CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-299

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-299

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

Dear Ms. Harts:

Please refer to your new drug application (NDA) dated July 26, 2000, received July 26, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for paroxetine mesylate 10 mg, 20 mg, 30 mg, and 40 mg Tablets.

We acknowledge receipt of your submissions dated January 8, February 18, March 3, March 25, and April 24, 2003.

The February 18, 2003, submission constituted a complete response to our tentative approval letter dated March 11, 2002.

This new drug application provides for the use of paroxetine mesylate tablets for major depressive disorder, obsessive compulsive disorder, and panic disorder.

The reference listed drug (RLD) product referenced in your application, Paxil Tablets of GlaxoSmithKline, is subject to periods of patent protection (including pediatric exclusivity under section 505A of the Act) which expire on June 29, 2007 (U.S. Patent No. 4,721,723 [the '723 patent]), July 6, 2009 (U.S. Patent No. 5,789,449 [the '449 patent]), November 19, 2015, (U.S. Patent No. 5,872,132 [the '132 patent]), November 19, 2015 (U.S. Patent No. 5,900,423 [the '423 patent]), October 23, 2019 (U.S. Patent No. 6,063,927 [the '927 patent]), November 19, 2015 (U.S. Patent No. 6,080,759 [the '759 patent]), June 14, 2015 (U.S. Patent No. 6,113,944 [the '944 patent]), September 17, 2017 (U.S. Patent No. 6,121,291 [the '291 patent]), November 19, 2015 (U.S. Patent No. 6,133,289 [the '289 patent]), and July 15, 2018 (U.S. Patent No. 6,172,233 [the '233 patent]). Your application contains a Paragraph IV Certification to all of these patents under Section 505(b)(2)(A)(iv) of the Act.

Section 505(c)(3)(C) of the Act provides that the approval of a new drug application filed under section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of the patents that are the subject of the certification. This action must be taken before the expiration of forty-five days from the date the notice provided under section 505(b)(3)(A) is received by both the holder of the new drug application (NDA) and the patent owner. You have notified the Agency that Synthon Pharmaceuticals, Ltd. (Synthon) has complied with the requirements of Section 505(c)(3)(C) of the Act and that no action for patent infringement regarding the '449, '132, '423, '759, '291, '289, or '233 patents was brought against Synthon within the statutory forty-five day period. In addition, you have notified the Agency that litigation is underway in the Middle District of North Carolina involving a challenge to the

'723, '927, and '944 patents (SmithKline Beecham Corporation, SmithKline Beecham, P.L.C., and Beecham Group, P.L.C. v. Synthon Pharmaceuticals, Ltd. and Synthon B.V., Civil Action No. 1:00cv1179).
With respect to this litigation, the Agency recognizes that the 30-month period identified in section 505(c)(3)(C) of the Act, during which time the Agency is precluded from approving your application, has expired.

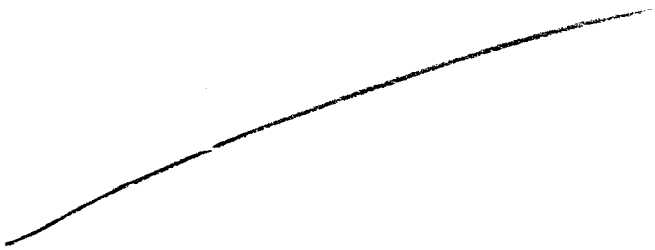
We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

Tradename
Please note that we are approving this application without a tradename since our Division of Medication Errors and Technical Support (DMETS) has reassessed your proposed tradename of Asimia, and they have found it unacceptable. In their reassessment of the proprietary name "Asimia", their primary concern for name confusion was Alinia, which already exists in the US marketplace.

Alinia has potential for look-alike and sound-alike confusion with Asimia. Alinia was approved on November 22, 2002 for the treatment of diarrhea in children caused by *Cryptosporidium parvum* and *Giardia lamblia*. Both names begin with the letter "A-", end with "-ia", and have the same number of letters. In addition, the letters "-m-" and "-n-" in the middle of the names can look the same when handwritten and sound similar. Both names contain three syllables and the sound-alike similarity is mainly due to their rhyming quality. Although Alinia and Asimia differ with respect to many characteristics, the name similarity is significant and the opportunities for errors are likely in any situation where the prescriber communication is not clear to the practitioners interpreting the medication order. This commonly occurs when the prescription is ambiguous or incomplete. DMETS anticipates that errors may occur between Alinia and Asimia despite their differing indications and characteristics.

DMETS has identified significant potential for confusion with Alinia, particularly in the case of handwritten orders and considers the proposed name unacceptable based on 21 CFR 201.10(c)(5). This regulation states, "The labeling of a drug may be misleading by reason of designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient."

DMETS also found your other proposed tradename of — submitted on April 24, 2003, to be unacceptable. In reviewing the proposed proprietary name ' — , the primary concerns raised were related to three look-alike and/or sound-alike names. The products considered to have potential for name confusion with — were —



1 Page(s) Withheld

Therefore, if you wish to market this drug with a tradename, you will be required to submit a "Prior Approval" labeling supplement to your NDA.

Labeling
We note your agreement, in correspondence dated March 25, 2003, to the labeling attached to this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-299." Approval of this submission by FDA is not required before the labeling is used.

Please submit one package of the drug product when it is available.

Dissolution Methodology
Additionally, we note your agreement to adopt the following dissolution method and specification for all strengths (10 mg, 20 mg, 30 mg, and 40 mg) of Paroxetine mesylate tablets:

[redacted]

Specification: Q = [redacted] in 30 minutes

Methods Validation
Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Promotional Materials
In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-299

APPROVABLE LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-299

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

Dear Ms. Harts:

Please refer to your new drug application (NDA) dated July 26, 2000, received July 26, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Paroxetine mesylate 10 mg, 20 mg, 30 mg, and 40 mg Tablets.

We acknowledge receipt of your submissions dated October 6, 12, 13, and 31, November 15, 21, 30, December 8, 2000, January 1, and 26, March 9, and 16, and April 3, and 18, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

CLINICAL

1. **Labeling**

   The attached labeling for Paroxetine mesylate is identical to the most recently approved labeling for Paxil (paroxetine hydrochloride) except for the following modifications:

   a) Brand name
   b) Hydrochloride changed to mesylate
   c) Chemical formula and molecular weight
   d) Melting point
   e) Solubility
   f) Tablet description and excipients
   g) Manufacturer
   h) NDA Labeler code
   i) Paroxetine mesylate is not labeled for the indication of social anxiety disorder since this indication is protected under the market exclusivity regulations
   j) Paroxetine mesylate is not labeled as an oral suspension
   k) The steady state pharmacokinetic data, under the **CLINICAL PHARMACOLOGY-Pharmacokinetics** section, have been replaced with data obtained with Paroxetine mesylate tablets.

   Additionally, please note that we have updated your proposed labeling, submitted with your July 26, 2000 application, to reflect additional safety revisions which have been incorporated into the Paxil labeling.

2. **Drug Product**
We note that all four of the paroxetine mesylate tablet strengths, 10 mg, 20 mg, 30 mg and 40 mg, will be [redacted] color, filmcoated, modified-oval tablets distinguished only by an inscription on one side of the tablet (e.g., "POT 10" on the 10 mg tablet). 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 medication errors. As noted in our letter dated April 3, 2001 (Point #8 under deficiencies pertaining to drug product), we are requiring that you amend your application to stipulate a single color for each of the paroxetine mesylate strengths.

Chemistry, Manufacturing, and Controls Deficiencies

1. The Agency issued you a deficiency letter dated April 3, 2001, regarding the chemistry, manufacturing, and controls portion of your NDA. We note that you have not formally responded to this request for additional information. These issues will need to be adequately addressed and resolved prior to the approval of this application.
2. The currently available stability data (i.e., [redacted] room temperature and [redacted] accelerated data) support a 2-year (24-months) expiration period for Paroxetine mesylate 10 mg, 20 mg, 30 mg, and 40 mg tablets. We note that your long-term stability studies are ongoing.

Clinical Pharmacology and Biopharmaceutics

We request that you adopt the following dissolution method and specification for all strengths (10 mg, 20 mg, 30 mg, and 40 mg) of Paroxetine mesylate tablets:

[redacted]

Specification: Q = [redacted] in 30 minutes

We would also like to point out that the study reports submitted in the pharmacology/toxicology section of the NDA were very well organized and easy to review.

Please submit 20 paper copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

17 Draft Labeling Page(s) Withheld

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

/s/

Russell Katz
5/25/01 08:18:13 AM