CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200045Orig1s000

OTHER REVIEW(S)

RHPM Overview
NDA 200045
Amturnide (aliskiren/amlodipine/hydrochlorothiazide) 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg and 300/10/25 mg

Sponsor: Novartis

Classification: Standard

Submission Date: February 25, 2010

Receipt Date: February 25, 2010

User Fee Goal Date: December 25, 2010

Background
Amturnide is a fixed dose triple combination antihypertensive indicated for the treatment of hypertension. This drug product consists of three currently approved drugs: amlodipine, a long acting dihydropyridine calcium channel blocker, approved in 1992 for the treatment of hypertension; aliskiren, a direct renin inhibitor, approved in 2008 for the treatment of hypertension, and hydrochlorothiazide, a thiazide diuretic, approved in 1965 for the treatment of edema.

The studies for Amturnide were conducted under IND 062976 (SP100A-aliskiren monotherapy) and IND 101386 (SAH100A-aliskiren/amlodipine/hydrochlorothiazide fixed dose combination). In total there were six clinical trials submitted. Two of the studies are considered pivotal, Study SAH2302 for efficacy, and SAH2301 for safety. There were two relative bioavailability studies and one bioequivalence study submitted. A drug-drug interaction study was performed as part of the pivotal efficacy trial.

Late in the review cycle, the Division was made aware of two protocol deviations in study SAH2302. The first protocol deviation pertained to the manner in which blood pressure readings were obtained. As per protocol, three blood pressure measurements were to be taken at each visit, one to two minutes apart. If any systolic blood pressure reading was $\geq$ 10 mmHg different from one of the other readings (aberrant), another set of blood pressure readings was supposed to be taken. If this second set of readings produced another aberrant reading, then the aberrant reading was considered acceptable and was to be included as the reading for that study visit. During the review of their site data, the sponsor discovered that this rule for taking a second set of blood pressure readings was not adhered to by all the sites. The sponsor conducted an analysis of the systolic blood pressure data with the full analysis set and another analysis excluding the subjects with aberrant readings at baseline and 8-week endpoint readings.

The second protocol deviation pertained to a large number of subjects, without proper inclusion criteria, were randomized into study SAH2302. The majority of the errors surrounded the matter of blood pressure criteria. The sponsor performed additional analyses looking at both the full analysis set and the population of subjects excluding those with the protocol deviations.

According to Dr. Aranoff, the clinical reviewer for this NDA, these protocol deviations are satisfactorily addressed by the sponsor. Dr. Karkowsky states that none of these deviations appears to introduce bias into the results, and the deviations from the protocol were not sufficient to compromise the results of the study.

The Division has concerns about the large food effect seen with aliskiren. Aliskiren concentrations, when taken fasting, are 8-fold C_{max} and 5-fold AUC, when compared to a high fat meal. Dr. Karkowsky recommends that the labeling state to use aliskiren in the fasted state before adding a combination drug product. The sponsor was informed of the Division's interest in the relationship of food on the blood pressure effect on aliskiren. The sponsor submitted two studies to the Tekturna (aliskiren) NDA (021985). At the time of this memo, the review for these studies has not been completed. Once fully reviewed, the result may affect the labeling of all aliskiren products.

User Fee
The user fee for this application was paid in full prior to the submission of the application.

Labeling
The original submission contains proposed draft labeling that reflects the formatting changes required by the Physician's Labeling Rule. The labeling was reviewed by DDMAC on December 13, 2010. The comments were conveyed to the sponsor and the appropriate labeling changes were completed.

Correspondence and meetings

1. March 14, 2008 – Pre-IND Meeting was held. The clinical development plan, biopharmaceutics development plan, preclinical development plan, and the technical development plan were discussed.
2. March 12, 2009 – Pre-NDA Meeting was scheduled for March 12, 2009 and subsequently cancelled by the sponsor after receiving Preliminary Responses to their submitted questions.
3. September 29, 2009 – Advice Letter sent accepting the sponsor's proposal not to pool studies CSPP100A2360 and CSPP100A2411 with other studies in the sponsor's submission.
4. November 3, 2010 – Advice Letter to tighten the sponsor's proposed dissolution specifications was sent.
5. November 10, 2010 – Teleconference to discuss the results of GCP inspections performed at three sites (One site in Latvia and two sites in Canada).
6. December 16, 2010 – Teleconference to discuss the Package Insert, and the carton and container labels.

Divisional Memo
In his memo, dated December 11, 2010, Dr. Stockbridge recommends approval of Amturnide.

Medical/Statistical Review
In his review, dated November 23, 2010, Dr. Aranoff noted that from a clinical perspective, I recommend that Amturnide, the fixed combination of aliskiren, amlodipine, and HCTZ, be approved for the treatment of hypertension. This conclusion is supported by efficacy and safety data from a short-term, double blind, pivotal efficacy study, a long-term, open-label major safety trial, as well as four other supportive clinical trials.

In the pivotal efficacy trial (SAH2302), the triple therapy combination demonstrated clinically and statistically significant reductions from baseline in blood pressure compared to each of the component double therapy combinations in patients with moderate to severe hypertension. Moreover, in this same pivotal study, triple therapy demonstrated superior reductions in BP from baseline over the entire 24 hour interdosing interval.

The greater BP lowering effect with triple combination over component dual combinations was generally demonstrated in a broad range of patient populations without regard to age, race, gender, BMI status and other demographic or disease status factors such as patients with diabetes.

In terms of safety, the safety profile for aliskiren/amlodipine/HCTZ was consistent with that previously known for aliskiren, amlodipine, or HCTZ when used as monotherapy or as dual combination. There were no unexpected safety findings in the clinical program. There were no deaths in any patients who took triple therapy. The incidence and severity of total and individual adverse events for aliskiren/amlodipine/HCTZ treatment were generally similar to the component dual combination treatments.

Peripheral edema, a known side effect of amlodipine, occurred more in treatment groups containing amlodipine. The aliskiren/amlodipine/HCTZ showed slightly less reported peripheral edema than aliskiren/amlodipine treatment. Peripheral edema was mostly mild to moderate in severity and rarely led to patient discontinuation.

With the exception of peripheral edema, there was no increase in AE incidence and severity when the dose of aliskiren/amlodipine/HCTZ was increased from 150/5/12.5 mg to 300/10/25 mg. AEs potentially related to low blood pressure such as hypotension, orthostatic hypotension, syncope and dizziness occurred at low incidence and rarely led to patient discontinuation in patients treated with aliskiren/amlodipine/HCTZ.

Hyperkalemia occurred uncommonly with the treatment of aliskiren/amlodipine/HCTZ triple combination with the incidence similar to the component dual combinations. No case of angioedema was reported in the entire clinical program. Changes in laboratory parameters observed with aliskiren/amlodipine/HCTZ were generally minor and consistent with the known effect of aliskiren, amlodipine, or HCTZ. There were no meaningful differences between aliskiren/amlodipine/HCTZ triple combination and component dual combinations.

Aliskiren/amlodipine/HCTZ was generally well tolerated regardless of gender, age, or race.

Dr. Aranoff also reviewed the submitted financial disclosure statement and found it acceptable.

Clinical Pharmacology

In his review dated November 24, 2010, Dr. Sudharshan writes: The Office of Clinical Pharmacology (OCP/DCP1) reviewed original NDA 200045 and recommends approval from a clinical pharmacology perspective.

The components of Amturnide are approved for use in hypertension, and their pharmacokinetic (PK) and pharmacodynamic (PD) properties were reviewed under submissions NDA 21-985 (aliskiren, Tekturna®), NDA 19-787 (amlodipine, Norvasc®) and NDA (b) (4) (hydrochlorothiazide, Esidrix®). The Clinical Pharmacology and Biopharmaceutics program for Amturnide was designed primarily to enable association of the efficacy and safety data of the monotherapies to the FDC. Of the four clinical pharmacology studies submitted to the NDA, one bioequivalence study, one relative bioavailability study and one food effect study were reviewed. The DDI sub-study performed as a part of pivotal efficacy trial was also reviewed.

The key clinical pharmacology and biopharmaceutics findings are listed below:

❖The FDC of aliskiren/amlodipine/hydrochlorothiazide is bioequivalent to the free combination.

- Bioequivalence was established in the relative bioavailability study (CSAH100A2104).

- In the bioequivalence study (CSAH100A2102), the 90% CI for C_{max} of aliskiren (0.76, 0.93) was not contained within the pre-determined BE limits of 0.8 – 1.25. However, this is not clinically significant, because of a shallow exposure-response relationship.

❖There is no clinically relevant food effect on Amturnide.

- Systemic exposure to amlodipine and hydrochlorothiazide was not affected by food.

- Systemic exposure to aliskiren was reduced by ~80% when Amturnide 300/10/25 mg was administered with a high fat meal. This observation is consistent with prior findings for aliskiren and its fixed dose combinations, where this effect was judged to be clinically not significant. This is supported by the shallow exposure-response relationship of aliskiren. The current label(s) recommends establishing a routine pattern for taking aliskiren (and its fixed dose combinations) with regard to meals. Therefore, the same labeling language should be used for Amturnide.

❖There is no clinically relevant drug-drug interaction between aliskiren, amlodipine and hydrochlorothiazide when administered in combination.

Nonclinical Review
No new studies with the combination were included with this application. Dr. Jagadeesh recommends approval from a Nonclinical perspective. In his review dated July 28, 2010, Dr. Jagadeesh wrote: The sponsor has not performed pharmacology, ADME, or toxicology studies for the combination product. Nonclinical studies of the individual active components of the combination product are summarized in the pharmacology and toxicology reviews of related NDAs listed in sections 2.3 and 3.1 below.

Clinical trials supporting the current NDA were conducted under Novartis Pharmaceuticals Corporations IND 62,976 (aliskiren monotherapy) and IND 101,386 (aliskiren/amlodipine/ hydrochlorothiazide). Novartis Pharmaceuticals Corporation's NDA 21,985 for aliskiren (Tekturna→) was approved for the treatment of hypertension in March 2007. Pfizer's NDA 19,787 for racemic amlodipine besylate (Norvasc→) was approved for the treatment of hypertension, chronic stable angina, and vasospastic angina in 1992. Other related NDAs are: 022107 (aliskiren and HCTZ), 022217 (aliskiren and valsartan), 022545 (aliskiren and amlodipine).

Previous Reviews Referenced
NDA 21,985 for aliskiren (Tekturna→)

NDA 22,107 for aliskiren and HCTZ (Tekturna→ HCT)
NDA 22,217 for aliskiren and valsartan (Valturna®)
NDA 22,545 for aliskiren and amlodipine (Tekamlo®).

Chemistry Review
In his review dated October 22, 2010, Dr. Lu wrote the following: From a CMC perspective, Novartis has submitted sufficient and appropriate information to support the approval of the drug product. There were several CMC concerns that were sent to the sponsor on September 28, 2010. Novartis has adequately addressed these CMC comments.
Based on the available cross-referenced information, the drug substances, aliskiren hemifumarate, amlodipine besylate and hydrochlorothiazide, are acceptable from the CMC point of view for the manufacturing of Aliskiren/Amlodipine/ Hydrochlorothiazide (SAH100) tablet drug products.

Clinical Pharmacology Review
In his review dated, November 24, 2010, Dr. Hariharan recommends approval from a clinical pharmacology perspective. The key findings are listed below:

❖The FDC of aliskiren/amlodipine/hydrochlorothiazide is bioequivalent to the free combination.
- Bioequivalence was established in the relative bioavailability study (CSAH100A2104).
- In the bioequivalence study (CSAH100A2102), the 90% CI for Cmax of aliskiren (0.76,0.93) was not contained within the pre-determined BE limits of 0.8 – 1.25. However, this is not clinically significant, because of a shallow exposure-response relationship.

❖There is no clinically relevant food effect on Amturnide.
- Systemic exposure to amlodipine and hydrochlorothiazide was not affected by food.
- Systemic exposure to aliskiren was reduced by ~80% when Amturnide 300/10/25 mg was administered with a high fat meal. This observation is consistent with prior findings for aliskiren and its fixed dose combinations, where this effect was judged to be clinically not significant. This is supported by the shallow exposure-response relationship of aliskiren. The current label(s) recommends establishing a routine pattern for taking aliskiren (and its fixed dose combinations) with regard to meals. Therefore, the same labeling language should be used for Amturnide.

❖There is no clinically relevant drug-drug interaction between aliskiren, amlodipine and hydrochlorothiazide when administered in combination.

Environmental Assessment
Drs. Bloom and Sadrieh reviewed the submitted environmental assessment and found it acceptable.

Division of Scientific Investigations
The Division did not request DSI inspections.

Pediatrics
The PeRC PREA Subcommittee reviewed Amturnide on June 30, 2010. The PeRC PREA Subcommittee issued a full waiver as Amturnide does not represent a meaningful benefit and is not likely to be used in pediatric patients.

CSO Summary
An approval letter was drafted for Dr. Stockbridge's signature.

_____
Lori Anne Wachter, RN, BSN
Regulatory Health Project Manager
December 3, 2010

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

/s/

Lori A WACHTER
12/22/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 200045	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: aliskiren/amlodipine/HCTZ Dosage Form: Tablet Strengths: 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg, 300/10/25 mg		
Applicant: Novartis		
Date of Receipt: February 25, 2010		
PDUFA Goal Date: December 25, 2010	Action Goal Date (if different): December 23, 2010	
Proposed Indication(s): The treatment of hypertension.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Amlodipine	Contraindications, Adverse Reactions, Drug Interactions, Overdosage, Description, Clinical Pharmacology, Non Clinical Pharmacology sections of label

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Two BA and one BE study

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

Amodipine and hydrochlorothiazide

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

APPEARS THIS WAY ON ORIGINAL

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Amlodipine	NDA 019787	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

<u>This application provides for a fixed dose triple combination of three approved drugs.</u>

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **<u>and</u> (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO X

*If "**NO**" to (a) proceed to question #11.*

*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

Lori A WACHTER
12/21/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: December 13, 2010

To: Lori Wachter – Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker – Regulatory Review Officer
Zarna Patel – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 200045 Amturnide (aliskiren,amlodipine, hydrochlorothiazide) Tablets

DDMAC has reviewed the proposed product labeling (Package Insert (PI) and Patient Package Insert (PPI)) for Amturnide (aliskiren, amlodipine and hydrochlorothiazide) tablets (Amturnide), submitted for consult on December 9, 2010. We also reviewed the comments on the PPI from the Division of Risk Management (DRISK) dated December 8, 2010. We agree with DRISK's comments and have no additional comments on the proposed PPI.

The following comments are provided in response to the proposed product labeling sent via email on December 9, 2010 by Lori Wachter. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

25 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

EMILY K BAKER
12/13/2010

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

PATIENT LABELING REVIEW

Date:	December 08, 2010
To:	Norman L. Stockbridge, MD, PhD., Director **Division of Cardiovascular and Renal Products (DCRP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management (DRISK)** Barbara Fuller, RN, MSN, CWOCN Patient Labeling Reviewer **Division of Risk Management**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Patient Package Insert)
Drug Name (established name):	Tradename (aliskiren, amlodipine and hydrochlorothiazide)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 200045
Applicant:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2010-775

1 INTRODUCTION

This review is written in response to a request by the Division of Cardiovascular and Renal Products (DCRP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Tradename (aliskiren, amlodipine and hydrochlorothiazide) Tablets.

Novartis Pharmaceutical Corporations submitted an original New Drug Application (NDA) 200045 for Tradename (aliskiren, amlodipine and hydrochlorothiazide) Tablets on February 25, 2010. Tradename is a combination of aliskiren, a renin inhibitor, amlodipine, dihydropyridine, calcium channel blocker and hydrochlorothiazide, a thiazide diuretic indicated for the treatment of hypertension.

DRISK conferred with DMEPA and a separate DMEPA review of the PPI will be forthcoming.

2 MATERIAL REVIEWED

- Draft Tradename (aliskiren, amlodipine and hydrochlorothiazide) Tablet, Patient Package Insert (PPI) received on February 25, 2010, revised by the Review Division throughout the current review cycle and sent by the Review Division to DRISK on November 30, 2010.
- Draft Tradename (aliskiren, amlodipine and hydrochlorothiazide) Tablet, Prescribing Information (PI) received on February 25, 2010, revised by the Review Division throughout the current review cycle and sent by the Review Division to DRISK on November 30, 2010.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI

- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- This reviewer did not review the Risk Management Plan submitted by the Applicant. DCRP, please notify DRISK if you determine that there are serious risks that may warrant a Risk Evaluation and Mitigation Strategy (REMS) for Tradename (aliskiren, amlodipine and hydrochlorothiazide) Tablets.
- Our annotated versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

/s/

LATONIA M FORD
12/08/2010
12/8/2010
Tradename (aliskiren, amlodipine and hydrochlorothiazide) Tablets

LASHAWN M GRIFFITHS
12/08/2010