CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022545Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 22545 Aliskiren + amlodipine (Tekamlo) for hypertension.

Sponsor: Novartis

Review date: 14 August 2010

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

Distribution: NDA 22545
HFD-110/Monteleone/Marciniak

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

This application has been the subject of reviews of CMC (Soldatova; 8 December 2009 and 4 August 2010), pharmacology/toxicology (Jagadeesh; 3 June 2010), clinical pharmacology (Menon-Anderson; 6 June and 21 July 2010), medical (Xiao; 7 July 2010) and statistics (Freidlin; 2 June 2010). There is a comprehensive CDTL memo (Marciniak, 9 August 2010) with which I am wholly in agreement.

Both components are approved antihypertensives, as are other combinations of aliskiren and amlodipine.

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

Aliskiren is poorly bioavailable and has a substantially reduced bioavailability when taken with food. Despite this, in studies where it is administered without regard to meals, its effects on blood pressure do not appear to be more variable than with other RAS antihypertensives. In combination, aliskiren may be a little less bioavailable and is still affected by food, but amlodipine exposure is unaffected.

The sponsor conducted a conventional, parallel, 8-week, factorial study (2305) with 1688 subjects randomized to aliskiren 0, 150, and 300 mg and amlodipine 0, 5, and 10 mg. The key comparison is whether addition of the second drug gives incremental blood pressure reduction compared with each high-dose monotherapy. The results were as follows. The incremental effect of adding amlodipine was -7.8/-6.3 mmHg, both highly statistically significant, and the incremental effect of adding aliskiren was -2.2/-2.6 mmHg, with only the diastolic effect being statistically significant.

The sponsor then performed an 8-week, parallel study (2304) with a 4-week run-in on amlodipine 10 mg and then 847 subjects randomized to aliskiren/amlodipine doses of 150/10, 300/10, and 0/10. This time, the incremental effect of aliskiren was -6.2/-3.8 mmHg, with both systolic and diastolic effects highly statistically significant.

An ABPM substudy amply demonstrated persistence of the difference between combination therapy and monotherapy throughout the inter-dosing interval.

Rates of withdrawal were low. 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.

All CMC issues 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. Marciniak notes, amlodipine needs to be started at 2.5 mg in some populations; this dose is unavailable with Tekamlo.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
08/16/2010