DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021985 / S-008 **SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation
Attention: Lily Chan, PharmD
Associate Director
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Chan:

Please refer to your supplemental new drug application dated May 11, 2009, received May 11, 2009, submitted under section 505(b)1 of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tekturna (aliskiren) tablets.

This "Prior Approval" supplemental new drug application provides for revision to the labeling of Tekturna in accordance with FDA's issuance of the Physician's Labeling Rule and the following content changes:

In **HIGHLIGHTS**, **Boxed Warning,** revise to read:

> When pregnancy is detected, discontinue Tekturna as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Under **WARNINGS AND PRECAUTIONS,** ***Fetal/neonatal mobidity and mortality***

> Add:
>
> > If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Under **WARNINGS AND PRECAUTIONS,** ***Impaired Renal Function*** the following sentence was added:

> Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances particularly in patients with severe renal impairment.

Under **WARNINGS AND PRECAUTIONS**

From:

5.2 Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with Tekturna®. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in black than in non-black patients, but whether angioedema rates are higher in blacks with Tekturna® is not known. Tekturna® should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred.

Experience with ACE inhibitors indicates that even in those instances where only swelling of the tongue is seen initially without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Very rarely, fatalities have been reported in patients with angioedema associated with laryngeal edema or tongue edema with ACE inhibitors. Patients with involvement of the tongue, glottis or larynx are more likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and measures necessary to ensure a patent airway, should be promptly provided. [See Adverse Reactions (6.1)]

To:

5.2 Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with Tekturna and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACE inhibitors or angiotensin receptor antagonists. If angioedema involves the throat, tongue, glottis or larynx, or if the patient has a history of upper respiratory surgery, airway obstruction may occur and be fatal. Patients who experience these effects, even without respiratory distress, require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Prompt administration of subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 ml) and measures to ensure a patient airway may be necessary.

Discontinue Tekturna immediately in patients who develop angioedema, and do not readminister.

Under **ADVERSE REACTIONS,** ***Clinical Studies Experience***

Add:

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.

Under **DRUG INTERACTIONS,** ***Effects of Aliskiren on Other Drugs***

Revise and add:

Furosemide: When aliskiren was coadministered with furosemide, the AUC and C_{max} of furosemide were reduced by about 30% and 50%, respectively. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Under **USE IN SPECIFIC POPULATIONS,** ***Pregnancy***

Add:

When pregnancy is detected, Tekturna® should be discontinued as soon as possible.

Under **USE IN SPECIFIC POPULATIONS,** ***Pediatric Use***

Revised and add:

Safety and effectiveness of aliskiren in pediatric patients <18 years have not been established.

Under **CLINICAL STUDIES,** ***Aliskiren in Combination with Other Antihypertensives***

Change the header ***Diuretics*** to ***Hydrochlorothiazide***.

Under **PATIENT COUNSELING INFORMATION,** ***Information for Patients***

Add:

Symptomatic Hypotension: A patient receiving Tekturna should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, Tekturna should be discontinued until the physician has been consulted.

All patients should be cautioned 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.

Potassium Supplements: A patient receiving Tekturna should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Relationship to Meals: Patients should establish a routine pattern for taking Tekturna with regard to meals. High-fat meals decrease absorption substantially.

Under **PATIENT COUNSELING INFORMATION,** ***FDA Approved Patient Labeling***

Under **What Is Tekturna?**

Revise and add:

Tekturna can help your blood vessels relax and reduce and widen so blood pressure is lower. Tekturna is a type of prescription medicine called a direct renin inhibitor. By reducing renin, it helps to reduce blood pressure.

Under **What Is High Blood Pressure?**

Add:

Drugs that lower blood pressure lower your risk of having a stroke or heart attack.

Under **Who Should Not Take Tekturna?**

Revise and add:

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.

Under **What Are Possible Side Effects Of Tekturna?**

Add:

- **Angioedema**: Aliskiren can cause swelling of the face, lips, tongue, throat, arms and legs or the whole body. 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.

Common side effects of Tekturna include:

diarrhea
cough
dizziness
headache
flu-like symptoms

back pain
tiredness

Less common side effects include rash.

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**.**

Under **How Do I Store Tekturna?**

Revise and add:

Medicines are sometimes prescribed for condition not listed in the patient information leaflet. Do not take Tekturna for a condition for which is was not prescribed. Do not give Tekturna to other people, even if they have the same condition or symptoms you have. It may harm them.

This leaflet summarizes the most important information about Tekturna. If you have more questions about Tekturna talk with your doctor. You can ask your doctor or pharmacist for information that is written for healthcare professionals.

Under **PATIENT INFORMATION,** ***What Should I Tell My Doctor Before Taking Tekturna?***

Tell your doctor about all your medical conditions, including whether you:

Added:

Have ever had a reaction called angioedema, to an ACE inhibitor medicine. Angioedema causes swelling of the face, lips, tongue, throat, arms, and legs, and may cause difficulty breathing.

Tell your doctor about all the medicines you take

Added:

Atorvastatin (medicine to lower cholesterol in your blood)

Under **PATIENT INFORMATION,** ***What Are Possible Side Effects Of Tekturna?***

Added:

Injury or death to an unborn baby. See **IMPORTANT WARNING**

Under **PATIENT INFORMATION,** ***How Should I Take Tekturna?***

The second bullet was changed:

From:

> Tekturna can be taken by itself or safely in combination with other medicines to lower high blood pressure. It can also be safely taken in combination with medications for other conditions such as high cholesterol or diabetes. Your doctor may change your dose if needed.

To:

> Tekturna can be taken by itself or safely in combination with other medicines to lower high blood pressure. Your doctor may change your dose if needed.

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

Please resubmit the enclosed content of labeling in SPL format as soon as possible, but no later than 14 days from the date of this letter. For administrative purposes, please designate this submission, "SPL for approved NDA 021985 / S-008."

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

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 Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director

Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Agreed upon labeling text

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21985	SUPPL-8	NOVARTIS PHARMACEUTICALS CORP	TEKTURNA

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
11/10/2009