



NDA 200045/S-016

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Annemarie Van der Merwe
Global Program Regulatory Director
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Van der Merwe:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 25, 2014, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amturnide (aliskiren/amlodipine besylate/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

This supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strike through text~~):

In the Package Insert:

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following text was added:

Warnings and Precautions (5.1, 5.2, 5.6) 02/2015

2. In **HIGHLIGHTS/DOSAGE AND ADMINISTRATION**, the following text was added/deleted:

- Dose once-daily. Titrate as needed ~~up~~ to a maximum dose of 300/10/25 mg.
- Amturnide may be used as add-on/switch therapy for patients not adequately controlled on any ~~two~~ of the following: aliskiren, dihydropyridine calcium channel blockers, and thiazide diuretics. (2.2)
- Amturnide may be substituted for its individual components ~~individually titrated aliskiren, amlodipine and HCTZ.~~ (2.3)

3. In **HIGHLIGHTS/CONTRAINDICATIONS**, the following text was added/deleted from the first bullet:

- Do not use with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme ~~ACE~~ inhibitors (~~ACEIs~~ ~~ACEI~~) in patients with diabetes. (4)

4. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, The following text was added to the first, third, fourth, and eighth bullets:

- Avoid concomitant use with ARBs or ACEIs particularly in patients with renal impairment [creatinine clearance (CrCl) (GFR < 60 mL/min)]. (5.2, 5.4)
- Anaphylactic Reactions and Head and Neck Angioedema. ~~(- Discontinue Amturnide and monitor until signs and symptoms resolve.~~ (5.3)

- Hypotension: Correct imbalances –in volume and/or salt–depleted patients. (5.4) ~~–or with combined use of other agents acting on RAAS : Correct imbalances before initiating therapy with Amturnide. (5.4)~~
- Increased angina or myocardial infarction may occur upon dosage initiation or increase in amlodipine. (5.5)
- Impaired Renal Function~~renal function~~: Monitor serum creatinine periodically. (5.6)
- Systemic~~HCTZ may exacerbate or activate systemic~~ lupus erythematosus activation or exacerbation. (5.8)–(5.8)
- Hyperkalemia: Monitor potassium levels periodically. (5.10)
- Acute Myopia and Secondary Angle Closure Glaucoma. (5.12)
- Acute myopia and secondary angle closure glaucoma: Discontinue HCTZ. (5.12)
- Hypersensitivity Reactions: May occur from HCTZ component. (5.7)

5. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following text was added/deleted to/from the second, third, and fifth bullets:

- Cyclosporine or Itraconazole: Avoid concomitant use (5.11, ~~(7, 12.3)~~)
- ~~(b) (4)~~ Anti-Inflammatory Drugs (Itraconazole: Avoid concomitant use (7, 12.3)
- NSAIDs): Increased use may lead to increased risk of renal impairment and loss of antihypertensive effect. (7)
- Simvastatin: Avoid~~If simvastatin is co-administered with amlodipine, do not exceed doses greater than 20 mg daily. (7) 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. (7)–Monitor serum lithium concentrations during concurrent use. (7)

6. Under **WARNINGS AND PRECAUTIONS**, the following sections were revised to read::

5.1 Fetal Toxicity

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Amturnide as soon as possible [see *Use in Specific Populations* (8.1)].

Thiazides cross the placenta, and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia, and possible other adverse reactions that have occurred in adults.

5.2 Renal Impairment/Hyperkalemia/Hypotension when Amturnide is Given in Combination~~combination~~ with ARBs or ACEIs

Amturnide is contraindicated in patients with diabetes who are receiving ARBs or ACEIs because of the increased risk of renal impairment, hyperkalemia, and hypotension. In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with creatinine clearance (CrCl) less than 60 mL/min [see *Contraindications* (4), *Drug Interactions* (7)–[see *Contraindications* (4) and *Clinical Studies* (14.2)].

~~Avoid use of Amturnide with ARBs or ACEI in patients with moderate renal impairment (GFR <60 mL/min).~~

5.6 Impaired Renal Function

Monitor renal function periodically in patients treated with Amturnide. Changes in renal function, including acute renal failure, can be caused by drugs that affect the ~~RAAS~~renin-angiotensin-aldosterone system and by diuretics. Patients whose renal function may depend in part on the

activity of the ~~RAAS~~renin-angiotensin-aldosterone system (e.g., patients with renal artery stenosis, severe heart failure, post-myocardial infarction or volume depletion) or patients receiving ARB, ACEI, or ~~nonsteroidal~~non-steroidal anti-inflammatory drug (NSAID), including selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors), therapy may be at particular risk of developing acute renal failure on Amluride [see ~~Contraindications (4), Warnings and Precautions (5.2), Drug Interactions (7), and Use in Specific Populations (8.7) and Clinical Studies (14.2)~~]. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Amluride [see Dosage and Administration (2.1)].

5.9 — Lithium Interaction

~~Lithium generally should not be given with thiazides [see Drug Interactions (7)].~~

7. Under **ADVERSE REACTIONS**, the following text was added/deleted in 6.1:

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- ~~Risk of fetal/neonatal morbidity and mortality~~Fetal Toxicity [see Warnings and Precautions (5.1)]
- Anaphylactic Reactions and Head and neck angioedema~~Neck Angioedema~~ [see Warnings and Precautions (5.3)]

8. Under **ADVERSE REACTIONS**, the following sections were revised:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, ~~tachycardia~~postural hypotension, vasculitis

Gastrointestinal: anorexia, constipation, ~~dyspepsia,**~~ dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia

9. Under **ADVERSE REACTIONS/Postmarketing Experience**, the following terms were added:

Aliskiren:

Hypersensitivity: anaphylactic reactions and angioedema requiring airway management and hospitalization.

Peripheral edema, severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, urticaria, hepatic enzyme increase with clinical symptoms of hepatic dysfunction, pruritus, erythema, nausea , vomiting.

10. Under **DRUG INTERACTIONS/Aliskiren**, the following text was added/deleted:

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS):~~renin-angiotensin-aldosterone system.~~ The concomitant use of aliskiren with other agents acting on the ~~RAAS~~renin-angiotensin-aldosterone system such as ACEIs or ARBs is associated with an increased risk of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two drugs that inhibit the renin-angiotensin system do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with CrCl less than 60 mL/min.

Monitor blood pressure, renal function, and electrolytes in patients on aliskiren and other agents that affect the ~~RAAS~~renin-angiotensin-aldosterone system [see Warnings and Precautions (5.4, 5.6, 5.10)].

The concomitant use of aliskiren with an ARB or an ACEI in diabetic patients is contraindicated ~~and should be avoided in patients with moderate renal impairment [see Contraindications (4) and Warnings and Precautions (5.2)].~~

11. Under **DRUG INTERACTIONS/HCTZ**, the following text was added/deleted:

~~*Lithium:* Diuretic agents increase the risk of lithium toxicity. Increases in serum concentrations and lithium toxicity have been reported during concomitant administration before use of lithium such preparation with angiotensin II receptor antagonists. Amturnide. Monitoring of serum lithium levels concentrations is recommended during concomitant concurrent use.~~

12. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, Table 1 and Table 2 were update to include:

Figure 1 was updated with superscript ** after Ramipril, valsartan, and irbesartan. The text “no dose adjustment” was deleted.

The following text was added below Table 1: *Ketoconazole: A 400 mg once daily dose was not studied, but would be expected to increase aliskiren blood levels further.

**Ramipril, valsartan, irbesartan: In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with CrCl less than 60 mL/min [see Drug Interactions (7)].

Figure 2 was updated with superscript ** after Ramipril, valsartan, and irbesartan. The text “no dose adjustment” was deleted.

The following text below Table 2: *Furosemide: Patients receiving furosemide could find its effects diminished after starting aliskiren

13. Under **PATIENT COUNSELING INFORMATION**, the following text was added/deleted:

~~Advise the patient to read the See FDA-approved patient labeling Approved Patient Labeling (Patient Information).~~

~~Instruct patients to read the Patient Package Insert before starting Amturnide and to reread each time the prescription is renewed. Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.~~

Pregnancy

~~Advise female Female patients of childbearing age should be told about the consequences of exposure to Amturnide during pregnancy. Discuss treatment options with women planning to become pregnant. Advise patients Patients should be asked to report pregnancies to their physicians as soon as possible.~~

Symptomatic Hypotension

Caution patients receiving Amturnide that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. Tell patients that if syncope occurs, discontinue Amturnide until the physician has been consulted.

Caution all patients that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Anaphylactic Reactions and Angioedema

Advise patients to ~~report~~ immediately report any signs or symptoms suggesting a severe allergic reaction (difficulty breathing or swallowing, tightness of the chest, hives, general rash, swelling, itching, dizziness, vomiting, or abdominal pain) or angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. Angioedema, including laryngeal edema, may occur at any time during treatment with Amturnide.

Potassium Supplements

Tell patients receiving Amturnide not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Relationship to Meals

Advise patients to ~~Patient should~~ establish a routine pattern for taking Amturnide either with or without a meal. High-fat meals decrease absorption substantially.

14. The following sections contain multiple editorial changes: 1, 2.2, 4, 5.3, 5.4, 5.7, 5.8, 5.10, 5.12, 5.13, 6.1, 6.2, 7, 8.1, 8.5, 8.6, 8.7, 10, 12.1, 12.2, 12.3, 13.1, 13.2, 14.1, 14.2, and 16.
15. The revision date and version number were updated.

In the Amturnide PPI:

1. The heading section was revised to read:

~~FDA Approved Patient Labeling~~

Patient Information

Amturnide™ (AM-turn-ide)

**Amturnide
(aliskiren, amlodipine and hydrochlorothiazide)
Tablets**

2. Under the **What is high blood pressure (hypertension)?** section was moved from the end of the PPI to the beginning of the PPI.
3. Under **Who should not take Amturnide?**, the following text was added/deleted:
 1.
 - ~~If you get pregnant, stop.~~ Stop taking Amturnide and call your doctor right away. If you plan to become pregnant, talk to your doctor about other treatment options for your high blood pressure.
 - have diabetes and are taking a kind of medicine called an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI).
 - have low or no urine output
 - are allergic to ~~any ingredients in Amturnide~~ aliskiren, hydrochlorothiazide, amlodipine or other medicines that contain sulfonamide. See the end of this leaflet for a complete list of ingredients in Amturnide.
4. Under **Before taking Amturnide, tell your doctor if you:**, the following text was added/deleted:
 - have a kidney problem ~~problems~~
 - have liver problems

- have signs of systemic lupus erythematosus (SLE). Amturnide can make your SLE active or worse.
- ~~have lupus~~
- have ever had an allergic reaction to another blood pressure medicine. Symptoms may include: swelling of the face, lips, tongue, throat, arms and legs, and trouble breathing (angioedema);
- ~~suffer from heart disorders or if you experienced a heart attack~~
- have any other medical problems
- are pregnant or planning to become pregnant. **See “What is the most important information I should know about Amturnide?”**
- are breastfeeding, breast-feeding. It is not known if Amturnide passes into your breast milk and if it can harm your baby. You and your doctor should decide if you will take Amturnide or breastfeed. You should not do both.

5. Under **Especially tell your doctor if you are taking:**, the following text was added/deleted:

- a kind of medicine to control blood pressure called angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI)
- medicines used to lower blood pressure, water pills (also called “diuretics”); especially potassium-sparing diuretics”)
- medicines for treating fungus or fungal infections (like itraconazole or ketoconazole)
- cyclosporine (Gengraf[®], Neoral, Sandimmune), a medicine used to suppress the immune system
- potassium-containing medicines, potassium supplements, or salt substitutes containing potassium
- cholesterol lowering medicines
 - simvastatin (Zocor[®]) or atorvastatin (Lipitor[®])
 - cholestyramine (Questran, Questran Light, Cholestyramine Light, Locholest Light, Locholest, Prevalite)
 - colestipol (Colestipol hydrochloride, Colestid, Flavored Colestid)
- medicines used to treat diabetes, including insulin
- lithium, a medicine used to treat some types of depression. ~~You should not take Amturnide if you are taking lithium.~~
- nonsteroidal anti-inflammatory drugs (NSAIDs) (like ibuprofen or naproxen), including selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors). ~~medicines.~~ Ask your doctor if you are not sure if you are taking one of these medicines.
- ~~sleeping pills and anti-seizure medicines called barbiturates~~
- medicines used to treat AIDS or HIV infections (such as ritonavir, indinavir)
- ~~narcotic pain medicines.~~

6. Under **What are the possible side effects of Amturnide?**, the following text was added/deleted:

- **Harm to an unborn baby causing injury or death. See “What is the most important information I should know about Amturnide?”**
- **Severe Allergic Reactions and Angioedema (hypersensitivity).** Aliskiren, one of the medicines in Amturnide, can cause difficulty breathing or swallowing, tightness of the chest, hives, general rash, swelling, itching, dizziness, vomiting, or abdominal pain (signs of a severe allergic reaction called anaphylactic reaction); Aliskiren can also cause swelling of your face, lips, tongue, throat, arms and legs, or the whole body (signs of angioedema). **Stop taking Amturnide and get medical help right away. Tell your doctor if you get any one or more of these symptoms.** Serious allergic reactions can happen at any time while you are taking Amturnide.
- **Low blood pressure (hypotension).** Your blood pressure may get too low if you also take water pills, are on a low-salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Drinking alcohol and taking certain medicines (barbiturates or narcotics)

can cause low blood pressure to get worse. Lie down if you feel faint or dizzy, and call your doctor right away.

- **Worsening chest pain or heart attack.** When you first start taking Amturnide or increase your dose, you may have a heart attack or your angina may get worse. If that happens, call your doctor right away or go directly to the nearest hospital emergency room.
- **Allergic reactions:** Hydrochlorothiazide, one of the medicines in Amturnide, can cause allergic reactions.
- **Active or Worsened Systemic Lupus Erythematosus (SLE), ~~Worsening of lupus.~~** One of the medicines in Amturnide may cause your lupus to become active or get worse. Tell your doctor if your lupus gets worse or becomes active while taking Amturnide.
- **Amturnide may affect your Low potassium levels level (hypokalemia).** Your doctor will do blood tests to check your potassium levels.
- **Eye problems.** One of the medicines in Amturnide can cause eye problems that may lead to vision loss. Symptoms of eye problems can happen within hours to weeks of starting Amturnide. Tell your doctor right away if you have:
 - decrease in vision
 - eye pain
- **Renal impairment or failure.** Aliskiren, one of the medicines in Amturnide, may cause renal disorder with symptoms such as severely decreased urine output or decreased urine output (signs of renal impairment or failure).

7. Under **The most common side effects of Amturnide include:**, the following text was added:

Less common side effects include rash, severe skin reactions (signs may include severe blistering of the lips, eyes or mouth, rash with fever and skin peeling) and liver disorder (signs may include nausea, loss of appetite, dark colored urine or yellowing of skin and eyes), stomach pain, nausea, flushing (hot or warm feeling in your face), arrhythmia (irregular heartbeat), heart palpitations (very fast heartbeat)

8. 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, 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, PharmD.
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
03/27/2015