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RESEARCH**

APPLICATION NUMBER:

22-026

OTHER REVIEW(S)

Project Manager Overview

Application: NDA 22-026
Amlodipine Orally Disintegrating Tablets
2.5, 5, and 10 mg

Sponsor: Synthon Pharmaceuticals, Inc.
Classification: Standard
Original Submission Date: January 31, 2006
Resubmission Date: March 27, 2007
Receipt Date: March 28, 2007
User Fee Goal Date: September 28, 2007

Overview:

Synthon developed an orally disintegrating tablet formulation of the amlodipine besylate active ingredient that is currently marketed by Pfizer Inc. under the trade name Norvasc Tablets. Synthon sought approval of this new dosage form of amlodipine besylate for the same indications and strengths as Norvasc with the exception of the indication for Angiographically Documented CAD.

They supported the approval of the 505(b)(2) with the following:

- published literature with regard to amlodipine besylate active ingredient
- FDA's previous findings of the safety and efficacy of the Norvasc drug product (NDA 19-787)
- data from comparative bioavailability (i.e. bioequivalence) studies comparing the proposed 10 mg amlodipine besylate orally disintegrating tablet with the approved Norvasc 10 mg tablet in the fasting and non-fasting conditions

Synthon Pharmaceuticals submitted their 505(b)(2) application, dated January 31, 2006, received February 1, 2006, in paper and Common Technical Document format for NDA 22-026 for Amlodipine besylate orally disintegrating 2.5, 5, and 10 mg Tablets. On December 1, 2006, the sponsor received an "Approvable" letter based on a DSI inspection conducted at the _____ on May 15-18, 2006. The firm was issued a Form FDA 483 after the audit revealed a number of significant deficiencies with the bioequivalence study thus resulting in the data from the bioequivalence study being considered unacceptable.

The sponsor conducted a second BE study and resubmitted a complete response to the 1Dec06 Approvable letter on March 27, 2007, received by the Agency on March 28, 2007.

b(4)

Division Director's Memo

Dr. Norman Stockbridge:

In his memo dated 26Sep07, Dr. Stockbridge confirmed that there were no outstanding issues preventing an approval action on this application, as the repeat BE study was deemed acceptable by DSI and the clinical pharmacology reviewer.

Clinical Pharmacology and Biopharmaceutics-Carol Noory, Ph.D.

In her review dated April 25, 2007, Dr. Noory recommended an approval action for this application as the following issues were addressed in the March 27, 2007 resubmission

1. The deficiencies cited in the DSI audit were addressed and resolved.
2. The Sponsor submitted information to address the noted difference in Tmax between the TEST and REFERENCE treatments.
3. The biowaiver request for the lower strengths of 2.5 mg and 5 mg orally disintegrating tablets is acceptable.
4. The sponsor has agreed to incorporate the following dissolution method and specifications:

USP Apparatus 2: Paddle Method

Rotation speed: 50 rpm

Volume: 500 mL

Medium: 0.01 M HCl

Tolerance: Q \leftarrow in 15 minutes

b(4)

Pharmacology Review-Charles Resnick, Ph.D.

In his review dated, May 9, 2006, Dr. Resnick recommended an approvable action and wrote that the previous findings of safety and efficacy for the Pfizer product serve as an acceptable substitute for toxicology studies of the Synthon product.

Chemistry Review- Martin Haber, Ph.D.

In his review dated July 11, 2007 Dr. Haber recommended an approval action for this application. The sponsor addressed the deficiencies listed in the 1Dec06 action letter. On June 13, 2007, Synthon Pharmaceuticals, Inc. submitted an amendment stating a commitment to perform release and stability dissolution testing to provide for a 15 minute time point.

Stability data supports an expiry period of 24 months, which will be communicated in the approval letter.

EES: Acceptable on 29Nov06

Methods of Validation: Pending

Categorical Exclusion from the Environmental Assessment: Acceptable

NDA 22-026
Amlodipine Orally Disintegrating Tablets
Synthon Pharmaceuticals, Inc.

Division of Scientific Investigations (DSI) _____

See the 1Dec06 Approvable letter for full detail of the deficiencies that needed to be addressed resulting from the DSI inspection conducted at _____ on May 15-18, 2006. The firm was issued a Form FDA 483 after the audit revealed a number of significant deficiencies with the bioequivalence study.

b(4)

In his review dated May 21, 2007, Dr. Viswanathan wrote that Synthon reported the results of its repeat amlodipine study conducted at _____ to NDA 22-026 Amlodipine Orally Disintegrating Tablets, in Amendment 004, letter dated March 27, 2007. DSI made a decision not to inspect the repeat study at the site. However, Dr. Michael Skelly of DSI reviewed the data submitted with respect to the repeat study and further requested representative copies of the underlying source documentation. Upon evaluation of such records, it was found that the source records were completed satisfactorily. In conclusion, DSI removed the deficiencies of the prior inspectional findings. The subject relief applies to the following studies:

b(4)

Studies CPA 235-05 and CPA 236-05 for NDA 22-026 Amlodipine ODT

Study CPA 226-05 for NDA 2 1-961 Simvastatin ODT

Studies CPA 182-03 and CPA 183-03 for ANDA 77-080 Amlodipine Tablets

b(4)

DDMAC Memo: Lisa Hubbard, R.Ph.

In her review dated July 18, 2006, Ms. Hubbard provided suggestions for revisions with regard to promotional considerations in the Description, Indications and Usage, and Adverse Reactions sections of the package insert.

On August 9, 2007, Lisa Hubbard responded via email and agreed with the following revisions as requested by Dr. Noory:

1. DOSAGE AND ADMINISTRATION

The in vivo study submitted by the firm compared the ODT with no co-administered water to the reference tablet dosed with 240 mL of water concomitantly. The products were bioequivalent. The product does not "dissolve" it "disintegrates". The firm can add the following statement to the label under DOSAGE AND ADMINISTRATION:

Administration of Amlodipine Orally Disintegrating Tablets: Place the orally disintegrating tablet on the tongue where it will disintegrate and then be swallowed with the saliva. If necessary, follow with water.

2. DESCRIPTION

In the description of the product, the firm states that the product is an orally disintegrating tablet. This is correct. It also states that it is formulated to be equivalent to Norvasc. This is correct. Dr. Noory recommended the following changes:

NDA 22-026

Amlodipine Orally Disintegrating Tablets
Synthon Pharmaceuticals, Inc.

Amlodipine Orally Disintegrating Tablets (ODT) are formulated as tablets equivalent to 2.5 mg, 5 mg, or 10 mg of amlodipine for oral administration. The tablets disintegrate in the mouth allowing the contents to be swallowed with or without liquid.

The above recommendations were incorporated into the labeling by the sponsor as seen in the agreed-upon labeling attached to the approval letter.

DMETS Memo:

A tradename was not requested by the sponsor.

Pediatric Statement:

The sponsor's request for a waiver of pediatric studies was granted for this application, as the studies have been previously conducted by Pfizer.

Action:

On August 29, 2007, Ms. Kim Colangelo, Associate Director of Regulatory Affairs and Janice Weiner, J.D, Regulatory Counsel in the Office of Regulatory Policy cleared this 505(b)(2) application for action. Dr. Weiner, confirmed that the pending litigation and citizen petitions from Pfizer with regard to their Norvasc (amlodipine besylate) Tablet do not bear on issues related to this 505(b)(2) application. The '303 patent that had been listed for Norvasc (claims 1-3 of which were found to be invalid by the Court of Appeals for the Federal Circuit) does not currently appear in the Orange Book, having been delisted by FDA at Pfizer's request on or about June 22, 2007. As a result, the '303 patent and pediatric exclusivity that had attached to that patent would no longer delay approval of a 505(b)(2) application that contained a Paragraph III certification to the '303 patent.

An approval letter based on agreed-upon labeling has been drafted for Dr. Stockbridge's signature.

To my knowledge, there are no issues that may prevent action on this NDA.

Denise M. Hinton
Senior Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

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/s/

Denise Hinton
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NDA 22-026
Amlodipine besylate
Orally disintegrating tablets
Synthon Pharmaceuticals, Inc.

Project Manager Overview
for
NDA 22-026
Amlodipine besylate orally disintegrating tablets
Synthon Pharmaceuticals, Inc.

Overview:

Synthon Pharmaceuticals submitted their 505(b)(2) application, dated January 31, 2006, received February 1, 2006, in paper and Common Technical Document format for NDA 22-026 for Amlodipine besylate orally disintegrating 2.5, 5, and 10 mg Tablets.

Synthon has developed an orally disintegrating tablet formulation of the amlodipine besylate active ingredient that is currently marketed by Pfizer Inc. under the trade name Norvasc Tablets. Synthon is seeking approval of this new dosage form of amlodipine besylate for the same indications and strengths as Norvasc. They propose to support the approval of the 505(b)(2) with the following:

- published literature with regard to amlodipine besylate active ingredient
- FDA's previous findings of the safety and efficacy of the Norvasc drug product (NDA 19-787)
- data from comparative bioavailability (i.e. bioequivalence) studies comparing the proposed 10 mg amlodipine besylate orally disintegrating tablet with the approved Norvasc 10 mg tablet in the fasting and non-fasting conditions

Division Director's Memo

Dr. Norman Stockbridge:

In his memo dated 1Dec06, Dr. Stockbridge confirmed the approvable action pending the outcome of the repeat bioequivalence study and the recommended revisions to the dissolution testing.

Clinical Pharmacology and Biopharmaceutics-Carol Noory, Ph.D.

In her review dated November 1, 2006, Dr. Noory recommended an approvable action for this application based on the following:

1. The deficiencies cited in the DSI audit need to be addressed and resolved.
2. The Sponsor needs to submit information to address the noted difference in T_{max} between the TEST and REFERENCE treatments.
3. The dissolution specification should be tightened as follows:

USP Apparatus 2: Paddle Method
Rotation speed: 50 rpm
Volume: 500 mL
Medium: 0.01 M HCl
Tolerance: Q  in 15 minutes

b(4)

The waiver request for the lower strengths of 2.5 mg and 5 mg orally disintegrating tablets is denied, as the sponsor needs to submit additional dissolution data to support the biowaiver requested.

Pharmacology Review-Charles Resnick, Ph.D.

NDA 22-026
Amlodipine besylate
Orally disintegrating tablets
Synthon Pharmaceuticals, Inc.

In his review dated, May 9, 2006, Dr. Resnick recommended an approvable action and wrote that the previous findings of safety and efficacy for the Pfizer product serve as an acceptable substitute for toxicology studies of the Synthon product.

Chemistry Review- Martin Haber, Ph.D.

In his review dated September 27, 2006, Dr. Haber recommended an approvable action pending resolution of chemistry deficiencies and satisfactory facility inspections. He wrote that the chemistry, manufacturing, and control information provided is not adequate. The application is deficient for the drug substance DMF, drug product specifications, and insufficient stability data. Facility inspection results are pending.

An information request letter was sent on September 27, 2006.

EES: Pending

Methods of Validation: Pending

Categorical Exclusion from the Environmental Assessment: Acceptable

DSI-CT Viswanathan, Ph.D.

DSI conducted an inspection at _____ on May 15-18, 2006. The firm was issued a Form FDA 483 after the audit revealed a number of significant deficiencies with the bioequivalence study. The data from the bioequivalence study is considered unacceptable. b(4)

In an email correspondence dated November 20, 2006, Dr. Viswanathan wrote that FDA inspections revealed significant deficiencies in the documentation and procedural aspects of Synthon's bioequivalence studies conducted at _____. The primary concern is a lack of documentation to verify at the time of dosing the treatment received by each subject. Synthon submitted several of these studies to the Agency. Some of these applications, both generic and NDA 505 b(2), have been disapproved by the agency due to the inspectional findings and some are pending their regulatory decisions. Recently, the firm met with OC to address the inspectional findings and presented its case. The firm did explain their processes in detail as to how subjects receive articles subject to testing and why they felt confident subjects received the correct article. The fact remained that there was not a specific document which as its sole purpose definitely recorded administration of the test or reference article. In an attempt to resolve the subject issues and to assist the firm to move forward with _____ applications, the following proposal is being made by the Office of Compliance. The basis of this proposal is two fold. b(4)

- 1) Since the study procedure has raised doubts about specific documentation for administration amongst some other issues, a limited repeat of these procedures with proper documentation is necessary, as a proof of concept that the firm really carried out the studies as they claimed in their verbal statements to the Agency.
- 2) Since several of Synthon's applications are affected by these procedural flaws, the Agency will exercise due diligence in reviewing these applications. b(4)

Proposal:

Therefore it is proposed that Synthon repeat a relatively small study at _____ to demonstrate that, with proper documentation and procedures, the results of an earlier study can be reproduced. It is suggested that Synthon conduct a bioequivalence study of its Amlodipine ODT 10 mg vs Pfizer's Norvasc 10 mg in 26 subjects. The acceptance criteria of this study are outlined below. The Agency shall provide relief to Synthon by removing the adverse inspectional findings from _____ (Amlodipine ODT _____) if it is determined that the new study meets the predefined criteria. We believe that this proposal can save resource and time for the firm over its projected course of dispute resolution and appeal as well as provide the b(4)

¹ Specifically, the subject relief applies to the following studies.
Studies CPA 235-05 and CPA 236-05 for NDA 22-026 Amlodipine ODT b(4)

Study CPA 226-05 for NDA 21-961 Simvastatin ODT
Studies CPA 182-03 and CPA 183-03 for ANDA 77-080 Amlodipine Tablets

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Agency with the minimal assurance that the data from Synthon's bioequivalence studies conducted at _____ is accurate and valid. b(4)

Criteria for Acceptance of Synthon's Repeat Amlodipine Study

The repeat amlodipine study [comparing Synthon's 10 mg amlodipine orally disintegrating tablets (ODT) versus Pfizer's NORVASC® 10 mg tablets] to be conducted at _____. should satisfy the following criteria: b(4)

- The repeat study must have adequate documentation of the drug products that addresses the FDA audit findings for shipment, receipt, storage, dispensing, and administration of drugs, and blood collection to assure that subjects received the intended product on each occasion.
- It is recommended that the number and gender distribution of subjects should be similar to that of the original study (i.e., 13 males and 13 females), and the age distribution should be similar (18-55 years).
- The repeat study outcome should have similar bioequivalence outcome (i.e., 90% confidence intervals for AUC_{0-t} , AUC_{0-inf} and C_{max} within 80-125%) as the original study.
- The point estimates for AUC_{0-t} , AUC_{0-inf} and C_{max} for the two studies should be within 15%* of each other.
- Any pharmacokinetic (PK) repeats are subject to the same PK repeat criteria established for the original study's SOP. If there was no SOP with such criteria for the original study, then no PK repeats can be performed for the repeat study.
- The study records both clinical and analytical may be subject to FDA inspection. Reserve samples of the drug products, selected at _____ from the products supplied to them, must be available for collection by FDA or submission to FDA upon request. b(4)

Background information and for use within FDA:

* The AUC_{0-t} , AUC_{0-inf} and C_{max} values for NORVASC (RLD) in the fasting studies conducted at _____ Division of Cardio vascular and Renal Products were within 15%. It is reasonable to expect the same results for the repeat study. b(4)

DDMAC Memo: Lisa Hubbard, R.Ph.

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Action:

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To my knowledge, there are no issues that may prevent action on this NDA.

Denise M. Hinton
Senior Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

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/s/

Denise Hinton
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CSO