DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022217/S-020

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Lily Chan, PharmD
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Chan:

Please refer to your Supplemental New Drug Application (sNDA) dated and received April 13, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Valturna (aliskiren/valsartan) 150/196 mg and 300/320 mg.

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

In Highlights:

1. Under **RECENT MAJOR CHANGES,** the following was added/~~deleted~~:

Contraindications: Patients with diabetes (4)	04/201
Boxed Warning: Fetal Toxicity	02/2012
~~Indications and Usage: Benefits of lowering blood pressure (1)~~	~~10/2011~~
Warnings and Precautions: Fetal Toxicity (5.1)	02/2012
Warning and Precautions (5.2, 5.4, 5.5, 5.8)	03/2012
~~Warnings and Precautions: Cyclosporine or Itraconazole (5.9)~~	~~04/2011~~

2. Under **INDICATIONS AND USAGE**, the following was deleted:

   Valturna is a combination of aliskiren, a renin inhibitor, and valsartan, an angiotensin II receptor blocker (ARB), indicated for the treatment of hypertension, to lower blood pressure.
   - ~~In patients not adequately controlled with monotherapy. (1)~~
   - ~~May be substituted for titrated components. (1)~~
   - ~~As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals. (1)~~

   Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

3. Under **CONTRAINDICATIONS,** the following was added/~~deleted~~:

   ~~None~~
   Do not use in patients with diabetes (4)

4. Under **WARNINGS AND PRECAUTIONS**, the following was added/~~deleted~~:

- ~~Avoid fetal and neonatal exposure. (5.1)~~
- Avoid use in patients with renal impairment (GFR<60 mL/min) (5.2)
- Head and neck angioedema: Discontinue Valturna and monitor until signs and symptoms resolve. (5.3~~2~~)
- Hypotension in volume- and/or salt-depleted patients: Correct imbalances before initiating therapy with Valturna. (5.4~~3~~)
- Impaired renal function: Monitor serum creatinine periodically. (5.5) ~~Patients with renal impairment: Decrease in renal function may be anticipated with susceptible individuals. (5.5)~~
- Patients with hepatic impairment: Slower clearance may occur. (5.6~~5~~)
- Hyperkalemia: ~~Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalance, particularly in patients at risk~~Monitor potassium levels periodically. (5.8) (b) (4)

5. Under **DRUG INTERACTIONS**, the following was ~~deleted~~:

~~**Aliskiren:**~~
• Cyclosporine: Avoid concomitant use (7, 12.3)
• Itraconazole: Avoid concomitant use (7, 12.3)
• NSAIDS use may lead to increased risk of renal impairment and loss of antihypertensive effect (7)
~~**Valsartan**~~
• If simvastatin is co-administered with amlodipine, do not exceed doses greater than 20 mg daily of simvastatin (7)

~~Aliskiren and Valsartan:~~
- NSAID use may lead to increased risk of renal impairment and loss of antihypertensive effect (7)

In Full Prescribing Information:

1. Under **DOSAGE AND ADMINISTRATION**, the following text was ~~deleted~~:

~~2.6 Use with Other Antihypertensives~~
~~Valturna may be administered with other antihypertensive agents. There are no data available with use of Valturna with angiotensin-converting enzyme inhibitors or other renin-angiotensin-aldosterone blockers.~~

~~**2.8 Dosing in Specific Populations**~~
~~*Renal Impairment*~~
~~Adjustment of the starting dose is not required in patients with mild to moderate renal impairment. Clinical experience with dosing Valturna in patients with moderate renal impairment is limited. No data are available in patients with severe renal impairment *[see Warnings and Precautions (5.5)]*.~~

~~*Hepatic Impairment*~~
~~Adjustment of the starting dose is not necessary with mild or moderate hepatic impairment. Valturna in patients with severe hepatic impairment is limited *[see Warnings and Precautions (5.5)]*.~~

~~*Elderly Patients*~~
~~Adjustment of the starting dose is not required for elderly patients.~~

2. Under **CONTRAINDICATIONS**, the following text was added/~~deleted~~:

Do not use in patients with diabetes *[see Warnings (5.2), Clinical Trials (14.2)]*.~~None.~~

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

5.2 Renal Impairment/Hyperkalemia/Hypotension when Valturna is given in combination with ARBs or ACEI

Valturna is contraindicated in patients with diabetes because of the increased risk of renal impairment, hyperkalemia, and hypotension *[see Contraindications (4) and Clinical Trials (14.2)]*.

Avoid use of Valturna in patients with moderate renal impairment (GFR <60 ml/min).

5.4~~3~~ Hypotension
~~An excessive fall in blood pressure (hypotension) was rarely seen (<0.5%) in patients with uncomplicated hypertension treated with Valturna in controlled trials.~~

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. Correct these conditions prior to administration of Valturna, or the treatment should start under close medical supervision.
Initiate therapy cautiously in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

I~~f an excessive fall in blood pressure occurs, place the patient in the supine position and, if necessary, given an intravenous infusion of normal saline.~~ A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.5~~4~~ ~~Patients with Severe Renal Impairment~~Impaired Renal Function

~~*Valturna*~~

~~Patients with severe renal impairment were excluded from clinical trials with Valturna in hypertension.~~ Monitor renal function periodically in patients treated with Valturna. Changes in renal function, including acute renal failure, can be caused by drugs that affect the renin-angiotensin system. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, severe heart failure, post-myocardial infarction or volume depletion) or non-steroidal anti-inflammatory (NSAID) therapy may be at particular risk for developing acute renal failure on Valturna *[see*

Contraindications (4), Warnings (5.2), Clinical Trials (14.2)]. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function.

~~*Aliskiren*~~
~~Patients with severe renal dysfunction (creatinine 1.7 mg/dL for women and 2.0 mg/dL for men and/or estimated GFR <30 mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of aliskiren in hypertension. Safety information with aliskiren and the potential for other drugs acting on the renin-angiotensin-aldosterone system to increase serum creatinine and blood urea nitrogen are not available.~~

~~*Valsartan*~~
~~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. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.~~

~~As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may occur particularly in volume depleted patients. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia and (rarely) with acute renal failure or death. Similar outcomes have been reported with valsartan.~~

5.8 Serum Electrolyte Abnormalities

~~*Valturna*~~

Monitor serum potassium periodically in patients receiving Valturna. Drugs that affect the renin-angiotensin system can cause hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes *[see Contraindications (4), Warnings (5.2), and Clinical Trials (14.2)]*, NSAIDs, potassium supplements or potassium sparing diuretics.

In the short-term controlled trials of various doses of Valturna, in patients without renal insufficiency the incidence of hyperkalemia (serum potassium >5.5 mEq/L) was about 1%-2% higher in the combination treatment group compared with the monotherapies aliskiren and valsartan, or with placebo.

In a long-term, uncontrolled study with median treatment duration of about one year, about 4% of the patients had at least one serum potassium >5.5 mEq/L at some time during the study; about 0.8% of patients discontinued study treatment and had a high serum potassium at some point during the study. Patients with hyperkalemia were older (median age 65 vs. 55) with slightly lower mean baseline estimated creatinine clearance compared to patients without hyperkalemia. While about 25% of the hyperkalemic episodes occurred in the first two months, other initial episodes were reported throughout the study.

~~Periodic determinations of serum electrolytes to detect possible electrolyte imbalances is advised, particularly in patients at risk for hyperkalemia such as those with renal impairment.~~

~~Caution is advised with concomitant use of Valturna with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium.~~

~~5.8 Renal Artery Stenosis~~

~~*Aliskiren*~~
~~No data are available on the use of Valturna or aliskiren in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.~~

~~*Valsartan*~~
~~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. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.~~

4. Under **ADVERSE REACTIONS**, the following text was added/~~deleted~~:

6.1 Clinical Trials Experience

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

- Risk of fetal/neonatal morbidity and mortality *[See Warnings and Precautions (5.1)]*.
- Head and neck angioedema *[See Warnings and Precautions (~~5.2~~5.3)]*.
- Hypotension *[See Warnings and Precautions (~~5.3~~5.4)]*.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Valturna

Valturna has been evaluated for safety in more than 1,225 patients, including over 316 patients for over 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event (including uncontrolled hypertension) occurred in 1.4% of patients treated with Valturna versus 2.7% of patients given placebo.

Adverse events in placebo-controlled trials that occurred in at least 1% of patients treated with Valturna and at a higher incidence than placebo included fatigue (2.6% vs. 1.4%), nasopharyngitis (2.6% vs. 2.2%), diarrhea (1.4% vs 0.9%), upper respiratory tract infection (1.4% vs. 1.1%), urinary tract infection (1.4% vs. 0.6%), influenza (1.1% vs 0.2%), and vertigo (1.1% vs. 0.3%).

~~Hyperkalemia has been observed as a serum electrolyte abnormality in Valturna clinical trials *[see Warning and Precautions (5.7)].*~~

Aliskiren

Aliskiren has been evaluated for safety in 6,460 patients, including 1,740 treated for longer than 6 months, and 1,250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event, including uncontrolled

hypertension occurred in 2.2% of patients treated with aliskiren, versus 3.5% of patients given placebo. These data do not include information from the ALTITUDE study which evaluated the use of aliskiren in combination with ARBs or ACEI *[see Contraindications (4), Warnings (5.2), and Clinical Trials (14.2)].*

Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%.

In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation.

In the placebo-controlled studies, however, the incidence of edema involving the face, hands, or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long-term active-controlled study with aliskiren and HCTZ arms, the incidence of edema involving the face, hands, or whole body was 0.4% in both treatment arms.

Aliskiren produces dose-related gastrointestinal (GI) adverse reactions. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg similar to those seen at 300 mg for men or younger patients (all rates about 2%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use vs. 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Other adverse reactions with increased rates for aliskiren compared to placebo included rash (1% vs. 0.3%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One patient had predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures; for the other patient, EEG and imaging results were not reported. Aliskiren was discontinued and there was no rechallenge in either case.

~~The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dizziness, fatigue, upper respiratory tract infection, back pain and cough.~~

No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with aliskiren.

Clinical Laboratory Test Abnormalities

Blood Urea Nitrogen (BUN)/Creatinine:

~~Elevations~~In patients without renal dysfunction, elevations in BUN (>40 mg/dL) and creatinine (>2.0 mg/dL) in any treatment group were less than 1.0%. For creatinine, 0.5% (3/599) of patients on combination treatment had a creatinine level >1.5 mg/dL at the end of

the study and a 30% increase from baseline compared to none in either monotherapy or placebo *[see Warnings* (5.2)*]*.

~~*Serum Electrolytes: [See Warnings and Precautions (5.7)]*~~

6.2 Post-Marketing Experience

~~*Blood creatinine increased*~~

5. Under **DRUG INTERACTIONS**, the following text was added/~~deleted~~:

Aliskiren

Cyclosporine: Avoid co-administration of cyclosporine with aliskiren.

Itraconazole: Avoid co-administration of itraconazole with aliskiren *[see Clinical Pharmacology (12.3).]*

Non-Steroidal Anti-Inflammatory Agents (NSAIDS) including selective Cyclooxygenase 2 inhibitors (COX-2 inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors with agents that affect ~~acting on~~ the renin-angiotensin system, including aliskiren, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving aliskiren and NSAID therapy.

The antihypertensive effect of [redacted] (b) (4) may be attenuated by NSAIDS~~s~~.

6. Under **USE IN SPECIFIC POPULATIONS**, the following text was added:

8.6 Renal impairment
Safety and effectiveness of aliskiren in patients with severe renal impairment (CrC1 ≤ 30 mL/min) have not been established as patients with eGFR <30ml/min were excluded in clinical trials *[see Clinical Trials (14)].*

7. Under **CLINICAL STUDIES**, the following text was added:

14.2 Aliskiren in Patients with Diabetes treated with ARB or ACEI (ALTITUDE study)
Patients with diabetes with renal disease (defined either by the presence of albuminuria or reduced GFR) were randomized to aliskiren 300 mg daily (n=4283) or placebo (n=4296). All patients were receiving background therapy with an ARB or ACEI. The primary efficacy outcome was the time to the first event of the primary composite endpoint consisting of cardiovascular death, resuscitated sudden death, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure, onset of end stage renal disease, renal death, and doubling of serum creatinine concentration from baseline sustained for at least one month. After a median follow up of about 27 months, the trial was terminated early for lack of efficacy. Higher risk of renal impairment, hypotension and hyperkalemia was observed in aliskiren compared to placebo treated patients, as shown in the table below.

Table5. Incidence of selected adverse events in ALTITUDE

	Aliskiren N=4283		Placebo N=4296	
	Serious Adverse Events* (%)	Adverse Events (%)	Serious Adverse Events* (%)	Adverse Events(%)
Renal impairment †	4.7	12.4	3.3	10.4
Hypotension ††	2.0	18.6	1.7	14.8
Hyperkalemia †††	1.1	36.9	0.3	27.1

† renal failure, renal failure acute, renal failure chronic, renal impairment

†† dizziness, dizziness postural, hypotension, orthostatic hypotension, presyncope, syncope

††† Given the variable baseline potassium levels of patients with renal insufficiency on dual RAAS therapy, the reporting of adverse event of hyperkalemia was at the discretion of the investigator.

* A Serious Adverse Event (SAE) is defined as: an event which is fatal or life-threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, requires inpatient hospitalization or prolongation of existing hospitalization, or is medically significant (i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes previously listed).

The risk of stroke (2.7% aliskiren vs 2.0% placebo) and death (6.9% aliskiren vs. 6.4% placebo) were also numerically higher in aliskiren treated patients.

The following changes were made to the Patient Package Insert (PPI):

1. Under **Who should not take Valturna?**, the following text was added:

   - **If you have diabetes.**

2. Under **Tell your doctor about all the medicines you take:,** the following text was added/~~deleted~~:

   - a kind of medicine called angiotensin receptor blocker or angiotensin converting enzyme inhibitor
   - ~~other medicines for high blood pressure or a heart problem.~~

3. Under **The most common side effects of Valturna include:,** the following bullet was added:

   Common side effects of Valturna include:
   - high levels of potassium in the blood (hyperkalemia)

4. The Table of Contents was updated to reflect the recent changes.
5. In **CLINICAL PHARMACOLOGY/Pharmacokinetics**, several of the cross references were updated from *[see Dosage and administration]* to *[see Warnings and Precautions]*, to reflect the new information.
6. Various sections were updated to reflect the addition/deletion of information.

7. 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.

We note that you have voluntarily ceased the marketing of Valturna Tablets. We remind you, per our agreement that you are not to re-initiate marketing of Valturna without holding discussions with the Division of Cardiovascular and Renal Products.

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
04/25/2012