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APPLICATION NUMBER:

22-026

SUMMARY REVIEW

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS



Secondary Review of Complete Response

NDA: 22-026
Drug: amlodipine besylate orally disintegrating tablets
Indication: treatment of hypertension, chronic stable angina, and vasospastic angina
Sponsor: Synthon Pharmaceuticals, Inc.
Review date: August 31, 2007
Reviewer: Thomas A. Marciniak, M.D.
Acting Deputy Director

Recommendation and Conclusions

I recommend that amlodipine orally disintegrating tablets be improved for all indications of the innovator drug amlodipine besylate not protected by marketing exclusivity, i.e., the treatment of hypertension, chronic stable angina, and vasospastic angina but not

_____ These tablets are a new formulation (i.e., orally disintegrating) of an approved product eligible for generic duplication. The sponsor has demonstrated that its orally disintegrating tablets are bioequivalent to the innovator product. The labeling for this formulation should be identical to that of the innovator product except for the descriptions of physical product and its disintegration in the mouth and the omission of the angiographically documented coronary artery disease indication.

b(4)

Materials Used in Review

1. CMC reviews by Martin Haber, Ph.D., dated September 27, 2006, November 29, 2006, and July 11, 2007
2. Clinical pharmacology reviews by Carol Noory, Ph.D., dated November 1, 2006, and April 25, 2007
3. Financial disclosures review by Thomas A. Marciniak, M.D., dated December 1, 2006
4. Division memorandum by Norman Stockbridge, M.D., Ph.D., dated December 1, 2006
5. Approvable letter dated December 1, 2006
6. DSI Review of Synthon's Repeat Bioequivalence Study of Amlodipine ODT by Gary J. DellaZanna, D.O., dated May 18, 2007

Background

Amlodipine besylate orally disintegrating tablets is a new formulation of an approved antihypertensive and antianginal for which the marketing exclusivity and patient protection expired recently. The sponsor submitted a 505(b)(2) NDA for the orally disintegrating tablets on January 31, 2006. That NDA included bioequivalence studies between the orally disintegrating tablets and the innovator drug and information on

chemistry, manufacturing and controls but it referenced the innovator drug NDA 019-787 for summary findings on safety and efficacy.

The review of the initial submission confirmed that the submitted studies documented bioequivalence with the exception of a slight deviation in T_{max} . However, a Division of Scientific Investigation (DSI) audit of the site performing the bioequivalence studies found numerous problems. DSI issued a Form 483 and recommended that the results from this site not be used. The Division issued an approvable letter dated December 1, 2006, pending the results of acceptable repeat bioequivalence studies, resolution of the T_{max} deviation, and addressing of some dissolution and stability test issues. The sponsor submitted a complete response dated Mary 27, 2007.

Chemistry, Manufacturing, and Controls (CMC)

The CMC reviewer, Dr. Martin Haber, recommends for approval from a CMC perspective with an acceptance of the proposed 24 month expiration period for the drug product. The deficiencies related to CMC identified in the approvable letter were regarding dissolution and stability testing. Dr. Noory addressed the dissolution data in her review of the complete response. Dr. Haber notes that the sponsor, inn their June 13, 2007, amendment, committed to performing release and stability dissolution testing as recommended by the Agency, changing the specification to provide for a 15 minute time point. The stability protocol was not changed because it references the drug product specifications which incorporate the change. Dr. Haber considers these changes to be acceptable for approval.

COMMENT: The sponsor has addressed all CMC deficiencies identified in the approvable letter.

Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology and biopharmaceutics reviewer, Dr. Carol Noory, finds the clinical pharmacology and biopharmaceutics portion of NDA 22-026 acceptable provided that the sponsor adopts the dissolution method recommended in her review. Regarding the T_{max} deviation, she confirmed that the repeated fasting bioavailability study did not show a significant difference from the innovator drug. She considered the biowaiver requested for the 2.5 mg and 5.0 mg tablets to be acceptable. She confirmed that the repeat bioequivalence studies met the requirements outlined in the approvable letter. DSI reviewed the data submitted with respect to the repeat study and further requested representative copies of the underlying source documentation. Upon evaluation of these records, DSI concluded that the source records were completed satisfactorily and removed the deficiencies from the prior inspections.

COMMENT: The sponsor has addressed all clinical pharmacology and biopharmaceutics deficiencies identified in the approvable letter. The results are judged to be reliable and confirming that amlodipine besylate disintegrating tablets are bioequivalent to the innovator drug.

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/s/

Thomas Marciniak
8/31/2007 11:53:48 AM
MEDICAL OFFICER