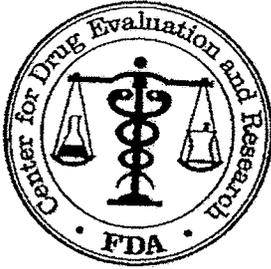


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-026

MEDICAL REVIEW(S)



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 22-026 (amlodipine orally disintegrating tablets)

Sponsor: Synthon Pharmaceuticals

Review date: 26 September 2007

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22-026

HFD-110/Hinton

ONDQA/Haber

HFD-860/Noory

The sponsor is seeking approval of a new formulation of amlodipine—an orally disintegrating tablet. This is otherwise a 505(b)(2) application referencing Pfizer's Norvasc. Full reviews were provided by Drs. Haber (CMC; 28 September 2006, 30 November 2006) and Noory (Clinical Pharmacology and Biopharmaceutics; 13 November 2006).

The new formulation was found to be bioequivalent to Norvasc in a clinical pharmacology study conducted for the sponsor by [redacted]. There is also a food-effect study performed by the same CRO. DSI audited these studies for cause based on problems seen in a previous inspection in November 2005. This inspection, in May 2006, found numerous problems, possibly restricted to documentation and not procedures. These included failure to label dispensed medication, failure to record batch numbers, failure to confirm and document identity of dispensed medication, failure to record timing of study drug administration, and failure to document timely processing of PK samples. These deficiencies resulted in issuance of a form 483 and a recommendation that FDA not rely upon these results.

b(4)

Similar issues affected studies by this CRO in support of applications for [redacted] and amlodipine. DSI and the corresponding review divisions have agreed that Synthon and [redacted] should re-do the amlodipine-Norvasc comparison for this application and reconsider the acceptance of the other studies if the new study results are adequately similar to the previous study results. (Closely matching the previous bioequivalence trial for amlodipine—not strictly necessary to achieve approval here—would be remarkable because the previous study shows very close matching of plasma levels in response to Norvasc and the ODT formulation at most time points.)

b(4)

The sponsor submitted a new bioequivalence study in March 2007. This study was reviewed by Dr. Noory (20 April 2007) and found to be acceptable for showing the new formulation to be similar in pharmacokinetic performance to the reference NORVASC, to which the new product's label now resembles.

A DSI audit of the repeat bioequivalence study was satisfactory.

The sponsor and FDA have come to agreement on dissolution specifications.

There are no remaining issues, and NDA 22-026 should now be approved.

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/s/

Norman Stockbridge
9/26/2007 09:37:00 AM
MEDICAL OFFICER



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 22-026 (amlodipine orally disintegrating tablets)
Sponsor: Synthon Pharmaceuticals
Review date: 1 December 2006

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22-026

HFD-110/Hinton
ONDQA/Haber
HFD-860/Noory

The sponsor is seeking approval of a new formulation of amlodipine—an orally disintegrating tablet. This is otherwise a 505(b)(2) application referencing Pfizer's Norvasc. Full reviews were provided by Drs. Haber (CMC; 28 September 2006, 30 November 2006) and Noory (Clinical Pharmacology and Biopharmaceutics; 13 November 2006).

The new formulation was found to be bioequivalent to Norvasc in a clinical pharmacology study conducted for the sponsor by ———. There is also a food-effect study performed by the same CRO. DSI audited these studies for cause based on problems seen in a previous inspection in November 2005. This inspection, in May 2006, found numerous problems, possibly restricted to documentation and not procedures. These included failure to label dispensed medication, failure to record batch numbers, failure to confirm and document identity of dispensed medication, failure to record timing of study drug administration, and failure to document timely processing of PK samples. These deficiencies resulted in issuance of a form 483 and a recommendation that FDA not rely upon these results. b(4)

Similar issues affected studies by this CRO in support of applications for ———, ———, and amlodipine. DSI and the corresponding review divisions have agreed that Synthon and ——— should re-do the amlodipine-Norvasc comparison for this application and reconsider the acceptance of the other studies if the new study results are adequately similar to the previous study results. (Closely matching the previous bioequivalence trial for amlodipine—not strictly necessary to achieve approval here—would be remarkable because the previous study shows very close matching of plasma levels in response to Norvasc and the ODT formulation at most time points.) b(4)

The sponsor denied inappropriate financial incentives to investigators per 21CFR54.

At the current time, this application must be considered approvable, pending the outcome of the repeat bioequivalence study. A number of minor issues relating to dissolution testing will also be conveyed in the action letter. There are no other outstanding review issues.

Labeling can be easily crafted once the new bioequivalence study has been reviewed.

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/s/

Norman Stockbridge
12/1/2006 08:34:31 AM
MEDICAL OFFICER

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Review of Financial Disclosures



NDA: 22-026
Drug: Amlodipine besylate orally disintegrating tablets
Indication: Hypertension
Sponsor: Synthon Pharmaceuticals, Inc.
Review date: December 1, 2006
Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

This application included two bioequivalence studies (fasting 235 and food effect 236) between the applicant's product and the reference listed drug (Norvasc). The submission includes financial disclosure forms FDA 3455 for the principal investigator (the same individual) for both of these studies that declare that the principal investigator has no financial arrangements or financial interests that are required to be disclosed. The submission also includes financial interest certification forms FDA 3454 for both studies in which the applicant certifies that he has not entered into any financial arrangements for which the value of compensation could be affected by the study outcome.

Recommendation and Conclusions

The financial disclosures are complete and do not reveal any disqualifying or suspicious financial arrangements.

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Thomas Marciniak
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