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 Asimia (paroxetine mesylate) 10 mg, 20 mg, 30 mg, and 40 mg Tablets.

We acknowledge receipt of your submissions dated June 7, June 15, July 17, September 19, December 13, 2001, and March 6, 2002. Your submission of September 19, 2001, constituted a complete response to our May 25, 2001 action letter.

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

We have completed the review of this application, as amended, and have concluded that based upon the information you have presented to date, the drug product is safe and effective for use as recommended in the enclosed labeling (text for the prescriber package insert). Accordingly, the application is **tentatively approved** under 21 CFR 314.105. This determination is contingent upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in manufacturing and testing of the drug product) and is, therefore, subject to change on the basis of new information that may come to our attention.

The referenced listed drug (RLD) product referenced in your application, Paxil Tablets of GlaxoSmithKline, is subject to periods of patent protection which expire on December 29, 2006 (U.S. Patent No. 4,721,723 [the '723 patent]), January 6, 2009 (U.S. Patent No. 5,789,449 [the '449 patent]), May 19, 2015, (U.S. Patent No. 5,872,132 [the '132 patent]), May 19, 2015 (U.S. Patent No. 5,900,423 [the '423 patent]), April 23, 2019 (U.S. Patent No. 6,063,927 [the '927 patent]), May 19, 2015 (U.S. Patent No. 6,080,759 [the '759 patent]), December 14, 2014 (U.S. Patent No. 6,113,944 [the '944 patent]), March 17, 2017 (U.S. Patent No. 6,121,291 [the '291 patent]), May 19, 2015 (U.S. Patent No. 6,133,289 [the '289 patent]), and January 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. This certification states that the above listed patents are invalid, unenforceable or would not be infringed by your manufacture, use, offer for sale, or sale of this drug product. Section 505(c)(3)(C) of the Act provides that the approval of a new drug application submitted pursuant

to 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 the patent owner and/or NDA holder initiated a patent infringement suit against Synthon with respect to the '723, '927, and '944 patents in the United States District Court for the Middle District of North Carolina (Durham) (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). Therefore, final approval cannot be granted, with respect to each patent for which a paragraph IV certification was submitted and patent litigation was initiated, until:

1. a) expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3)(A), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b) the date of a court action described in Section 505(c)(3)(C)(i), (ii), or (iii), , or,

   c) the patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may effect the final approval. This amendment must provide the following information:

1. Please include updated information related to labeling or chemistry, manufacturing, and controls data, or any other change in the conditions outlined in your application.

2. Please submit a copy of a final order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information.

An amendment should be submitted even if no changes were made to the application since the date of this tentative approval. In addition to this amendment, the Agency may request at any time prior to the date of final approval that you submit an additional amendment containing the information described above. Failure to submit either or, if requested, both amendments, may result in rescission of the tentative approval status of your application, or result in a delay in the issuance of the final approval letter.

We additionally have the following comments pertaining to this application.

Labeling
We additionally reference a faxed communication dated March 6, 2002, between Mr. Paul David, of this Agency, and yourself agreeing to the labeling attached to this letter (enclosure) as well as to the following revisions to the labeling as stated below. Please note, however, that the labeling may need to be updated as safety related labeling changes are made to the RLD, Paxil, prior to final approval of this application.

1. We note your agreement to use a minimum four-point type font size for the prescriber labeling.
2. In regard to the container/carton labeling, we note your agreement to the following:
   a) On the container and carton label, the proposed product strengths statement "Each tablet contains..." will be replaced by the following statement: "Each tablet contains paroxetine mesylate equivalent to XX mg paroxetine base" (where XX corresponds to 10, 20, 30, or 40 mg).
   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 under the established name as well as removing the rays that surround the circle. Also the number, i.e., strength, will be accompanied by its unit of measure "mg".
   d) The container labeling dosage statement will be revised to read: "USUAL DOSAGE: See package insert

   e) The "Rx only" statement will be relocated to appear on the principal display panel.

Clinical Pharmacology and Biopharmaceutics
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

Chemistry, Manufacturing, and Controls
Please provide the FDA with a complete updated Methods Validation Package (four copies) which encompasses all the relevant updated methods and validation reports used to analyze Paroxetine (as mesylate) Tablets 10 mg, 20 mg, 30 mg, 40 mg. The description of the Methods Validation Package is available in the Guidance entitled Guideline for Submitting Samples and Analytical Data for Method Validation (February 1987). 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.

Tradename
Your proposed tradename of Asimia has been found to be acceptable. This is considered a tentative decision and the tradename will need to be re-evaluated approximately 90 days prior to the expected final approval of this application.

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

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

Any significant change in the conditions outlined in this new drug application requires Agency review before final approval may be granted.

The drug product that is the subject of this new drug application may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, the drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book") published by the Agency.

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

Enclosure

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
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