DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 16273/S-061

SUPPLEMENT APPROVAL

Debra Wiel
Sanofi-Aventis
55 Corporate Drive
P.O. Box 5925
Bridgewater, NJ 08807-0890

Dear Ms. Wiel:

Please refer to your supplemental new drug application (sNDA) dated December 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lasix (furosemide) Tablets.

We acknowledge receipt of your amendments dated January 13 and September 22, 2010.

The September 22, 2010, submission constituted a complete response to our June 18, 2009, action letter.

This "Changes Being Effected" supplemental new drug application provides for revisions as follows:

1. Under **WARNINGS**, a 3rd paragraph was revised so that it reads:

   Cases of tinnitus and reversible or irreversible hearing impairment and deafness have been reported. Reports usually indicate that Lasix ototoxicity is associated with rapid injection, severe renal impairment, the use of higher than recommended doses, hypoproteinemia or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid, or other ototoxic drugs. If the physician elects to use high dose parenteral therapy, controlled intravenous infusion is advisable (for adults, an infusion rate not exceeding 4 mg Lasix per minute has been used). (See **PRECAUTIONS, Drug Interactions**).

2. Under **PRECAUTIONS, General**, the last two sentences of the first paragraph were changed from:

   Hypokalemia may develop with Lasix, especially with brisk diuresis, inadequate oral electrolyte intake, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Digitalis therapy may exaggerate metabolic effects of hypokalemia, especially myocardial effects.

To read:

   Hypokalemia may develop with Lasix, especially with brisk diuresis, inadequate oral electrolyte intake, when cirrhosis is present, or during concomitant use of corticosteroids,

ACTH, licorice in large amounts, or prolonged use of laxatives. Digitalis therapy may exaggerate metabolic effects of hypokalemia, especially myocardial effects.

3. Under **PRECAUTIONS, General**, three additional paragraphs were added to the middle of this section. These new paragraphs read as follows:

   In patients with severe symptoms of urinary retention (because of bladder emptying disorders, prostatic hyperplasia, urethral narrowing), the administration of furosemide can cause acute urinary retention related to increased production and retention of urine. Thus, these patients require careful monitoring, especially during the initial stages of treatment.

   In patients at high risk for radiocontrast nephropathy, Lasix can lead to a higher incidence of deterioration in renal function after receiving radiocontrast compared to high-risk patients who received only intravenous hydration prior to receiving radiocontrast.

   In patients with hypoproteinemia (*e.g.,* associated with nephrotic syndrome) the effect of Lasix may be weakened and its ototoxicity potentiated.

4. Under **PRECAUTIONS, Laboratory Tests**, a paragraph was added to the end that reads:

   In premature infants Lasix may precipitate nephrocalcinosis/nephrolithiasis, therefore renal function must be monitored and renal ultrasonography performed (see **PRECAUTIONS, Pediatric Use**).

5. The entire **PRECAUTIONS, Drug Interactions** section was revised to read:

   Lasix may increase the ototoxic potential of aminoglycoside antibiotics, especially in the presence of impaired renal function. Except in life-threatening situations, avoid this combination.

   Lasix should not be used concomitantly with ethacrynic acid because of the possibility of ototoxicity. Patients receiving high doses of salicylates concomitantly with Lasix, as in rheumatic disease, may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

   There is a risk of ototoxic effects if cisplatin and Lasix are given concomitantly. In addition, nephrotoxicity of nephrotoxic drugs such as cisplatin may be enhanced if Lasix is not given in lower doses and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

   Lasix has a tendency to antagonize the skeletal muscle relaxing effect of tubocurarine and may potentiate the action of succinylcholine.

   Lithium generally should not be given with diuretics because they reduce lithium's renal clearance and add a high risk of lithium toxicity.

Lasix combined with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers may lead to severe hypotension and deterioration in renal function, including renal failure. An interruption or reduction in the dosage of Lasix, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers may be necessary.

Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Lasix may decrease arterial responsiveness to norepinephrine. However, norepinephrine may still be used effectively.

Simultaneous administration of sucralfate and Lasix tablets may reduce the natriuretic and antihypertensive effects of Lasix. Patients receiving both drugs should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix is achieved. The intake of Lasix and sucralfate should be separated by at least two hours.

In isolated cases, intravenous administration of Lasix within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure, and tachycardia. Use of Lasix concomitantly with chloral hydrate is therefore not recommended.

Phenytoin interferes directly with renal action of Lasix. There is evidence that treatment with phenytoin leads to decrease intestinal absorption of Lasix, and consequently to lower peak serum furosemide concentrations.

Methotrexate and other drugs that, like Lasix, undergo significant renal tubular secretion may reduce the effect of Lasix. Conversely, Lasix may decrease renal elimination of other drugs that undergo tubular secretion. High-dose treatment of both Lasix and these other drugs may result in elevated serum levels of these drugs and may potentiate their toxicity as well as the toxicity of Lasix.

Lasix can increase the risk of cephalosporin-induced nephrotoxicity even in the setting of minor or transient renal impairment.

Concomitant use of cyclosporine and Lasix is associated with increased risk of gouty arthritis secondary to Lasix-induced hyperurecemia and cyclosporine impairment of renal urate excretion.

One study in six subjects demonstrated that the combination of furosemide and acetylsalicylic acid temporarily reduced creatinine clearance in patients with chronic renal insufficiency. There are case reports of patients who developed increased BUN, serum creatinine and serum potassium levels, and weight gain when furosemide was used in conjunction with NSAIDs.

Literature reports indicate that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients by inhibiting prostaglandin synthesis. Indomethacin may also affect plasma renin levels, aldosterone excretion, and renin profile evaluation. Patients receiving both indomethacin and Lasix should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix is achieved.

6. Under **PRECAUTIONS, Pregnancy,** a second paragraph was added that reads:

   Treatment during pregnancy requires monitoring of fetal growth because of the potential for higher fetal birth weights.

7. Under **PRECAUTIONS, Nursing Mothers**, a sentence was added that reads:

   Lasix may inhibit lactation.

8. A new **PRECAUTIONS, Pediatric Use** section was added that reads:

   In premature infants Lasix may precipitate nephrocalcinosis/nephrolithiasis. Nephrocalcinosis/nephrolithiasis has also been observed in children under 4 years of age with no history of prematurity who have been treated chronically with Lasix. Monitor renal function, and renal ultrasonography should be considered, in pediatric patients receiving Lasix.

   If Lasix is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

9. Under **ADVERSE REACTIONS, Gastrointestinal System Reactions**, "increased liver enzymes" was added as the new #4 and the subsection was re-ordered.

10. Under **ADVERSE REACTIONS, Systemic Hypersensitivity Reactions**, "severe anaphylactic or anaphylactoid reactions (*e.g.*, with shock)" was added to the top of the list and the subsection was re-ordered.

11. Under **ADVERSE REACTIONS, Hematologic Reactions**, "eosinophilia" was added to the end of the list and the word "rare" was deleted.

12. Under **ADVERSE REACTIONS, Dermatologic Hypersensitivity Reactions**, Stevens-Johnson Syndrome and toxic epidermal necrolysis were added.

13. Under **ADVERSE REACTIONS, Cardiovascular Reactions**, "Increase in cholesterol and triglyceride serum levels" was added at the end of the list.

14. The underlining from the **DOSAGE AND ADMINSTRATION** and **HOW SUPPLIED** section headers was removed.

We have completed our review of this supplemental application, as amended. 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, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 pending "Changes Being Effected" (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.

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.(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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to 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, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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, M.S.
Regulatory Health Project Manager
(301) 796-1952

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 I
Center for Drug Evaluation and Research

Enclosure:
Agreed-upon labeling text

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
10/18/2010