DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 11-287/ S-018

Sanofi- Synthelabo, Inc.
Attention: Mr. Kenneth Palmer
90 Park Avenue
New York, NY 10016

Dear Mr. Palmer:

Please refer to your supplemental new drug application dated March 12, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kayexalate (sodium polystyrene sulfonate, USP) Powder.

We acknowledge receipt of your submissions dated September 17 and October 3, 2003.

Your submission dated October 3, 2003 constituted a complete response to our approvable letter dated September 9, 2003.

This supplemental new drug application provides for final printed labeling with the following changes:

1. Under the CONTRAINDICATIONS section, additional contraindications were added to read:

   Kayexalate is contraindicated in the following conditions: patients with hypokalemia, patients with a history of hypersensitivity to polystyrene sulfonate resins, obstructive bowel disease, neonates with reduced gut motility (postoperatively or drug induced) and oral administration in neonates (see PRECAUTIONS).

2. Under the PRECAUTIONS section, the following paragraph was deleted:

   If constipation occurs, patients should be treated with sorbitol (from 10 mL to 20 mL of 70 percent syrup every two hours or as needed to produce one or two watery stools daily), a measure which also reduces any tendency to fecal impaction.

   The following paragraph was added:

   In the event of clinically significant constipation, treatment with KAYEXALATE should be discontinued until normal bowel motion is resumed. Magnesium-containing laxatives or sorbitol should not be used (see PRECAUTIONS, Drug Interactions).

3. Under the PRECAUTIONS, Drug Interactions section, the following subsections were added:

   - The second paragraph under the "Antacids" sub-section was split-out and titled as a new subsection:
     Non-absorbable cation-donating antacids and laxatives:
   - Sorbitol: Concomitant use of Sorbitol with KAYEXALATE has been implicated in cases of colonic necrosis. Therefore, concomitant administration is not recommended.
   - Lithium: KAYEXALATE may decrease absorption of lithium.
   - Thyroxine: KAYEXALATE may decrease absorption of thyroxine.

4. A Pediatric Use section was added under PRECAUTIONS as follows:

   Pediatric Use
   The effectiveness of KAYEXALATE in pediatric patients has not been established. In neonates, KAYEXALATE should not be given by the oral route. In both children and neonates, particular care should be observed with rectal administration, as excessive dosage or inadequate dilution could result in impaction of the resin.

   Due to the risk of digestive hemorrhage or colonic necrosis, particular care should be observed in premature infants or low birth weight infants.

5. Under the ADVERSE REACTIONS section:

   - The statements, "and their related clinical manifestations" and "(see WARNINGS)" were added to the second sentence in the first paragraph to read:

     Also, hypokalemia, hypocalcemia and significant sodium retention, and their related clinical manifestations, may occur (see WARNINGS).

   - The fifth sentence, "This effect may be obviated through usage of the resin in enemas as described under DOSAGE AND ADMINISTRATION," was deleted from the first paragraph.

   - The following text was added to the end of the section:

     The following events have been reported from worldwide post marketing experience:
     - fecal impaction following rectal administration, particularly in children;
     - gastrointestinal concretions (bezoars) following oral administration;
     - gastrointestinal tract ulceration or necrosis which could lead to intestinal perforation; and,
     - rare cases of acute bronchitis and/or broncho-pneumonia associated with inhalation of particles of polystyrene sulfonate.

6. An **OVERDOSAGE** section was added as follows:

   OVERDOSAGE
   Biochemical disturbances resulting from overdosage may give rise to clinical signs and symptoms of hypokalemia, including: irritability, confusion, delayed thought processes, muscle weakness, hyporeflexia, which may progress to frank paralysis and/or apnea.

Electrocardiographic changes may be consistent with hypokalemia or hypercalcemia; cardiac arrhythmias may occur. Appropriate measures should be taken to correct serum electrolytes (potassium, calcium), and the resin should be removed from the alimentary tract by appropriate use of laxatives or enemas.

7. Under the **DOSAGE AND ADMINISTRATION** section**,** fourth paragraph, the sentence "Sorbitol may be administered in order to combat constipation" was deleted.

We have completed our review of this supplemental new drug application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on October 3, 2003.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office for Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doug Throckmorton

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