ##-###**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

Recommend approval of NDA 21-299 from the CMC standpoint.

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-299 is no longer deficient for the following reason:

- The applicant has adequately responded to the CMC deficiencies listed in the FDA Approvable Letter dated 5/25/01, and the FDA Discipline Review Letter dated 7/17/01 (see also Telecon: Fax to Synthon, dated 8/28/01).
- The Office of Compliance has found all manufacturing facilities acceptable.

In concurrence with the recommendations from the Division of Medication Error and Technical Support (DMETS) (see ODS Consult 01-0208, dated February 19, 2002), the applicant needs to address the following issues with regard to the container and carton labels for each strength of Paroxetine (as mesylate) Tablets and the Asimia™ (paroxetine mesylate) Tablet insert.

- On the container and carton label please replace the current product strengths statement " _____ " with the following: ' _____ ' _____
- Please ensure the insert font size is a minimum of four-point type.

Please note: GlaxoSmithKline has officially filed a lawsuit against Synthon for patent infringement on their marketed drug Paxil®. The lawsuit was filed within the 45 day timeframe and, therefore, the FDA cannot legally approve this drug until the lawsuit has been acted on by the courts or after the 30 months noninfringement notification, which is April 9, 2003.

Executive Summary Section

- 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)

Paroxetine (as mesylate) Tablets 10 mg, 20 mg, 30 mg, 40 mg are oval film-coated tablets with a single distinct color for each strength of paroxetine mesylate tablets with a differentiating size, scoring and inscription characteristics for each strength. The Paroxetine (as mesylate) Tablet is formulated as an immediate release formulation. Paroxetine (as mesylate) tablets have recently been assigned the proprietary name, Asimia™. Asimia™ tablets are packaged in either a _____ container (30 and 100 count) or in a _____ container (500 count) with _____ closure with _____ seal and cotton dunnage.

Paroxetine mesylate is a white powder, with a very bitter taste and is highly water-soluble (>1g/mL). The current retest period for paroxetine mesylate is _____. Paroxetine has two chiral centers, and is marketed as an enantiomeric pure compound in the (3S,4R)-configuration. The correct chirality of the final product is assured by using as a starting material _____ for which the applicant establishes the limiting amount of _____ to be _____. Synthon has provided the FDA with data showing the enantiomeric purity of all GMP batches of paroxetine mesylate, and _____

_____ Paroxetine mesylate appears to be enantiomerically stable and does not show polymorphic characteristics. The release specification for the impurity _____, in Paroxetine mesylate drug substance was recently reduced (see NDA 21-299 Amendment 7 N-BZ, December 8, 2000) from _____ for all future batches of drug substance. The reduced specification was required by the FDA in order not to meet the requirements for qualifying _____. At the same time the Paroxetine mesylate drug substance impurity release specification for _____ was set at _____. The specifications for _____ correspond to the maximum levels that do not require qualification. The remaining impurity release specifications for Paroxetine mesylate drug substance are acceptable as proposed. The drug substance release specifications provide adequate control of the identity, quality and purity of the paroxetine mesylate used to manufacture Asimia™ Tablets.

Paroxetine (as mesylate) Tablets are manufactured by _____. The tablets are film coated with colorants which are CFR listed and that may be safely used in amounts consistent with the appropriate Federal Food Additives regulation (i.e., 21CFR 73.1200).

Executive Summary Section

Specific in-process controls are carried out during the manufacturing process to assure control of the manufacturing process, and final release testing assure the identity, quality, strength and purity of Asimia™ Tablets. The release specification for the impurity _____, in Paroxetine (as mesylate) tablets was recently reduced (see NDA 21-299 Amendment 7 N-BZ, December 8, 2000) from _____ for all future batches of drug substance. The reduced specification was required by the FDA in order to meet the requirements for not qualifying _____. The remaining impurity release specifications for Paroxetine (as mesylate) Tablets are acceptable as proposed. The applicant's proposed dissolution specifications have been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (HFD-860) (see OCPB Review, dated November 2, 2001). Synthon has accepted the dissolution specifications as requested by the OCPB (i.e. _____ Specification: Q = _____ in 30 minutes). Methods validation is pending. The applicant needs to provide the FDA with an updated methods validation package before their analytical methods can be submitted to the appropriate FDA analytical laboratory for validation.

The clinical formulation of Paroxetine (as mesylate) tablets is identical to the commercial product. The commercial formulation of Asimia™ Tablets 10 mg, 20 mg, 30 mg and 40 mg was developed using as the starting point for development the commercial formulation of Paroxetine (hydrochloride) Tablet (i.e., Paxil®). During development the applicant chose to use _____ dibasic calcium phosphate (_____ as opposed to dibasic calcium phosphate which is used in the formulation of Paxil®. Also included in their formulation, Synthon has added hydroxypropyl cellulose, in addition to hydroxypropyl methylcellulose as _____

Since there are no differences between the clinical and commercial formulations compatibility studies are not needed.

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

Asimia™ (paroxetine mesylate) will be supplied as 10 mg, 20 mg, 30 mg and 40 mg oral tablets. The recommended initial dosage in treating depression is 20 mg/day (with or without food), up to a maximum of 50 mg/day as a single dose (10 mg/day increments, of interval of at least 1 week). The recommended initial dosage in treating obsessive compulsive disorder is 20 mg/day, with a recommended dose of 40 mg/day (the maximum dosage should not exceed 60 mg/day). The recommended initial dosage in treating panic disorder should be 10 mg/day, with the target dose of 40 mg/day (the maximum dosage should not exceed 60 mg/day).

The recommended expiration period for Asimia™ (paroxetine mesylate) Tablets 10 mg, 20 mg, 30 mg, 40 mg is 24 months. Tablets should be stored between 15 and 30° C (59° and 86° F).

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

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 listed in the Agency Approvable Letter dated May 25, 2001, and the Agency Discipline Review Letter dated July 7, 2001 (see also Telecon: Fax response dated August 28, 2001).
- The applicant has provided adequate information to assure the identity, strength, quality and purity of the drug product.
- All facilities involved in the manufacture and control of the drug substance and drug product were found to have acceptable cGMP.

In concurrence with DMETS recommendations (see ODS Consult No. 01-0208, dated February 19, 2002) the following changes should be made, concerning the container and carton labels and drug product insert.

- On the container and carton label please replace the current product strengths statement ' _____ ' with the following: ' _____ '
- Please ensure the insert font size is a minimum of four-point type.

III. Administrative**A. Reviewer's Signature**

Executive Summary Section

B. Endorsement Block

LRocca/Date
HPatel (TL-acting)/Date
PDavid (PM)/Date

C. CC Block

Orig. NDA 21-299
HFD-120/Division File
HFD-120/PDavid
HFD-120/LRocca
HFD-120/HPatel

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/s/

Lorenzo Rocca
3/6/02 09:20:39 AM
CHEMIST

Hasmukh Patel
3/6/02 09:23:06 AM
CHEMIST