



NDA 020758/S-067

**SUPPLEMENT APPROVAL**

Sanofi-aventis U.S. LLC  
Attention: Payal Patel, PharmD.  
Manager, U.S. Regulatory Affairs Marketed Products  
55 Corporate Drive  
Mailstop: 55C-205A  
Bridgewater, NJ 08807

Dear Dr. Patel:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 14, 2014, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Avalide (irbesartan/hydrochlorothiazide) 75/12.5 mg and 150/12.5 mg.

We also refer to our May 28, 2014 Approval letter, which had an incorrect label attached. A sentence under the Drug Interactions section was inadvertently deleted during labeling negotiations. This replacement letter incorporates the correction of the error. The effective approval date will remain May 28, 2014, the date of the original approval letter.

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

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following text was deleted:

~~Warnings And Precautions, Fetal Toxicity (5.1) ————— 1/2012~~  
~~Warnings And Precautions, Electrolyte And Metabolic Imbalances (5.6) ————— 2/2012~~

2. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following language was added/deleted:

- Lithium: ~~Reduced renal clearance and high risk of lithium toxicity when used with diuretics. Should not be given with diuretics.~~ Increased risk of lithium toxicity. Monitor serum lithium concentrations during concurrent use.

3. Under **WARNINGS AND PRECAUTIONS**, the following section was deleted:

~~**5.5 — Lithium Interaction**  
Hydrochlorothiazide  
Lithium generally should not be given with thiazides. [See Drug Interactions (7).]~~

4. Under **DRUG INTERACTIONS**, the following language was added/deleted:

*Irbesartan*  
~~No significant drug-drug pharmacokinetic (or pharmacodynamic) interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, and nifedipine [see Clinical Pharmacology (12.3)].~~  
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 Avapro and lithium.

5. Under **DRUG INTERACTIONS/Dual Blockade of the Renin-Angiotensin System (RAS)**, the following text was added as the second paragraph:

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

6. 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.

### **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, PharmD.  
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  
05/28/2014