CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200045Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 200045 Aliskiren + amlodipine + HCTZ (Amturnide) for hypertension.

Sponsor: Novartis

Review date: 11 December 2010

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

Distribution: NDA 200045
HFD-110/Wachter/Karkowsky

This memo conveys the Division's decision to issue an Approval letter for Amturnide for hypertension (pending resolution of one CMC issue).

This application has been the subject of reviews of CMC (Lu; 22 October 2010), pharmacology/toxicology (Jagadeesh; 28 July 2010), clinical pharmacology (Hariharan; 24 November 2010), biopharmaceutics (Chen; 2 November 2010), and medical and statistics (Aranoff and Kong; 23 November 2010). There is a comprehensive CDTL memo (Karkowsky, 10 December 2010) with which I am largely in agreement.

All 3 components are approved antihypertensives, as are combinations of aliskiren with amlodipine or HCTZ.

The sponsor conducted no toxicology study with the triple combination, and the review team believes no such study was necessary.

Pharmacokinetic interaction was studied by comparing the triple (300/5/25—not the maximum dose of amlodipine) to a single arm in which subjects received all three drugs as separate tablets (not three arms each on one drug). Although different from what others have done, the review team believes this design is adequate, and I agree. The study shows that exposure to aliskiren from the triple falls marginally below bioequivalence criteria. The review team is not concerned about this, and, given incremental effects on blood pressure with the triple, neither am I.

Aliskiren has low bioavailability, and fasting increases Cmax 8-fold and AUC 5-fold compared to a high-fat meal; the effect with other meals is not known. There are also large excursions in exposure over the inter-dosing interval such that the fast Cmin is about the same as the fed Cmax. The blood pressure response to aliskiren is a poorly characterized function of dose or exposure and time, but the effect of food appears to be clinically relevant. Thus Dr. Karkowsky recommends that labeling for all aliskiren products specify use fasting (say, by administration at night) before use in combination. There is a supplement in-house dealing further with the food effect, and the sponsor has been informed of our interest in understanding better the food-dose-time-pressure relationships. For now, we will label the triple combination as we have other aliskiren products and revisit the problem in coming months.

The high dose triple (300/10/25) was compared with high dose doubles in one study of 1191 subjects. After one titration step, subjects were on target doses for 4 weeks. Incremental effects attributable to aliskiren were (trough cuff) 7.2/3.6 mmHg, to amlodipine were 9.9/6.3 mmHg, and to HCTZ were 6.6/2.6 mmHg, all highly statistically significant. By ABPM, the triple was superior to each double throughout the inter-dosing interval.

There were few withdrawals, and the safety profile of the combination was entirely consistent with those of the components.

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

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

At this writing, one manufacturing site has not passed inspection.

Labeling remains to be negotiated, but there are few novel issues. Amlodipine needs to be started at 2.5 mg in some populations; this dose is unavailable with Amturnide.

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
12/21/2010