CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-107

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 2, 2007
To:	Norman Stockbridge, M.D., Ph.D., Director Division of Cardiovascular and Renal Products
Thru:	Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Division of Risk Management Office of Surveillance and Epidemiology
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Labeling and Education Team Division of Risk Management (DRM) Office of Surveillance and Epidemiology
Subject:	DRM review of Patient Labeling (Patient Package Insert)
Drug Name(s):	Tekturna HCT (aliskiren/hydrochlorothiazide, USP) Combination Tablets
Application Type/Number:	NDA 22-107
Applicant/sponsor:	Novartis
OSE RCM #:	2007-1028

1 INTRODUCTION

Novartis received original approval of its New Drug Application (NDA) for Tekturna (aliskiren), NDA 21-985, on March 5, 2007, indicated for the treatment of hypertension. Novartis submitted NDA 22-107 for Tekturna HCT Tablets, a fixed dose combination of aliskiren and hydrochlorothiazide, for the treatment of hypertension. The sponsor amended the proposed labeling for Tekturna HCT (aliskiren/hydrochlorothiazide) Tablets on December 18, 2007.

The Office of Surveillance and Epidemiology, Division of Risk Management, Patient Labeling and Education team has been requested to review the proposed Patient Labeling (Patient Package Insert) for this NDA.

2 MATERIAL REVIEWED

Review division first draft changes to the revised proposed sponsor PI dated December 18, 2007, including the revised PPI of the same date.

3 DISCUSSION

See the attached document for our recommended revisions to the revised proposed Patient Package Insert (PPI) for Tekturna HCT. The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. We have simplified the PPI, removed unnecessary and redundant information, relocated information to appropriate sections, and ensured that the PPI is consistent with the proposed PI. These recommended changes are consistent with current research to improve risk communication to a wide range of audiences including those with lower levels of literacy.

Comments to the review division are ***bolded, italicized, and underlined.***

4 CONCLUSIONS AND RECOMMENDATIONS

- A PPI for Tekturna HCT is voluntary. The sponsor proposes to distribute Tekturna HCT in bottles of 30, bottles of 90 and in blister packages of 100. Unless Tekturna HCT is packaged in unit-of-use packaging with the PPI enclosed, patients are unlikely to receive the PPI. The sponsor should clarify how they intend to distribute the PPI to patients.
- The sponsor's proposed revised PPI, dated December 18, 2007, has a Flesch Kincaid Grade Level of 8.8 and a Flesch Reading Ease score of 56.5. To enhance comprehension, patient materials should have a 6th to 8th grade reading level and a Flesch Reading Ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised PPI has a Flesch Kincaid Grade Level of 7.4 and a Flesch Reading Ease score of 64.2.
- Under the section, "How should I take Tekturna HCT?" patients are given the instruction, [redacted] This bullet is very poorly worded for patient comprehension; however, it is consistent with the language in the PI. The review division should propose more meaningful language that is also patient-friendly for the PPI. The sponsor's proposed bullet stated ' [redacted] The PPI must be consistent with the PI; therefore, this should be addressed with the sponsor in the PI as well. This is information is unclear

b(4)

to the reviewer, and it is likely to be unclear to patients. Be more direct in telling doctors and patients whether to avoid taking Tekturna HCT with fatty foods and if it should or should not be taken with meals.

- The PPI must always be consistent with the PI. All future relevant changes to the PI should also be reflected in the PPI.

We will provide marked up and clean copies of our suggested PPI revisions to the review division as Word documents. We recommend using the clean copy as the working document. Please let us know if you have any questions.

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11 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

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/s/

Sharon Mills
1/2/2008 04:43:45 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
1/2/2008 04:49:02 PM
CSO

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 9, 2007
To:	Norman L. Stockbridge, M.D., Ph.D. Director, Division of Cardiovascular and Renal Products
Thru:	Ellis Unger, M.D., Acting Deputy Director Office of Surveillance and Epidemiology (OSE)
From:	**OSE Risk Management Team** Mary Dempsey, Risk Management Program Coordinator, OSE-IO Claudia B. Karwoski, Pharm.D., Team Leader Risk Management Team, OSE-IO Joyce Weaver, Pharm.D., BCPS, Senior Drug Risk Management Analyst, OSE-IO
Subject:	Review of RMP, submission dated March 2, 2007
Drug Name(s):	Tekturna-HCT (aliskiren and hydrochlorothiazide)
Application Type/Number:	NDA 22-107
Applicant/sponsor:	Novartis
OSE RCM #:	2007-1027

1 INTRODUCTION

A risk management plan was submitted for Tekturna-HCT tablets, an antihypertensive edication. The tablets consist of aliskiren and hydrochlorothiazide in four strengths, 150mg/12.5mg, 150mg/25mg, 300mg/12.5mg, and 300mg/25mg. The proposed dosage is one tablet once daily. The Sponsor proposes labeling and routine pharmacovigilance to manage the risks of this prescription-only product. Tekturna, a single-ingredient antihypertensive was approved March 5, 2007. No risk minimization measures beyond labeling and routine pharmacovigilance were put into place for Tekturna. Hydrochlorothiazide was first approved in 1959. Hydrochlorothiazide is marketed as both a single-ingredient product, and in combination with numerous other antihypertensive medications. No risk minimization measures beyond labeling and routine pharmacovigilance are in place for hydrochlorothiazide and hydrochlorothiazide-containing combination products.

2 MATERIAL REVIEWED

The following documents were reviewed—

- Safety Risk Management Plan/ Risk Minimization Action Plan, document dated March 2, 2007, submitted for Tekturna-HCT, available in EDR;
- Tekturna-HCT proposed package insert, document dated March 13, 2007, available in EDR; and
- Medical Officer review for Tekturna, review signed 12-07-2006; available in DFS.

3 DISCUSSION

Tekturna-HCT was administered to more than 2700 patients in clinical testing. Exposure was short-term (8 weeks). The Sponsor addressed risk management to the following known risks: diarrhea, rash, hyperkalemia, decreases in hemoglobin and hematocrit, and a drug interaction with furosemide. Additionally, colorectal hyperplasia was identified as a potential risk, based on preclinical findings. Other potential risks listed are peripheral edema and hypotension. Finally, the Sponsor considered known class effects for this direct renin inhibitor. Although aliskiren is the first drug in this class, the class is closely related to the angiotensin converting enzyme inhibitors and the angiotensin receptor blockers. The Sponsor identified cough, angioedema, and renal dysfunction as known class effects for Tekturna.

Dr. Thomas Marciniak, the clinical reviewer for the NDA for Tekturna, single-ingredient tablets, identified seizures (two cases in clinical trials) and renal cell carcinoma (two cases in clinical trials) as additional potential risks for aliskiren. However, these potential risks were not sufficiently concerning to delay approval of Tekturna, or to ask the Sponsor to institute any risk minimization measures upon marketing. b(4)

Regarding deaths occurring during clinical testing of Tekturna, Dr. Marciniak judged that deaths in patients receiving Tekturna did not distinguish Tekturna from placebo, or from active control.

4 CONCLUSIONS

We agree with the Sponsor's assessment. The risks associated with the use of Tekturna-HCT do not require additional postmarketing risk minimization and risk assessment measures beyond labeling and routine pharmacovigilance. We note that Tekturna, the single-ingredient product, does not have a RiskMAP in place. We do not recommend establishing a RiskMAP for this product.

Should accumulating safety data for Tekturna-HCT show unanticipated risks associated with its use, we ask that you consult OSE again to reconsider the risk management plan.

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/s/

Mary Dempsey
10/9/2007 10:35:53 AM
DRUG SAFETY OFFICE REVIEWER

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10/9/2007 02:27:27 PM
MEDICAL OFFICER