



NDA 020758/S-058  
NDA 020758/S-59

## SUPPLEMENT APPROVAL

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

Dear Dr. Wollenben:

Please refer to your Supplemental New Drug Applications (sNDAs) dated February 14, and April 4, 2011, and received February 14 and April 4, 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, and 300/25 mg Tablets.

These "Changes Being Effected" supplemental new drug applications provide for labeling revised as follows:

### For S058:

1. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, a fifth bullet was added:
  - Acute myopia and secondary angle-closure glaucoma. (5.9)
2. Under **WARNINGS**, the following section was added:

#### **5.9 Acute Myopia and Secondary Angle-Closure Glaucoma**

Sulfonamide or sulfonamide derivative drugs, such as hydrochlorothiazide, can cause an idiosyncratic reaction, resulting in transient myopia and acute angle-closure glaucoma. Cases of acute angle-closure glaucoma have been reported with hydrochlorothiazide. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

**For S-059:**

1. Under **HIGHLIGHTS/DRUG INTERACTIONS**, the following was added:

Irbesartan(7)

- NSAIDs and selective COX-2 inhibitors: May lead to increased risks of renal impairment and loss of antihypertensive effect. Monitor renal function periodically.

2. Under **DRUG INTERACTIONS/Irbesartan**, the first sentence of the first paragraph was changed from:

No significant drug-drug interactions have been reported with irbesartan. [*See Clinical Pharmacology (12.3).*]

To:

No significant drug-drug interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, and nifedipine. [*See Clinical Pharmacology (12.3).*]

3. Under **DRUG INTERACTIONS/Irbesartan**, the following paragraph was added:

*Non-Steroidal Anti-Inflammatory Agents 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 angiotensin II receptor antagonists, including irbesartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function 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.

4. The version number and revision date were updated.

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

We have completed our review of these supplemental applications, and they are 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 Effectuated” (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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
06/06/2011