DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020758/S-070

SUPPLEMENT APPROVAL

Sanofi-aventis U.S. LLC
Attention: John Cook
Director, US Regulatory Affairs Marketed Products
55 Corporate Drive
Mailstop 55C-205A
Bridgewater, NJ 08807

Dear Mr. Cook:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 12, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Avalide (irbesartan/hydrochlorothiazide) 150/12.5 mg and 300/25 mg Tablets.

This supplemental new drug application provides for revisions to the package insert as follows (additions are shown as underlined text and deletions are shown as ~~strikethrough~~ text):

1. Under **WARNINGS AND PRECAUTIONS/Electrolyte and Metabolic Imbalances**, the following text was added as the second paragraph:

   Irbesartan-Hydrochlorothiazide
   In double-blind clinical trials of various doses of irbesartan and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 7.5% versus 6.0% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was <1.0% versus 1.7% for placebo. No patient discontinued due to increases or decreases in serum potassium. On average, the combination of irbesartan and hydrochlorothiazide had no effect on serum potassium. Higher doses of irbesartan ameliorated the hypokalemic response to hydrochlorothiazide.

   ~~Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium. Concurrent therapy with hydrochlorothiazide may reduce the frequency of this effect.~~

   Coadministration of AVALIDE with potassium sparing diuretics, potassium supplements, potassium-containing salt substitutes or other drugs that raise serum potassium levels may result hyperkalemia, sometimes severe. Monitor serum potassium in such patients.

2. Under **ADVERSE REACTIONS/Post-Marketing Experience** the following terms were added/deleted to/from the second and fifth paragraphs:

The following have been very rarely reported: urticaria, angioedema (involving swelling of the face, lips, pharynx, and/or tongue), ~~and~~ hepatitis and tinnitus. Hyperkalemia has been rarely reported.

Cases of increased CPK ~~and rhabdomyolysis~~ have been reported in patients receiving angiotensin II receptor blockers.

3. Under **DRUG INTERACTIONS**, the section was revised to read:

~~Irbesartan~~

7.1 Non-Steroidal Anti-Inflammatory Agents Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

Irbesartan

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including irbesartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The antihypertensive effect of ARBs may be attenuated by NSAIDs. Therefore, ~~M~~monitor renal function and blood pressure periodically in patients receiving irbesartan and NSAID therapy.

~~The antihypertensive effect of angiotensin II receptor antagonists, including irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.~~

Hydrochlorothiazide

Administration of a non-steroidal anti-inflammatory agent, including a selective COX-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when AVALIDE (irbesartan-hydrochlorothiazide) Tablets and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

7.2 Dual Blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on AVALIDE and other agents that affect the RAS.

In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors.

Do not coadminister aliskiren with AVALIDE in patients with diabetes. Avoid use of aliskiren with AVALIDE in patients with renal impairment (GFR <60 mL/min).

7.3 Agents Increasing Serum Potassium

Coadministration of AVALIDE with other drugs that raise serum potassium levels may result in hyperkalemia, sometimes severe. Monitor serum potassium in such patients.

~~*Hydrochlorothiazide*~~

~~When administered concurrently the following drugs may interact with thiazide diuretics: Alcohol, Barbiturates, or Narcotics: potentiation of orthostatic hypotension may occur.~~

7.4 Antidiabetic Drugs (oral agents and insulin)~~:~~

D~~d~~osage adjustment of the antidiabetic drug may be required when coadministered with hydrochlorothiazide.

~~Other Antihypertensive Drugs: additive effect or potentiation.~~

7.~~6~~5 Cholestyramine and Colestipol Resins:

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Stagger the dosage of hydrochlorothiazide and the resin such that AVALIDE is administered at least 4 hours before or 4 to 6 hours after the administration of the resin.~~Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively. Take AVALIDE should be taken at least one hour before or four hours after these medications.~~

~~**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 relaxant.~~

7.~~10~~6 Lithium:

Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of irbesartan or thiazide diuretics. Monitor lithium levels in patients receiving Avalide and lithium.

~~**7.11 Non-steroidal Anti-inflammatory Drugs**:~~
~~In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when AVALIDE (irbesartan-hydrochlorothiazide) Tablets and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.~~

7.~~12~~7 Carbamazepine:

Concomitant use of carbamazepine and hydrochlorothiazide has been associated with the risk of symptomatic hyponatremia. Monitor electrolytes ~~should be monitored~~ during concomitant use.

4. Under **CLINICAL PHARMACOLOGY/Pharmacodynamics**, the following text was added:

Drug Interactions

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

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

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.

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

~~**17.1 Pregnancy**~~
Tell ~~F~~female patients of childbearing age ~~should be told~~ about the consequences of exposure to AVALIDE during pregnancy. Discuss treatment options with women planning to become pregnant. Ask ~~P~~patients ~~should be asked~~ to report pregnancies to their physician as soon as possible.

~~**17.2 Symptomatic Hypotension**~~
Tell ~~P~~patients using AVALIDE ~~should be told~~ that they may feel lightheaded, especially during the first days of use. Tell patients ~~should~~ to inform their physician if they feel lightheaded or faint. Tell the patient, i~~I~~f fainting occurs, ~~the patient should~~ stop using AVALIDE and contact the prescribing doctor.

Tell ~~P~~patients using AVALIDE ~~should be told~~ that getting dehydrated can lower their blood pressure too much and lead to lightheadedness and possible fainting. Dehydration may occur with excessive sweating, diarrhea, or vomiting and with not drinking enough liquids.

Potassium Supplements
Advise patients not to use potassium supplements or salt substitutes containing potassium without consulting their healthcare provider. *[see Drug Interactions (7.3)]*.

Acute myopia and secondary angle-closure glaucoma
Advise patients to discontinue AVALIDE and seek immediate medical attention if they experience symptoms of Acute Myopia or Secondary Angle-Closure Glaucoma *[see Warnings and Precautions (5.8)]*.

6. Multiple editorial revisions were made throughout the label (cross references were re-formatted, the Drug Interactions section was numbered, numbers were deleted from the Information for Patients sub-sections).

7. The revision date was updated.

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

APPROVAL & LABELING

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 that includes labeling changes 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
Office of Prescription Drug Promotion (OPDP)
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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, RAC
Regulatory Project Manager for Safety
(301) 301 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
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
02/05/2016