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RESEARCH**

*APPLICATION NUMBER:*

**21-961**

**APPROVAL LETTER**



NDA 21-961

**NDA APPROVAL**

Synthon Pharmaceuticals, Inc.  
Attention: Michael H. Hinckle  
Vice President and General Counsel  
9000 Development Drive  
P.O. Box 110487  
Research Triangle Park, North Carolina 27709

Dear Mr. Hinckle:

Please refer to your new drug application (NDA) dated July 28, 2005, received July 29, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Simvastatin Orally Disintegrating Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

We acknowledge receipt of your submissions dated April 16, May 23, September 4 and 18 (email), 2007. The April 16, 2007, submission constituted a complete response to our May 25, 2006, action letter.

This new drug application provides for the use of Simvastatin Orally Disintegrating Tablets for the following indications:

*Reductions in Risk of CHD Mortality and Cardiovascular Events*

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, Simvastatin Orally Disintegrating Tablets are indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

*Patients with Hypercholesterolemia Requiring Modifications of Lipid Profiles*

Simvastatin Orally Disintegrating Tablets are indicated to:

- Reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb).
- Treat patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).
- Treat patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).

- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

*Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH)*

Simvastatin Orally Disintegrating Tablets are indicated as an adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolemia, if after an adequate trial of diet therapy the following findings are present:

1. LDL cholesterol remains  $\geq 190$  mg/dL; or
2. LDL cholesterol remains  $\geq 160$  mg/dL and
  - There is a positive family history of premature cardiovascular disease (CVD) or
  - Two or more other CVD risk factors are present in the adolescent patient.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert) submitted September 18, 2007, by email. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-961."

**CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed container labels that are identical to the September 4, 2007, submitted immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Container Labels for approved NDA 21-961.**" Approval of this submission by FDA is not required before the labeling is used. We note that you will not use carton labels for these products.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

**PROPRIETARY NAME**

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

**PEDIATRIC RESEARCH EQUITY ACT (PREA)**

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

**POSTMARKETING COMMITMENTS**

We remind you of your postmarketing study commitment in your submission dated May 23, 2007. The following commitment should be submitted by April 30, 2008.

1. The dissolution method QC.WO.SVT.odt.020.C/12.02 will be validated concurrently while the product release testing is performed using the dissolution method QC.US01.SVT.020.C/6. The dissolution method QC.WO.SVT.odt.020.C/12.02 will be validated to support the acceptance criterion described in your May 23, 2007, submission. The validated method will be included in the regulatory specification for release and stability testing. Stability data generated by using this method will be submitted in the annual reports to support the proposed dating period.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see [www.fda.gov/cder/ddmac](http://www.fda.gov/cder/ddmac).

### **METHODS VALIDATION**

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch  
Food and Drug Administration  
HFD-001, Suite 5100  
5515 Security Lane  
Rockville, MD 20852

### **REPORTING REQUIREMENTS**

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 Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology  
Products (DMEP)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Eric Colman  
10/9/2007 09:09:59 AM  
Eric Colman for Mary Parks