CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200175Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 200175 Olmesartan + amlodipine + HCTZ (Tribenzor) for hypertension.

Sponsor: Daiichi-Sankyo

Review date: 19 July 2010

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

Distribution: NDA 200175
HFD-110/Fortney/Karkowsky

This memo conveys the Division's decision to issue an Approval letter for Tribenzor for hypertension.

This application has been the subject of reviews of CMC (Shiromani; 31 March and 16 July 2010), pharmacology/toxicology (Jagadeesh; 20 April 2010), clinical pharmacology (Kumi, Madabushi, and Liu; 28 June 2010), and medical and statistics (Gordon and Kong; 22 April 2010). There is a comprehensive CDTL memo (Karkowsky, 15 July 2010) with which I am largely in agreement.

All 3 components are approved antihypertensives, as are combinations of olmesartan with amlodipine (Azor) or HCTZ (Benicar HCT).

The sponsor conducted a 3-month toxicology study in rodents; histological findings on the triple appeared to be the sum of findings on olmesartan + HCTZ and on amlodipine.

Exposure to each component of the triple was bioequivalent to that of the corresponding monotherapy. There was negligible effect of food.

Clinical study U301 had a run-in of at least two weeks on high-dose pairs of study drugs and then randomized subjects to remain on two drugs or receive the triple at 40/10/25 mg (highest approved doses of olmesartan and amlodipine, and usual highest dose of HCTZ) for 8 weeks (n=600-637 per group). The primary end point was trough diastolic pressure, analyzed by LOCF, with covariates of baseline blood pressure, age, race, and diabetes.

Based on the pooled three-drug group, component HCTZ contributed a blood pressure reduction of 7.1/3.8 mmHg, amlodipine contributed 7.4/4.9 mmHg, and olmesartan contributed 9.6/6.7 mmHg, with all differences (systolic and diastolic) being highly statistically significant. Dr. Karkowsky argues that differential dropouts from the run-in on two-drug combinations makes the three three-drug groups not quite the same. I agree that this is a reasonable concern; the corresponding effects, based upon unpooled three-drug combination groups are 7.7/4.2 mmHg for HCTZ, 5.3/4.3 mmHg for amlodipine, and 8.5/4.4 mmHg for olmesartan, all still statistically significant; these are the numbers that should be incorporated in labeling. Treatment effects were seen in various strata by age, gender, and race. Treatment effects were largely complete within 2 weeks, making that a reasonable titration interval.

An ABPM substudy in 440 subjects amply demonstrated persistence of the difference between triple therapy and dual therapy throughout the inter-dosing interval.

Rates of withdrawal were 18% on triple therapy and 11-17% on duals; withdrawals for adverse events were 8% on the triple and 4-7% on the duals. I note that subjects were

randomized without titration to a high-dose double, and then again without titration to high-dose triple therapy. Reported adverse events were much as predicted from the monotherapies.

As with other antihypertensive combination products, pediatric requirements are waived.

There was no Advisory Committee meeting, as this application raised no novel issues.

Various minor CMC issues were outstanding at the time of Dr. Karkowsky's review. They have all been resolved, including successful EA and the obligatory negotiation of dissolution specifications.

Labeling remains to be negotiated, but there are few novel issues. As Dr. Karkowsky notes, amlodipine needs to be started at 2.5 mg in some populations; this dose is unavailable with Tribenzor.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide

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/s/

NORMAN L STOCKBRIDGE
07/19/2010