DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020758/S-060

SUPPLEMENT APPROVAL

Sanofi-Aventis c/o Bristol-Myers Squibb Company
Attention: Charles D. Wolleben
Group Director, Global Regulatory Sciences
5 Research Parkway
Wallingford, CT 06492

Dear Mr. Wolleben:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 1, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Avalide (irbesartan/hydrochlorothiazide) 150/12.5 mg, 300/12.5 mg, 300/25 mg.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows:

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, a statement reflecting the changes made to the **WARNINGS AND PRECAUTIONS** section of the package insert was added.

2. In **HIGHLIGHTS/DOSAGE AND ADMINISTRATION**, the following text was deleted from the third and fourth bullets respectively:

    - Not controlled on monotherapy.
    - Initial therapy: Initiate with 150/12.5 mg once daily for 1 to 2 weeks and titrate as needed up to a maximum of 300/25 mg once daily. (2.4)

3. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the following text was deleted from the first, second, and third bullets respectively:

    - Symptomatic hypotension with intravascular volume or sodium depletion. Not recommended as initial therapy in volume depleted patients (2.4)
    - Impaired hepatic function: Thiazides should be used with caution as minor fluid and electrolyte imbalances may precipitate hepatic coma. (5.7)
    - Use with caution. Oliguria or azotemia with acute renal failure and/or death has been reported in medications affecting the renin angiotensin system.

4. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following bullets were deleted:

    - Alcohol, Barbituates, Narcotics: Potentiation of orthostatic hypotension
    - Corticosteroids, ACTH: Hypokalemia, electrolyte imbalance

5. In **HIGHLIGHTS/DRUG INTERACTIONS**, the fourth bullet was revised from:

- NSAIDs: Can reduce diuretic, natriuretic, and antihypertensive effects of diuretics. Observe patient closely.

To:

- NSAIDs: Can reduce diuretic, natriuretic, and antihypertensive effects of diuretics and increase risk for renal impairment

6. In **HIGHLIGHTS/DRUG INTERACTIONS**, a seventh bullet was added:

    - Carbamazine: Increased risk of hyponatremia.

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

    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.

8. Under **WARNINGS AND PRECAUTIONS/Electrolyte and Metabolic Imbalances**/*Hydrochlorothiazide*, the section was changed from:

    Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps,
    muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

    Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

    Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

    Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

    Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.
In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

To:

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

9. Under **ADVERSE REACTIONS/Post-Marketing Experience**, the following text was added as the fourth paragraph:

Impaired renal function, including cases of renal failure in patients at risk, has been reported with irbesartan and AVALIDE.

10. Under **ADVERSE REACTIONS/Post-Marketing Experience**, the following text was changed from:

    Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

To:

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

11. Under **DRUG INTERACTIONS**/ *Cholestyramine and Colestipol Resins,* the following text was added to the end of the paragraph:

    AVALIDE should be taken at least one hour before or four hours after these medications.

12. Under **DRUG INTERACTIONS**, a new section was added:

    Carbamazepine: concomitant use of carbamazepine and hydrochlorothiazide has been associated with the risk of symptomatic hyponatremia. Electrolytes should be monitored during concomitant use.

13. The revision date and version number were updated.

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, 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
02/09/2012