CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-314

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-314 (Exforge HCT; valsartan+amlodipine+HCTZ for hypertension)

Sponsor: Novartis

Review date: 25 April 2009

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

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HFD-110/Nguyen/Marciniak

This memo conveys the Division's recommendation to approve the triple combination of valsartan, amlodipine, and HCTZ for hypertension.

Most issues have been addressed in Dr. Marciniak's CDTL memo (7 April 2009). I summarize very briefly.

The CMC reviewers (Soldatova; 3 March 2009; Sood 20 April 2009) have one remaining issue: b(4)

— Other proposed packages have no such issues, so we have simply dropped the problematic packages from labeling until the stability data are generated (or deemed unnecessary).

The pharmacology/toxicology review (Jagadeesh; 6 November 2008) describes one study of the triple combination in a 12-week study in rats. No unusual toxicological findings were reported.

The Biopharmaceutics review (Menon-Anderson; 27 Febrauary 2009) indicates that two studies established the bioequivalence of to-be-marketed valsartan/amlodipine/HCTZ 160/12.5/10 and 160/25/10 to corresponding single products. A third study ruled out significant food effect.

The clinical/statistical review (Lemtouni, Pendse, and Liu; 23 April 2009) describes the major supporting study. The sponsor was advised that the basis for approval would be a >3-mmHg nominal effect on blood pressure of the combination above the effects of each high-dose double combination.

Study 2302 was a multi-center, double-blind study in which 2271 subjects with blood pressure 145-200/110-120 or 180-200/100-110 upon washout of existing therapies were evenly randomized to V/H/A, V/A, V/H, and A/H at doses of 160/12.5/5 (force-titrated to 320/25/10 at 2 weeks) and followed for 8 weeks. The primary end point was mean seated systolic and diastolic pressure (Hochberg procedure) at the inter-dosing interval. A subset of 670 subjects underwent 24-hour ABPM at baseline and at 8 weeks. Data from one site were discarded.

The population was 70% Caucasian, 17% Black, 55% male, 14% >65 years old, and the mean blood pressure was 170/107 mmHg. Discontinuation rates were 10.5% on 3 drugs and 7.4-9.8% on 2 drugs. The most common cause for withdrawals was adverse events, about 1/3 of all withdrawals, and the differences among groups mirrored the overall withdrawals.

The 3-drug combination produced blood pressure reductions compared with V/H of -7.6/-5.2 mmHg, compared with V/A of -6.0/-3.2 mmHg, and with H/A of -7.5/-5.0

mmHg[1]. All of these differences were highly statistically significant. The ABPM data confirm that the triple was more effective than the doubles at all times (hourly means). Generally similar effects were seen in men/women, age </>65, race, and by region.

The most common adverse reactions are described below:

Table 1. Most common adverse reactions (%)

	VHA	VH	VA	HA
Dizziness				
Single term	7.7	7.0	2.3	3.9
Pooled terms	9.1	8.2	2.7	4.3
Edema				
Single term	4.5	0.9	8.5	8.9
Pooled terms	7.0	1.4	13.4	11.9

First-line use was not sought and I agree with Dr. Marciniak that it is inappropriate.

There are no issues other than manufacturing preventing approval. Labeling is modeled on the components.

This development program is a model for other possible combinations of 3 or more drugs for hypertension. It remains reasonable, in my view, to request a sponsor explore the dose-response surface for a pair of antihypertensives, but there is no feasible way to do that for larger collections of drugs. The main requirement should be to show that one can achieve greater blood pressure reduction with n drugs than one can with n-1, as was done here.

[1] *I site differences in raw means from the clinical review. The review has a slightly different table of differences based on least square means.*