CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-401

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-401 Twynsta (telmisartan/amlodipine for hypertension)

Sponsor: Boehringer-Ingelheim

Review date: 19 September 2009

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

Distribution: NDA 22-401
HFD-110/Nguyen

This memo conveys the Division's recommendation to approve Twynsta (telmisartan plus amlodipine) as step-up or initial therapy for treatment of hypertension.

This application has been the subject of reviews of CMC (Claffey 2 September 2009; Chen 31 August 2009), pharmacology and toxicology (Jagadeesh 26 March 2009), biopharmaceutics (Younis 8 May 2009), medical (Blank 9 September 2009) and statistics (Liu 31 August 2009).

Most issues have been addressed in Dr. Marciniak's CDTL memo (17 September 2009). I summarize very briefly.

Both angiotensin receptor blocker telmisartan and calcium channel blocker amlodipine are approved for hypertension alone and in combination with other antihypertensives.

The sponsor performed no toxicological assessment with the combination, nor was one expected.

All CMC issues are considered resolved, pending EA review. CMC staff and the sponsor do not agree on dissolution specifications.

High- (80/10 mg) and low- (40/5) dose combinations were bioequivalent (Cmax and AUC) to corresponding monotherapy doses. Food reduces telmisartan's AUC by a clinically irrelevant 24%.

Approval was supported by a double-blind, 8-week, parallel, factorial study (n=1461) in which hypertensive patients were unevenly randomized to amlodipine 0, 2.5, 5, and 10 mg and to telmisartan 0, 20, 40, and 80 mg. Subjects randomized to higher doses received a lower dose for the first 2 weeks. Trough blood pressure effects were statistically significantly larger on the high-dose combination than on high-dose monotherapies, but the results were somewhat less than additive. ABPM was performed in about 50% of subjects and demonstrated preserved differences throughout the 24-hour inter-dosing interval.

Conventional analyses describe the basis for approval as initial therapy in patients far from blood pressure goals.

No novel safety issues were found. Withdrawal rates from the 8-week study were very low.

All team members concur on approvability.

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/s/

NORMAN L STOCKBRIDGE
09/28/2009