DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200045/S-006

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Lori Ann Kneafsey
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Kneafsey:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 7, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amturnide (amlodipine/aliskiren/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 Tablets.

We acknowledge your submission dated October 25, 2011.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows (additions are shown as underlined text and deletions are shown as ~~strikethrough text~~):

1. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the following changes were made:

----------WARNINGS AND PRECAUTIONS----------

- ~~Avoid fetal and neonatal exposure. (5.1)~~
- Head and neck angioedema: Discontinue Amturnide. (5.2)
- Hypotension ~~volume or salt-depleted patients~~: Correct volume depletion prior to initiation. (5.3)
- Increased angina or myocardial infarction may occur upon dosage initiation or increase in amlodipine. (5.4)
- ~~Avoid in patients with severe renal impairment. (5.5)~~
- ~~Titrate gradually in patients with sever hepatic impairment (5.6)~~
- Monitor renal function in susceptible patients. (5.5)
- HCTZ may exacerbate or activate systemic lupus erythematosus. (5.~~9~~8)
- Acute myopia and secondary angle closure glaucoma: Discontinue HCTZ. (5.~~14~~12)
- Hypersensitivity Reactions: May occur from HCTZ component. (5.~~8~~7)

2. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following changes were made:

~~**Aliskiren:**~~

- Cyclosporine: Avoid concomitant use (7, 12.3)
- Itraconazole: Avoid concomitant use (7, 12.3)

~~**Amlodipine:**~~

- NSAIDS use may lead to increased risk of renal impairment and loss of antihypertensive effect (7)
- If simvastatin is co-administered with amlodipine, do not exceed doses greater than 20 mg daily of simvastatin (7)
- Antidiabetic Drugs: Antidiabetic dosage adjustment may be required.(7)
- Cholestyramine and Colestipol: Reduce absorption of thiazides. (7)
- Lithium: Increased risk of lithium toxicity when used with diuretics. Monitor serum lithium concentrations during concurrent use.. (7)

~~**HCTZ:**~~

~~• Alcohol, Barbiturates, Narcotics: Worsens orthostatic hypotension.~~
~~• Antidiabetic Drugs: Antidiabetic dosage adjustment may be required.~~
~~• Cholestyramine and Colestipol: Reduce absorption of thiazides.~~
~~• Corticosteroids, ACTH: Hypokalemia, electrolyte depletion.~~
~~• Lithium: Reduced renal clearance and high risk of lithium toxicity when used with diuretics. Avoid with diuretics.~~
~~• NSAIDs: Reduce diuretic, natriuretic, and antihypertensive effects of diuretics.~~

3. Under **DOSAGE AND ADMINSTRATION,** the following text was deleted:

~~**2.5 Dosing in Specific Populations**~~

~~***Renal Impairment***~~
~~The usual regimens of Amturnide may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Amturnide is not recommended *[see Warnings and Precautions (5.5)]*.~~

~~***Hepatic Impairment***~~
~~In patients with severe hepatic impairment, start amlodipine at 2.5 mg per day, a dose that is not available in Amturnide *[see Warnings and Precautions (5.6)]*.~~

~~***Elderly Patients***~~
~~Patients ≥75 years of age should start amlodipine at 2.5 mg, which is not available with Amturnide~~

4. Under **WARNINGS AND PRECAUTIONS/Impaired Renal Function,** the section was changed as follows:

~~In patients with severe renal impairment (GFR <30 mL/min), loop diuretics are preferred to thiazides,so Amturnide is not recommended.~~

~~Uptitrate HCTZ slowly; in patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.~~

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on Amturnide. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Amturnide.

5. Under **WARNINGS AND PRECAUTIONS,** the following was deleted:

~~**Patients with Hepatic Impairment**~~

~~Amlodipine is extensively metabolized by the liver. In patients with severe hepatic impairment, start amlodipine at 2.5 mg per day, a dose that is not available in Amturnide.~~

~~Uptitrate HCTZ slowly; minor alterations of fluid and electrolyte balance may precipitate hepatic coma.~~

6. Under **WARNINGS/Serum Electrolyte Abnormalities**, the section was changed as follows:

In a short-term controlled trial the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 11.0% of Amturnide-treated patients compared to 19.0% of amlodipine/HCTZ patients, 4.4% of aliskiren/HCTZ patients, and 2.1% of aliskiren/amlodipine patients; the incidence of hyperkalemia (serum potassium >5.5 mEq/L) was 3.0% compared to 2.0% of amlodipine/HCTZ patients, 0.7% of aliskiren/HCTZ patients, and 0.7% of aliskiren/amlodipine patients. No Amturnide-treated patients discontinued due to increase or decrease of serum potassium.

~~Perform periodic determinations of serum electrolytes to detect possible electrolyte imbalance at appropriate intervals.~~

~~Based on experience with the use of the other substances that affect the renin-angiotensin-aldosterone system (RAAS), concomitant use of Amturnide with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium~~.

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.

Hydrochlorothiazide

If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis, or ECG alterations), Amturnide should be discontinued. Correction of hypokalemia and any coexisting hypomagnesaemia is recommended prior to the initiation of thiazides.

7. Under WARNINGS AND PRECAUTIONS, the following section was ~~deleted~~:

~~5.12 Renal Artery Stenosis~~
~~No data are available on the use of Amtumide in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. However, in studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported~~.

8. Under **WARNINGS AND PRECAUTIONS**, a new section was added:

5.13 Metabolic Disturbances

Hydrochlorothiazide

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevation of serum calcium. Monitor calcium levels in patients with hypercalcemia receiving Amturnide**.**

9. Under **ADVERSE REACTIONS/Clinical Studies Experience/Hydrochlorothiazide** the section was changed as follows:

~~***Metabolic:***glycosiuria,hyperuricemia~~

10. Under **ADVERSE REACTIONS/Postmarketing Experience**, the following was added:

Hydrochlorothiazide:

Acute renal failure, renal disorder, aplastic anemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma, bone marrow failure, worsening of diabetes control, hypokalemia, blood lipids increased, hyponatremia, hypomagnesemia, hypercalcemia, hyperchloremic alkalosis, impotence, visual impairment.

Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic evaluation is necessary.

11. Under **DRUG INTERACTIONS/Hydrochlorothiazide**, the following was ~~deleted~~/added:

When administered concurrently, the following drugs may interact with thiazide diuretics.
~~*Alcohol, barbiturates, or narcotics:* Potentiation of orthostatic hypotension may occur.~~
Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.
~~*Other antihypertensive drugs:* Additive effect or potentiation.~~
~~*Cholestyramine and colestipol resins:* Absorption of HCTZ is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the HCTZ and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.~~
~~*Corticosteroids, ACTH:* Intensified electrolyte depletion, particularly hypokalemia.~~
~~*Pressor amines (e.g., norepinephrine):* Possible decreased response to pressor amines but not sufficient to preclude their use.~~
~~*Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine):* Possible increased responsiveness to the muscle relaxants.~~

Lithium: ~~Should not generally be given with diuretics~~. Diuretic agents ~~reduce the renal clearance of lithium and~~ increase the risk of lithium toxicity. Refer to the package insert for lithium before use of such preparation with Amturnide. Monitoring of serum lithium concentrations is recommended during concurrent use.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and cox2 selective agents~~: In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, w~~When Amturnide and nonsteroidal anti-inflammatory agents are used concomitantly, observe the patient to determine if the desired effect of the diuretic is obtained.

Ion exchange resins: Staggering the dosage of hydrochlorothiazide and resin (e.g., cholestyramine, colestipol) such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimize the interaction. *[See Clinical Pharmacology (12.3)]*

12. Under **USE IN SPECIFIC POPULATIONS**/*HCTZ*, the following text was added as the second paragraph:

Thiazides can cross the placenta, and concentrations reached in the umbilical vein approach those in the maternal plasma. Hydrochlorothiazide, like other diuretics, can cause placental hypoperfusion. It accumulates in the amniotic fluid, with reported concentrations up to 19 times higher than in umbilical vein plasma. Use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice or thrombocytopenia. Since they do not prevent or alter the course of EPH (Edema, Proteinuria, Hypertension) gestosis (pre eclampsia), these drugs should not be used to treat hypertension in pregnant women. The use of hydrochlorothiazide for other indications (e.g. heart disease) in pregnancy should be avoided.

13. Under **USE IN SPECIFIC POPULATIONS/Geriatric Use**, the following text was added as the second paragraph:

Patients ≥ 75 years of age should start amlodipine at 2.5 mg, which is not available with Amturnide.

14. Under **USE IN SPECIFIC POPULATIONS,** the following sections were added**:**

8.6 Renal Impairment

Safety and effectiveness of Amturnide in patients with severe renal impairment (CrCl ≤ 30 mL/min) have not been established. No dose adjustment is required in patients with mild (CrCl 60-90 mL/min) or moderate (CrCl 30-60) renal impairment.

8.7 Hepatic Impairment

Aliskiren

No dose adjustment is necessary for patients with mild-to-severe liver disease.

Hydrochlorothiazide

Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

15. Under **CLINICAL PHARMACOLOGY**/Drug Interactions/*Hydrochlorothiazide*, the following text was added:

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Skeletal muscle relaxants: Possible increased responsiveness to muscle relaxants such as curare derivatives.

Digitalis glycosides: Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.

16. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics/ *Absorption and Distribution****/Aliskiren*, the following text was added/~~deleted:~~

Aliskiren is poorly absorbed (bioavailability about 2.5%) ~~with an accumulation half life of about 24 hours. Steady state blood levels are reached in about 7-8 days.~~ Following oral administration, peak plasma concentrations of aliskiren are reached within 1-3 hours. When taken with a high fat meal, mean AUC and Cmax of aliskiren arc decreased by 71% and 85% respectively. In the clinical trials of aliskiren, it was administered without a fixed relation to meals.

17. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics/***HCTZ*, the section was changed as follows:

The estimated absolute bioavailability of hydrochlorothiazide after oral administration is about 70%. Peak plasma hydrochlorothiazide concentrations (C_{max}) are reached within 2 to 5 hours after oral administration. There is no clinically significant effect of food on the bioavailability of hydrochlorothiazide.

Hydrochlorothiazide binds to albumin (40 to 70%) and distributes into erythrocytes. Following oral administration, plasma hydrochlorothiazide concentrations decline bi-exponentially, with a mean distribution half-life of about 2 hours and an elimination half-life of about 10 hours

18. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics/*Metabolism and Elimination/Aliskiren,*** the following text was added/~~deleted~~:

The effective half-life for aliskiren is 24 hours. Steady state blood levels are reached in about 7 – 8 days. About one-fourth of the absorbed dose appears in the urine as parent drug. How much of the absorbed dose is metabolized is unknown. Based on the *in vitro* studies, the major enzyme responsible for aliskiren metabolism appears to be CYP 3A4. Aliskiren does not inhibit the CYP450 isoenzymes (CYP 1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A) or induce CYP 3A4.

19. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics/*Metabolism and Elimination/HCTZ,*** the section was changed as below:

~~HCTZ is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours. The elimination half-life is between 5.8 and 18.9 hours.~~ About 70% of an orally administered dose of hydrochlorothiazide is eliminated in the urine as unchanged drug.

20. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics/** *Drug Interactions,* the following text was added:

Hydrochlorothiazide

Drugs that alter gastrointestinal motility: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, pro-kinetic drugs may decrease the bioavailability of thiazide diuretics.

Cholestyramine: In a dedicated drug interaction study, administration of cholestyramine 2 hours before hydrochlorothiazide resulted in a 70% reduction in exposure to hydrochlorothiazide. Further, administration of hydrochlorothiazide 2 hours before cholestyramine, resulted in 35% reduction in exposure to hydrochlorothiazide.

Antineoplastic agents (e.g. cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.

21. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics/*Special Populations,*** the following language was added/~~deleted~~:

Geriatric Patients
Aliskiren
The pharmacokinetics of aliskiren were studied in the elderly (≥65 years). Exposure (measured by AUC) is increased in elderly patients. ~~Adjustment of the starting dose of aliskiren is not required in these patients *[see Dosage and Administration (2.5)].*~~

Amlodipine
Elderly patients have decreased clearance of amlodipine, with a resulting increase in AUC of approximately 40%-60%.

Hydrochlorothiazide

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

22. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics/Renal Impairment,** the section was changed as follows:

Aliskiren
The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal impairment. Rate and extent of exposure (AUC and Cmax) of aliskiren in subjects with renal impairment did not show a consistent correlation with the severity of renal impairment. ~~Adjustment of the starting dose is not required in patients with mild to moderate renal impairment, but Amturnide is not recommended in patients with severe renal impairment~~ *[see Dosage and Administration (2.5) and Warnings and Precautions (5.5)]*.

The pharmacokinetics of aliskiren following administration of a single oral dose of 300 mg was evaluated in patients with End Stage Renal Disease (ESRD) undergoing hemodialysis. When compared to matched healthy subjects, changes in the rate and extent of aliskiren exposure (Cmax and AUC) in ESRD patients undergoing hemodialysis was not clinically significant.

Timing of hemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, no dose adjustment is warranted in ESRD patients receiving hemodialysis

Amlodipine
The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose *[see Dosage and Administration (2.5)]*.

Hydrochlorothiazide
In a study in individuals with impaired renal function, the mean elimination half-life of hydrochlorothiazide was doubled in individuals with mild/moderate renal impairment (30 < CLcr < 90 mL/min) and tripled in severe renal impairment (≤ 30 mL/min), compared to individuals with normal renal function (CLcr > 90 mL/min). *[see Special Populations (8.6)].*

23. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics/Hepatic Impairment**, a new section was changed as follows:

Aliskiren
The pharmacokinetics of aliskiren were not significantly affected in patients with mild-to-severe liver disease. ~~Consequently, adjustment of the starting dose is not required in these patients~~ *[see ~~Dosage and Administration (2.5)~~ Special Populations (8.7)]*.

Amlodipine

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60%. A lower initial dose of amlodipine is required for patients with severe hepatic impairment *[see ~~Dosage and Administration (2.5)~~ Special Populations (8.7)].*

24. Under **NONCLINICAL TOXICOLOGY/ Carcinogenesis, Mutagenesis, Impairment of Fertility***/Studies with HCTZ,* the words "was not teratogenic" were added to the first sentence of the third paragraph:

25. The revision date and version number were updated.

There are no other changes from the last approved package insert.

We have completed our review of this supplemental application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MARY R SOUTHWORTH
02/14/2012