CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-107

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Norman Stockbridge
Subject	Division Director Summary Review
NDA/BLA # Supplement #	NDA 22-107
Applicant Name	Novartis
Date of Submission	19 March 2007
PDUFA Goal Date	19 January 2008
Proprietary Name / Established (USAN) Name	Aliskiren/HCTZ
Dosage Forms / Strength	150/12.5, 150/25, 300/12.5, 300/25 mg
Proposed Indication(s)	1. Hypertension
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Xiao (7 December 2007)
Statistical Review	None
Pharmacology Toxicology Review	Jagadeesh (31 August 2007)
CMC Review/OBP Review	Ysern (20 November 2007, 7 January 2008)
Microbiology Review	None
Clinical Pharmacology Review	Velzquez 13 December 2007)
DDMAC	
DSI	None
CDTL Review	None
OSE/DMETS	Fava (21 December 2007)
OSE/DDRE	
OSE/DSRCS	
OSE	Mills (2 January 2008)
SEALD	Masucci (8 January 2008)

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

1. Introduction

This is an utterly conventional development program for a combination antihypertensive, [redacted] The only regulatory issue of interest concerns [redacted] b(4)

2. Background

Development programs exist for aliskiren in combination with several agents. This is the first to come for review since aliskiren was approved in 2006.
While this review has been ongoing, Avalide (irbesartan/HCTZ) became the first combination antihypertensive approved for first-line use on the basis of the "disclosure principle", which basically asserts that one can provide adequate information in labeling to inform a physician about when they might reasonably choose to start treatment with a combination product. Aliskiren/HCTZ raises an issue that perhaps not every combination is appropriate for first-line use.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. There was one 13-week tox study performed with the combination.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. There is a substantial food effect; as with monotherapy, use in consistent relationship to meals is recommended.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

There were a total of 8 relevant studies of aliskiren in combination with HCTZ, but the main study (#2204) was an 8-week factorial study with all combinations or aliskiren 0, 75, 150, and 300 mg in combination with HCTZ 0, 6.25, 12.5, and 25 mg. This study provided highly statistically significant evidence that both products contribute to the efffects on diastolic and

systolic pressure at 8 weeks at trough. No statstical review was needed and no DSI audits were requested.
Dr. Xiao notes that the experience did not include enough Blacks to ascertain whether, like with other RAS blockers, use with HCTZ overcomes refractoriness to aliskiren alone.

8. Safety

The database for safety was large relative to usual for a fixed-dose combination. The only novel issue raised was low, but plausibly real, increase in uric acid and in the incidence of gout.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The Division has generally held that combination products should not receive Written Requests.

11. Other Relevant Regulatory Issues

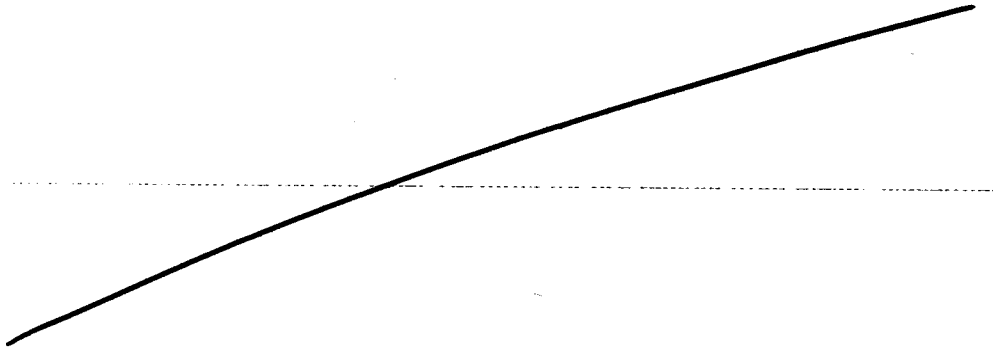
The DMETS review recommended against use of the name Tekturna HCT, finding similarity to Tekturna too close for comfort. We discussed the matter and they remain unfavorable to the name, but it is common with many HCTZ-containing combination products, and any error is not likely to be problematic.
There are no other unresolved relevant regulatory issues.

12. Labeling

The PLR labeling was ably reviewed by Ms. Masucci and the PPI by Ms. Mills.

13. Decision/Action/Risk Benefit Assessment

The application has been approved. The risk-benefit is similar to that for many other combination products of HCTZ in combination with an ACE inhibitor or ARB.



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/s/

Norman Stockbridge
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MEDICAL OFFICER