CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-961

MEDICAL REVIEW

DEPUTY DIVISION DIRECTOR MEMORANDUM

September 17, 2007

NDA: 21-961

DRUG: Simvastatin Oral Disintegrating Tablets (10, 20, 40, and 80 mg)

INDICATION: Hypercholesterolemia

COMPANY: Synthon Pharmaceuticals, Inc.

Background

This is my second memorandum for this NDA, which received a not approved letter following the initial review cycle.

Based on inadequate record keeping, specifically the lack of verification of the time of dosing and the specific treatments received by study subjects, noted during a For-Cause inspection, Dr. Viswanathan, Associate Director, FDA's Division of Scientific Investigation (DSI), issued on May 18, 2006, a form 483 to ——— for the bioequivalence study (BE) of simvastatin ODT. Similar findings were noted for an ANDA for amlodipine. The ANDA was not approved because of the DSI inspection findings. b(4)

In a memorandum of May 22, 2006, I recommended that this NDA not be approved due to the concerns raised by Dr. Viswanathan. In a memorandum of August 8, 2006, I reiterated my recommendation that the NDA not be approved. At the time I was willing to reconsider approval of the NDA if Synthon repeated the simvastatin BE study and DSI found the investigation acceptable or additional information was provided by Synthon that resulted in DSI rescinding its 483.

During a teleconference between Synthon and the Office of Compliance (OC), held November 30, 2006, the latter party stated that DSI's concerns about the conduct of the simvastatin ODT BE study (and the amlodipine BE study) could be alleviated if Synthon conducted a "proof-of-concept" BE study. The proof-of-concept study would serve as a model to address DSI's and OC's concerns that the proper test article was given at the appropriate times and to the appropriate subjects in the previously-conducted studies audited by FDA. Amlodipine was suggested as the drug to be tested in the proof-of-concept study. If the results of the repeat amlodipine ODT study were similar (i.e., $\pm$ 15%) to the original amlodipine ODT study, it would be assumed that the original study and the other ODT BE studies were conducted appropriately.

On December 1, 2006, Synthon agreed to the amlodipine proof-of-concept study as the path forward.

Amlodipine ODT Proof-of-Concept Study

On March 27, 2007, Synthon submitted to the Division of Cardiorenal Products the results of the repeat amlodipine ODT study. The study has been reviewed by Dr. Carol Noory of the Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation I.

As summarized by Dr. Noory, "the repeat study was conducted using the same protocol as the original study, samples were tested at the same facility, the TEST and REFERENCE products used were from the same lot, subject demographics were similar. The point estimates for AUC 0-t, AUC 0-inf, and Cmax for the two studies were within the 15% requested.

DSI Inspection of Amlodipine ODT Proof-of-Concept Study

Although DSI made a decision not to inspect the repeat amlodipine ODT study, copies of source documents were evaluated and found to be satisfactorily completed. In a memorandum of May 18, 2007, Dr. CT Viswanathan removed the deficiencies noted in the prior inspectional reports. The subject relief includes the simvastatin ODT study conducted under NDA 21-961.

Labeling

Some minor changes have been made to the labeling since the not approved letter was issued. The changes are limited to the Clinical Pharmacology and Dosage and Administration sections of the labeling.

Ms. Simoneau has completed a labeling review and confirms that the simvastatin ODT labeling includes all of the appropriate information contained in the most recently approved simvastatin innovator labeling.

Tradename

Synthon has decided against using a tradename for their product.

Phase 4 Commitments

In a letter dated May 23, 2007, Synthon agreed to the following phase 4 commitments:

1. ٣

b(4)

2.

3. ٤ To concurrently validate the more discriminating dissolution method to NDA 21-961 while performing simvastatin lot release testing using dissolution method

12.02. The new dissolution method test method will be validated to support a lot release specification of Q > ___ at 15 minutes. b(4)

Conclusion and Recommendation

This NDA was not approved during the first review cycle because of questions regarding the adequacy of the documentation for the pivotal BE study. The BE data were more or less the sole basis of approval of the NDA.

Following agreement between the company and the OC about a path forward, Synthon conducted a second amlodipine ODT BE study. Review of the repeat study indicated that the results were very similar to the findings from the original amlodipine BE study. It was thus concluded that the original amlodipine study, and by extension the original simvastatin ODT study, was conducted in a satisfactory manner.

Given that the original concerns regarding the conduct of Synthon's BE studies have been alleviated, I recommend that NDA 21-961 be approved.

Eric Colman, MD

Appears This Way
On Original

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

/s/

Eric Colman
10/10/2007 09:55:33 AM
MEDICAL OFFICER

Appears This Way
On Original

MEMORANDUM TO THE FILE

August 8, 2006

NDA: 21-961

DRUG: Simvastatin Orally Disintegrating Tablet

COMPANY: Synthon Pharmaceuticals, Inc.

SUBJECT: Sponsor's 1 August 2006 Correspondence

This memo is written in response to Synthon's 1 August 2006 submission to NDA 21-961. In this correspondence, Synthon responds to DMEP's 11 July 2006 letter in which the Division provided reasons why the information included in Synthon's 30 May 2006 response to the Not Approvable letter did not alleviate concerns regarding the deficiencies identified by a DSI inspection of the single bioequivalence study submitted as the sole source of clinical data supporting approval of NDA 21-961.

Synthon also uses this submission to provide DMEP with "all of the relevant information in the administrative file prior to the filing of the [dispute resolution] appeal." This is considered necessary by Synthon because DMEP, DSI, and Synthon all agree that the End-of-Review meeting scheduled for 17 July 2006 was unlikely to resolve the outstanding issues, and the meeting was canceled.

Synthon concludes that unless they receive notification of the approval of NDA 21-961 within ten business days of DMEP's receipt of their letter, they will assume that the Not Approvable decision remains in effect and they will proceed with a dispute resolution appeal.

I have read Synthon's 1 August 2006 submission and Dr. Vishwanathan's 7 August 2006 response to this correspondence. No additional data have been submitted for DMEP to disregard the deficiencies identified by DSI in its inspection of the sole bioequivalence study supporting approval of NDA 21-961. Consequently, I maintain that this application can not be approved until a new BE study is conducted and found acceptable or until additional information is provided to DSI that would result in its withdrawal of the initial inspection conclusions.

Eric Colman, MD
Acting Deputy Division Director
Division of Metabolic and Endocrine Products

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

/s/

Eric Colman
8/9/2006 10:20:02 AM
MEDICAL OFFICER

Mary Parks
8/9/2006 12:59:42 PM
MEDICAL OFFICER
I concur w/ Dr. Colman

Appears This Way
On Original

ACTING DEPUTY DIVISION DIRECTOR MEMORANDUM

May 22, 2006

NDA: 21-961

DRUG: Simvastatin Oral Disintegrating Tablets (10, 20, 40, and 80 mg)

INDICATION: Hypercholesterolemia

COMPANY: Synthon Pharmaceuticals, Inc.

Background

This 505b2 application for simvastatin was submitted on 29 July 2005. Synthon is seeking approval of their simvastatin for the same indications as that of the innovator product Zocor:

1) In patients with CHD or at high risk of CHD because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease to:
   - reduce risk of CHD mortality
   - and cardiovascular events (non fatal myocardial infarctions, stroke and need for coronary and non-coronary revascularization procedures)
2) In patients with Hypercholesterolemia requiring modifications of lipid profiles simvastatin is 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.
3) In adolescent patients with Heterozygous Familial Hypercholesterolemia (HeFH) simvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and Apo B.

The basis of approval of this 505b2 application is a bioequivalence study.

Discipline Reviews

The clinical review was conducted by Dr. Bill Lubas.
The clinical pharmacology review was conducted by Dr. Sang Chung

The chemistry review was conducted by Dr. John Hill.
There were no new pharmacology/toxicology data submitted with this 505b2 application.

Bioequivalence Study

This was a single-center [redacted], randomized, single-dose, two-period, crossover study comparing Zocor 80 mg to Synthon's 80 mg simvastatin under fasting conditions. b(4)

Thirty-four healthy males and 38 healthy females, mean age 28 years, received at least one dose of study medication.

Levels of parent compound and metabolite for the innovator and test simvastatin products are shown in the following tables.

Simvastatin 90% Confidence Intervals

Parameter	N	GEOMETRIC LEAST SQUARES MEANS		RATIO T/R (%)	90% CONFIDENCE LIMITS (%)	
		T	R		Lower	Upper
$AUC_{(0-t)}$ (ng·h/mL)	66	68.76	72.17	95.28	88.09	103.06
$AUC_{(0-inf)}$ (ng·h/mL)	63	78.69	86.84	90.61	81.47	100.79
C_{max} (ng/mL)	66	15.48	14.88	104.00	92.94	116.38
$C_{max}/AUC_{(0-inf)}$ (h^{-1})	63	0.195	0.171	113.80	100.47	128.89

Simvastatin Beta-Hydroxy Acid 90% Confidence Intervals

Parameter	N	GEOMETRIC LEAST SQUARES MEANS		RATIO T/R (%)	90% CONFIDENCE LIMITS (%)	
		T	R		Lower	Upper
$AUC_{(0-t)}$ (ng·h/mL)	66	32.45	31.44	103.22	97.85	108.89
$AUC_{(0-inf)}$ (ng·h/mL)	64	35.57	38.27	92.95	86.61	99.77
C_{max} (ng/mL)	66	3.76	3.28	114.45	106.38	123.13
$C_{max}/AUC_{(0-inf)}$ (h^{-1})	64	0.107	0.088	120.56	110.74	131.25

AUC and C_{max} for Synthon's simvastatin were within 80% to 125% of the corresponding values for the innovator simvastatin product.

Dr. Lubas did not identify any safety issues from the bioequivalence study.

Clinical Pharmacology

Following review of the bioequivalence study, Dr. Chung concluded that the "pharmacokinetics of simvastatin and simvastatin acid following ODT were comparable to those following Zocor."

Chemistry, Manufacturing, and Control

The drug substance was deemed acceptable.
The drug product was considered satisfactory.
EER status considered acceptable.

Chemistry and Clinical Pharmacology are recommending that the sponsor develop a more discriminative dissolution method and specification to assure characteristics of simvastatin ODT.

Financial Disclosure

The sponsor provided a form 3454 certifying that no financial arrangements or interest were held by the clinical investigators in the bioequivalence study.

Pediatric Requirements

Synthon requested a full waiver of the PREA requirements for their simvastatin product. The company's rationale was as follows:

- Zocor is already approved for the treatment of heterozygous familial hypercholesterolemia in adolescents age 10-17 years and Synthon's product would offer no meaningful therapeutic benefit over Zocor.
- The American Academy of Pediatrics does not recommend drug therapy for children with hypercholesterolemia under 10 years of age.

Trade Name

The sponsor does not plan to use a trade name. Instead the plan is to market the product using the name Simvastatin Orally Disintegrating Tablets. DMETS finds this approach acceptable, as do I.

Division of Scientific Investigation

A Synthon sponsored ANDA for amlodipine was recently not approved due to improper record keeping for the pivotal bioequivalence study, which was carried out at same contract research organizatior[redacted] in the [redacted] as the bioequivalence study for simvastatin ODT. b(4)

This history led DMEP to request a For-Cause inspection of [redacted] for the simvastatin bioequivalence study.

b(4)

On May 18, 2006, Dr. Viswanathan, Associate Director, FDA's Division of Scientific Investigation, issued a form 483 to [redacted] for the bioequivalence study of simvastatin ODT.

The basis of the 483 included:

1. Failure to include the correct name of the dispensed medication (dosage form) on the dispensing envelope prior to dosing.
2. Failure to include the batch number of the medication on the dispensed envelope.
3. Failure to visually confirm the identity of the medication at the time of drug administration and to document the results of the confirmation. Although the test and reference dosage forms are different, there are no records of the investigator confirming the identity of the dosage forms after removing them from the packaged envelope, prior to administering the dose.
4. Repackaging records of test and reference medications fail to indicate that individual checks were made. Only signature at the bottom of the page and one other checked signature were found to document 13 different repackaging operations.
5. The CRF fails to include signatures or initials to document individual dosing and dosing verification for study subjects.
6. Failure to record the actual time of the blood draws from the subjects. Only intended draw times are pre-filled.
7. Failure to maintain adequate and accurate records of receipt and to check for the conditions of the test medications such as intact safety seals, unopened bottles, description of the content, etc.
8. Failure to maintain laboratory records to indicate the blood processing procedures and the time elapsed in such procedures. This is necessary due to the conversion of simvastatin to simvastatin acid.
9. Failure to exclude subject 20 from simvastatin study since the subject vomited within 6 hours following the dosing.
10. The sponsor monitor has signed and approved the drug packaging record, drug administration, sample time record and dispensing envelope templates that were used in the studies. These forms fail to provide for individual check, correct name of the medications and actual blood collection times.
11. Although the simvastatin study was conducted at the [redacted] site at [redacted] the drug inventory and dispensing record was signed and verified by the sponsor clinical monitor in North Carolina, US, on April 21, 2006, after study completion.

b(4)

According to Dr. Viswanathan, the above referenced deficiencies were the same deficiencies that led the Office of Generic Drugs to not approve [redacted]

Labeling

If and when approved, simvastatin ODT will have the same label as Zocor, with the following exceptions:

1. The simvastatin ODT label will not list a 5 mg tablet.
2. The simvastatin ODT label will include instructions for use of the orally disintegrating tablet.
3. The simvastatin ODT label will list different excipients.

Conclusion

Although on its face the submitted information indicated that simvastatin ODT is bioequivalent to Zocor, the DSI inspection revealed major deficiencies in record keeping for the bioequivalence study. Taken together, these deficiencies are significant enough to call into question the veracity of the bioequivalency data and prevent one from confidently concluding that simvastatin ODT is bioequivalent to Zocor.

Regulatory Recommendation

Not Approve.

Before this application is approved, Synthon needs to conduct a bioequivalence study that passes DSI inspection and demonstrates bioequivalence of simvastatin ODT to Zocor.

_____

Eric Colman, MD
Acting Deputy Division Director

Appears This Way
On Original

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

/s/

Eric Colman
5/25/2006 08:46:31 AM
MEDICAL OFFICER
Acting Deputy Division Director

Appears This Way
On Original

Memo to Division Files

Medical Officer Review of NDA Submission

NDA#: 21-961 S 000
Sponsor: Synthon Pharmaceuticals, Inc.
Drug Product: Simvastatin Orally Disintegrating Tablets
Dosage Strength: 10, 20, 40 and 80mg

Background:
Simvastatin is an HMGCoA reductase inhibitor which is approved for the following indications:

1) In patients with CHD or at high risk of CHD because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease to:

- reduce risk of CHD mortality
- and cardiovascular events (non fatal myocardial infarctions, stroke and need for coronary and non-coronary revascularization procedures)

2) In patients with Hypercholesterolemia requiring modifications of lipid profiles simvastatin is 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.

3) In adolescent patients with Heterozygous Familial Hypercholesterolemia (HeFH) simvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and Apo B.

Simvastatin is available alone as film-coated tablets under the Trade name of Zocor® and in a combination tablet with ezetimibe under the trade name Vytorin®.

In this 505(b)(2) application the sponsor is submitting an orally disintegrating tablet of simvastatin. The sponsor is submitting a single fasting study to bridge their formulation to the reference listed product. No clinical studies of efficacy or safety were conducted

for this application, therefore the drug-product will be limited to the indications approved for the reference product.

Summary of Clinical Biopharmaceutical Studies:

OBJECTIVES OF STUDY

To assess the bioequivalence of the test product, Simvastatin 80mg oral disintegrating tablets (Synthon Pharmaceuticals), to the reference product, Zocor 80mg tablets (Merck & Co.) after a single dose administered to healthy volunteers under fasting conditions.

EXPERIMETNAL DESIGN

STUDY DESIGN

This is a single-center, randomized, single-dose, two-period, crossover, bioequivalence study comparing Simvastatin 80mg oral disintegrating tablets (Synthon Pharmaceuticals) to Zocor 80mg tablets (Merck & Co.) under fasting conditions.

INCLUSION CRITERIA

- male or female Caucasians age 18 to 55
- BMI 19 to 27 kg/m^2

EXCLUSION CRITERIA

- history of serious clinical illness, mental illness or allergic reactions to related drugs
- abnormal physical examination, vital signs, ECG or lab screening tests
- hepatitis C antibody, hepatitis B surface antigen or HIV positive
- history of caffeine, alcohol or drug abuse
- pregnancy or breast-feeding
- smoking more than 10 cigarettes per day
- use of prescription drugs within 14 days of the study
- use of over the counter drugs within 7 days of the study

TREATMENT

Subjects were admitted to a single center in [redacted] of the [redacted], on the evening before study dosing. A randomized single dose of Simvastatin 80mg Oral Disintegrating Tablets or Zocor 80mg was administered after a 10 hour overnight fast in Period 1. Blood samples were taken predose and at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 16, and 24 hours post dose. Subjects were discharged after completion of the final 24 hour post dose blood sample and readmitted 14 days later to receive the alternative study medication in Period 2. Blood samples were taken predose and at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 16, and 24 hours post dose. Subjects were discharged after completion of the final 24 hour post dose blood sample. A follow up physical exam, blood and urine sampling was performed 72 hours after Period 2 dosing.

b(4)

STUDY RESULTS

PATIENT POPULATION

There were 34 males and 38 females that received at least one dose of the study medication. The age range of the healthy volunteers was between 18 and 52 with a mean of 28yrs (SD 9yrs). Their weight ranged between 52.5 and 99.1kg with a mean of 71.2kg (SD 10.3kg). Their BMI was between 19.0 and 27.0 with a mean of 23.5 (SD2.0).

PHARMACOKINETIC RESULTS

Simvastatin 90% Confidence Intervals
(Table 29, Module 5, Section 3.1.2.1.5)

Parameter	N	GEOMETRIC LEAST SQUARES MEANS		RATIO T/R (%)	90% CONFIDENCE LIMITS (%)	
		T	R		Lower	Upper
$AUC_{(0-t)}$ (ng·h/mL)	66	68.76	72.17	95.28	88.09	103.06
$AUC_{(0-inf)}$ (ng·h/mL)	63	78.69	86.84	90.61	81.47	100.79
C_{max} (ng/mL)	66	15.48	14.88	104.00	92.94	116.38
$C_{max}/AUC_{(0-inf)}$ (h^{-1})	63	0.195	0.171	113.80	100.47	128.89

Simvastatin β-HydroxyAcid 90% Confidence Intervals
(Table 30, Module 5, Section 3.1.2.1.5)

Parameter	N	GEOMETRIC LEAST SQUARES MEANS		RATIO T/R (%)	90% CONFIDENCE LIMITS (%)	
		T	R		Lower	Upper
$AUC_{(0-t)}$ (ng·h/mL)	66	32.45	31.44	103.22	97.85	108.89
$AUC_{(0-inf)}$ (ng·h/mL)	64	35.57	38.27	92.95	86.61	99.77
C_{max} (ng/mL)	66	3.76	3.28	114.45	106.38	123.13
$C_{max}/AUC_{(0-inf)}$ (h^{-1})	64	0.107	0.088	120.56	110.74	131.25

AUC and Cmax were within the standard confidence interval range of 80% to 125%, confirming that the Simvastatin Orally Disintegrating Tablets and the Zocor tablets are bioequivalent.

EFFICACY EVALUATION
No formal analysis of lipid measurements was performed in this single dose study.

SAFETY EVALUATION
Eleven adverse events were recorded in nine patients, four in patients taking Simvastatin Orally Disintegrating Tablets and five in patients taking Zocor tablets. None of the adverse events was a serious or unexpected drug reaction. In the Simvastatin Orally Disintegrating Tablet group there were two cases of tonsillitis, one headache and one case of nausea. In the Zocor group there were four cases of the common cold, two headaches (one migraine), and one case of vomiting. There were no new safety concerns identified with the oral disintegrating tablets.

SUMMARY
The 90% confidence intervals for test to reference ratios of least square means based on natural log transformed data for AUC (0-t) and Cmax were within 80 to 125%.

CONCLUSIONS
- Simvastatin Orally Disintegrating Tablets and Zocor tablets are bioequivalent.
- There were no new safety concerns identified with Simvastatin oral disintegrating tablets compared to Zocor tablets in the single PK study which was submitted.
- The submission is acceptable from a clinical standpoint.

Other Discipline Review Issues:
The chemistry review was performed by Dr. John Hill. All chemistry issues were resolved and the application was deemed acceptable from a chemistry standpoint.

The clinical biopharmacokinetics review was performed by Dr. Sang Chung. Simvastatin Oral Disintegrating Tablets were found to be deficient with regards to dissolution method data (see biopharmacokinetics review) and the submission was found not acceptable.

Other Administrative Issues:

Audits:
The Division of Scientific Investigations (DSI) inspection revealed deficiencies concerning the accuracy of study drug administration dosing times and drug sampling times. This Division considers the inspection results to be significant enough to compromise the integrity of the bioequivalence studies and therefore, finds your bioequivalence studies unacceptable.

Financial Disclosure:
The sponsor provided a signed form FDA 3454 certifying that no financial arrangements or interests were held by the clinical investigators in this study performed at the [redacted]. Therefore, it appears unlikely that the results were biased due to financial arrangements. b(4)

Pediatric Requirements:
The sponsor requested a full waiver of the PREA requirements for Simvastatin Orally Disintegrating Tablets citing the following justification:

- Zocor (simvastatin) is already approved for the treatment of heterozygous familial hypercholesterolemia in adolescents age 10-17 years and Synthon's new product would offer no meaningful therapeutic benefit over the currently marketed product.
- The American Academy of Pediatrics does not recommend drug therapy for children with hypercholesterolemia under 10 years of age.

This reviewer agrees with the sponsor's justification and recommends that the waiver be granted.

Tradename:
No tradename was submitted by the sponsor. The sponsor will use the name Simvastatin Orally Disintegrating Tablets in the label instead of a trade name. This is acceptable by the Division of Medication Errors and Technical Support and the Division of Metabolic and Endocrine Drug Products.

Labeling:
The sponsor has a similar label to that of the reference product, Zocor®, with the following exceptions:

- the new drug product will not be available in a 5mg formulation and this information is included in the label
- the label mentions that this is an orally disintegrating tablet formulation and describes instructions for its administration
- a revised list of excipients is included for the new drug product

The sponsor will need to resubmit the labeling using the current safety information from the most recently approved Zocor label prior to approval.

Conclusions:
This application was found Not Acceptable (NA) due to deficiencies identified by the DSI inspection and because of inadequate development of tablet dissolution specifications.

Recommendations:
This 505(b)(2) application for Simvastatin Oral Disintegrating Tablets should not be approved.

Comments to be conveyed in action letter:
The most current approved Zocor label should be used as the source of safety information for the Simvastatin Oral Disintegrating Tablets label submitted during the resubmission.

REVIEWED BY:

5/19/2006

William Lubas, MD-PhD
FDA/CDER/ORM/ODEII/DMEP
Medical Officer

5/19/2006

Eric Colman, MD
FDA/CDER/ORM/ODEII/DMEP
Medical Team Leader

Appears This Way
On Original

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

/s/

William Lubas
5/19/2006 01:30:47 PM
MEDICAL OFFICER

Eric Colman
5/19/2006 03:04:10 PM
MEDICAL OFFICER

Appears This Way
On Original

Memo to Division Files

NDA 21-961
Submitted September 16, 2005
Sponsor: Synthon Pharmaceuticals, Inc.
Drug Name: Simvastatin Orally Disintegrating Tablets
Category: lipid-lowering agents

Synthon Pharmaceuticals requested a full waiver of the PREA requirements for simvastatin orally disintegrating tablets citing the following justification:

- Zocor (simvastatin) is already approved for the treatment of heterozygous familial in adolescents age 10-17 years and Synthon's new product would offer no meaningful therapeutic benefit over the currently marketed product.
- The American Academy of Pediatrics does not recommend drug therapy for children with hypercholesterolemia under 10 years of age.

The division agrees with the sponsor that this product can receive a full waiver of the PREA requirements for pediatric studies.

_____ **2/6/06**
William Lubas, MD-PhD
FDA/CDER/ORM/ODEII/DMEP
Medical Officer

_____ **2/6/06**
Eric Colman MD
Medical Officer and Team Leader

cc: Margaret Simoneau (Project Manager)

Appears This Way
On Original

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

/s/

William Lubas
2/7/2006 09:50:59 AM
MEDICAL OFFICER

Eric Colman
2/7/2006 05:21:12 PM
MEDICAL OFFICER

Appears This Way
On Original