CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-217

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-217 (aliskiren/valsartan for hypertension)

Sponsor: Novartis

Review date: 12 September 2009

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

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

This application has been the subject of reviews of CMC (Srinivasachar 11 December 2008; Shiromani 8 April 2009, 1 September 2009; Chen 15 June 2009, 11 August 2009), pharmacology and toxicology (Jagadeesh 23 April 2009), biopharmaceutics (Menon-Anderson 28 May 2009), and clinical studies (Xiao and Liu 10 July 2009).

Most issues have been addressed in Dr. Marciniak's CDTL memo (28 July 2009). I summarize very briefly.

Both renin-inhibitor aliskiren and angiotensin receptor blocker valsartan are approved for hypertension alone and in combination with other antihypertensives.

The sponsor performed one 13-week toxicology study in rats that found no novel toxicity of the combination.

All CMC issues are considered resolved with the following exceptions. (b) (4)

Four studies contributed data on safety and effectiveness. Study 2203 was a full factorial design 8-week study of aliskiren 0, 75, 150, and 300 mg and valsartan 0, 80, 160, and 320 mg. It was deemed unsuccessful, possibly because of small group sizes. Subsequent study 2327 (n=1797) was 8 weeks, 4 weeks at target doses of placebo, valsartan 320 mg, aliskiren 300 mg, or the combination. The combination demonstrated statistically significant and clinically relevant reductions in trough systolic and diastolic pressure on the combination compared with the corresponding high-dose monotherapies. ABPM data demonstrate that the treatment effect and the difference were preserved throughout the day-long inter-dosing interval. Blacks (n=286) had somewhat lower effects than did Caucasians. Study 2301 (n=601) provided safety data for 12 months; some subjects also received HCTZ 25 mg for blood pressure control. Finally, 8-week study 2331 (n=641) compared aliskiren 300 mg plus valsartan 320 mg plus HCTZ 25 mg to combinations of valsartan plus HCTZ and aliskiren plus HCTZ.

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

One safety issue was identified in the clinical review. A small number of subjects had isolated elevated serum potassium values, some probably incompatible with life. I agree with Dr. Marciniak that these are probably artifacts of hemolysis ex vivo.

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/s/

NORMAN L STOCKBRIDGE
09/13/2009