DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021985/S-027

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 Tekturna (aliskiren) 150 mg and 300 mg tablets.

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

In the Package Insert:

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

   Contraindications (4) 03/2015

   ~~Warnings and Precautions (5.4) 11/2013~~

2. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following bullet was deleted and the information moved up into the first bullet:

   ~~• Itraconazole: Avoid concomitant use (7,12,3)~~

3. In **HIGHLIGHTS/CONTRAINDICATIONS**, the following text was added:

   Hypersensitivity to any of the components. (4)

4. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the following text was added/deleted:

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

- Hypotension: Correct imbalances in volume and/or salt depleted patients. ~~or with combined use of other agents acting on the RAAS: Correct imbalances before initiating therapy with Tekturna.~~ (5.4)

5. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following text was added/deleted:

   - Cyclosporine or Itraconazole: Avoid concomitant use. (5.7, ~~(~~7, 12.3)
   - Nonsteroidal Anti-Inflammatory Drugs (~~Itraconazole: Avoid concomitant use (7, 12.3)~~
   - NSAIDs) ~~use may lead to i~~Increased~~increased~~ risk of renal impairment and loss of antihypertensive effect. (7)

6. Under **DOSAGE AND ADMINISTRATION**, the following section was deleted:

   ~~**2.2 Use with Other Antihypertensives**~~

   ~~Tekturna may be administered with some other antihypertensive agents. In diabetics, do not use in combination with angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEIs) *[see Contraindications (4)]*. Concomitant use of aliskiren with an ARB or ACEI is not recommended in patients with a glomerular filtration rate (GFR <) less than 60 mlmL/min *[see Warnings and Precautions (5.2)]*. Most exposure to date is with diuretics, an angiotensin receptor blockerARB (valsartan) or a calcium channel blocker (amlodipine). Aliskiren used together with these drugs has a greater effect at their maximum recommended doses than either drug alone. It is not known whether additive effects are present when Tekturna is used with angiotensin converting enzyme inhibitors (ACEIs)ACEIs or beta blockers (BB).~~

7. Under **CONTRAINDICATIONS,** the following text was added:

   Do not use aliskiren with ARBs or ACEIs in patients with diabetes [see Warnings and Precautions (5.2) and~~),~~ Clinical Studies (14.3)].

   Tekturna is contraindicated in patients with known hypersensitivity to any of the components *[see Warnings and Precautions (5.3)]*.

8. Under **WARNINGS AND PRECAUTIONS,** the following text was added/deleted:

   5.2 Renal Impairment/Hyperkalemia/Hypotension when Tekturna is Given in Combination with ARBs or ACEIs

   Tekturna 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 less than 60 mL *[see Contraindications (4), Drug Interactions (7) and Clinical Studies (14.3)]*.

   ~~Avoid use of Tekturna with ARBs or ACEIs in patients with moderate renal impairment (GFR <60 ml/min).~~

9. Under **ADVERSE REACTIONS**, the following text was added:

6.1 Clinical Trials Experience

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

- Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Anaphylactic Reactions and Head and Neck Angioedema *[see Warnings and Precautions (5.3)]*
- Hypotension *[see Warnings and Precautions (5.4)]*

6.2 Postmarketing Experience

The following adverse reactions have been reported in aliskiren postmarketing ~~post marketing~~ experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: anaphylactic reactions and angioedema requiring airway management and hospitalization

Urticaria

Peripheral edema

Hepatic enzyme increase with clinical symptoms of hepatic dysfunction

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis

Pruritus

Erythema

Nausea Vomiting

10. Under **DRUG INTERACTIONS/Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS)~~renin-angiotensin-aldosterone system~~**, the following text was added:

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 creatinine clearance 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, 5.5, 5.6)]*.

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 **USE IN SPECIFIC POPULATIONS/Renal Impairment**, the following text was added/deleted:

    Safety and effectiveness of Tekturna in patients with severe renal impairment [creatinine clearance (CrCl) less than ~~(CrCL <~~30 mL~~ml~~/min]~~)~~ have not been established ~~as patients with eGFR less than 30ml/min~~ these patients were excluded in clinical trials *[see Clinical Studies (14)]*.

12. Under **CLINICAL PHARMACOLOGY**, **Figure 1** was updated with superscript ** after the words "ramipril, valsartan, and irbesartan" and the words "no dose adjustment" were deleted; the following text was added below the figure:

    *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)].*

13. Under **CLINICAL PHARMACOLOGY**, **Figure 2** was updated with superscript ** after the words "ramipril, valsartan, and irbesartan" and the words "no dose adjustment" were deleted; the following text was added below the figure:

    *Furosemide: Patients receiving furosemide could find its effects diminished after starting aliskiren. In patients with heart failure, coadministration ~~co-administration~~ of aliskiren (300 mg/day) reduced plasma AUC and C_{max} of oral furosemide (60 mg/day) by 17% and 27%, respectively, and reduced 24 hour urinary furosemide excretion by 29%. This change in exposure did not result in statistically significant difference in total urine volume and urinary sodium excretion over 24 hours. However, a transient decrease in urinary sodium excretion and urine volume effects up to 12 hours were observed when furosemide was coadministered ~~co-administered~~ with aliskiren 300 mg/day.

    **Ramipril, valsartan: 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)].*

14. Under **CLINICAL STUDIES/Aliskiren in Combination with Other Antihypertensives**, the following text was added to the paragraph below Table 2:

    Aliskiren 150 mg and 300 mg and valsartan 160 mg and 320 mg were studied alone and in combination in an 8-week, 1,797-patient, randomized, double-blind, placebo-controlled, parallel-group, 4-arm, dose-escalation study. The dosages of aliskiren and valsartan were started at 150 mg and 160 mg, respectively, and increased at 4~~four~~ weeks to 300 mg and 320 mg, respectively. Seated trough cuff blood pressure was measured at baseline, 4, and 8 weeks. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 3. In general, the

combination of aliskiren and angiotensin receptor blocker should be avoided *[see Contraindications (4), Warnings and Precautions (5), and Drug Interactions (7)]*.

15. Under **CLINICAL STUDIES/Aliskiren in Combination with Other Antihypertensives**, the following text was deleted from the paragraph below Table 4

ACE inhibitors

~~Aliskiren has not been studied when added to maximal doses of ACE inhibitors to determine whether aliskiren produces additional blood pressure reduction.~~

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

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

17. Under **PATIENT COUNSELING INFORMATION** the passive voice was deleted and active voice added to the entire section.

18. Editorial changes were made in the following sections: 1.1, 5.3, 5.4, 5.5, 5.6, 6.1, 6.2, 7, 8.1, 8.4, 8.6, 11, 12.1, 12.2, 12.3, 13.1, 13.2, 14.1, 14.2, and 14.3,

19. The revision date and version number were updated.

In the Tekturna PPI:

1. The following text was deleted:

~~FDA approved patient labeling~~

PATIENT INFORMATION
Tekturna (~~pronounced~~ ® (tek-turn-a)
(aliskiren)
Tablets

~~Dosing Strengths:~~
~~150 mg tablets~~
~~300 mg tablets~~
~~Available by Prescription Only~~

2. Under **Who Should Not Take Tekturna?**, the following text was added/deleted:

Do not take Tekturna if you:

- ~~If you~~ get pregnant, stop taking Tekturna 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.
- ~~If you~~ have diabetes and are taking a kind of medicine called an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI).

- ~~Do not take Tekturna if you~~ are allergic to any of its ingredients. See the end of this leaflet for a complete list of the ingredients in Tekturna.

3. Under **What Should I Tell My Doctor Before Taking Teturna**, the fifth and sixth bullets were revised:

- have ever had ~~a~~ an allergic reaction called angioedema, ~~to an ACE inhibitor~~another blood pressure, medicine. ~~Angioedema causes~~ Symptoms may include: swelling of the face, lips, tongue, throat, arms, and legs, and may cause difficulty breathing (angioedema).
- have any other medical problems

4. Under **Tell you doctor about all the medicines you take**, 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)
- ~~Atorvastatin (medicine~~ simvastatin (Zocor®) or atorvastatin (Lipitor®) (medicines to lower cholesterol in your blood).
- 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~~Cyclosporine (Gengraf®, Neoral, Sandimmune), (a medicine used to suppress the immune system).
- potassium-containing medicines, potassium supplements, or salt substitutes containing potassium.
- nonsteroidal anti-inflammatory drugs (NSAIDs) (like ibuprofen or naproxen), including selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors)

Ask your doctor if you are not sure whether you are taking one of the medicines listed above. Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine. Your doctor or pharmacist will know what medicines are safe to take together.

5. Under **What Are Possible Side Effects of Tekturna?**, the following text was added/deleted:

- **Harm to ~~Injury or death to~~ an unborn baby causing injury or death. See "What is the most important information I should know about Tekturna?"**
- ~~**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. Lie down if you feel faint or dizzy. Call your doctor right away.~~
- **Severe Allergic Reactions and Angioedema (hypersensitivity).** ~~.~~ Aliskiren may 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~~s~~).~~)~~. Aliskiren can also cause swelling of the face, lips, tongue, throat, arms and legs or the whole body (signs of angioedema). Stop taking Tekturna and get~~Get~~ medical help right away and tell your doctor if you

get any one or more of these symptoms. Angioedema can happen at any time while you are taking Tekturna.

- 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. Lie down if you feel faint or dizzy. Call your doctor right away.
- **Renal impairment or failure**. Aliskiren may cause renal disorder with symptoms such as severely decreased urine output or decreased urine output (signs of renal impairment or failure).

Common side effects of Tekturna include:

diarrhea
cough
dizziness
headache
flu-like symptoms
~~back pain~~
tiredness
high levels of potassium in the blood (hyperkalemia)

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).

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of Tekturna. For a complete list of side effects, ask your doctor or pharmacist**.**

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1--800--FDA--1088.

6. 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