



NDA 18-557/S-015

Hoffmann-La Roche Inc.  
Attn: Ms. Lynn DeVenezia-Tobias  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Ms. DeVenezia-Tobias:

Please refer to your supplemental new drug application dated July 27, 1999, received July 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fansidar® (sulfadoxine and pyrimethamine) 500 mg/25 mg Tablets.

We acknowledge receipt of your submission dated May 13, 2003.

Your submission of November 14, 2003 constituted a complete response to our April 30, 2003 action letter.

This supplemental new drug application provides for the following revisions to the package insert (additions are double underlined and deletions are ~~strikethrough~~):

1. The **CLINICAL PHARMACOLOGY** section was revised to read:

**Microbiology:**

**Mechanism of Action:** Sulfadoxine and pyrimethamine, the constituents of Fansidar, are folic acid antagonists. Sulfadoxine inhibits the activity of dihydropteroate synthase whereas pyrimethamine inhibits dihydrofolate reductase.

**Activity *in vitro*:** Sulfadoxine and pyrimethamine are active against the asexual erythrocytic stages of *Plasmodium falciparum*. Fansidar may also be effective against strains of *P. falciparum* resistant to chloroquine.

**Drug Resistance:** Strains of *P. falciparum* with decreased susceptibility to sulfadoxine and/or pyrimethamine can be selected *in vitro* or *in vivo*. *P. falciparum* malaria that is clinically resistant to Fansidar occurs frequently in parts of Southeast Asia and South America, and is also prevalent in East and Central Africa. Therefore, Fansidar should be used with caution in these areas. Likewise, Fansidar may not be effective for treatment of recrudescing malaria that develops after prior therapy (or prophylaxis) with Fansidar.

Fansidar is an antimalarial agent which acts on the asexual intraerythrocytic forms of the human malaria parasites. By synergistic action of the two components, sulfadoxine

~~and pyrimethamine, two enzymes involved in the biosynthesis of folinic acid in the parasites are inhibited.~~

~~Fansidar is also effective against strains of *P. falciparum* resistant to chloroquine. However, in parts of South-East Asia and South America, *P. falciparum* malaria clinically resistant to Fansidar is frequent and also occurs in East and Central Africa. Therefore, Fansidar should be used with caution in these areas.~~

2. The *Metabolism* subsection of the **PHARMACOKINETICS** section was revised to read:

About 5% of sulfadoxine appears in the ~~blood~~ plasma as acetylated metabolite, about 2 to 3% as the glucuronide. Pyrimethamine is transformed to several unidentified metabolites.

3. The **INDICATIONS AND USAGE** section was revised to read:

Treatment of acute malaria: Fansidar is indicated for the treatment of acute, uncomplicated *P. falciparum* malaria for those patients in whom chloroquine resistance is suspected. However, strains of *P. falciparum* (see Microbiology) may be encountered which have developed resistance to Fansidar, in which case alternative treatment should be administered.

~~Fansidar is indicated for the treatment of *P. falciparum* malaria for those patients in whom chloroquine resistance is suspected.~~

Prevention of Malaria: Malaria prophylaxis with Fansidar is not routinely recommended and should only be considered for travelers to areas where chloroquine-resistant *P. falciparum* malaria is endemic and sensitive to Fansidar, and when alternative drugs are not available or are contraindicated (see CONTRAINDICATIONS). However, strains of *P. falciparum* may be encountered which have developed resistance to Fansidar.

4. The **CONTRAINDICATIONS** section was revised to read:

- Repeated prophylactic (prolonged) use of Fansidar is contraindicated in patients with renal or hepatic failure or with blood dyscrasias;
- Hypersensitivity to pyrimethamine, or sulfonamides, or any other ingredient of Fansidar;
- Patients with documented megaloblastic anemia due to folate deficiency;
- Infants less than 2 months of age;
- Prophylactic use of Fansidar in pregnancy at term and during the nursing period because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus.

5. The **PRECAUTIONS** section was revised as follows:

- a. The numbers (1-9) preceding each subsection were removed.
- b. The following paragraph was added to the beginning of the *General* subsection:

Oral Fansidar has not been evaluated for the treatment of cerebral malaria or other severe manifestations of complicated malaria, including hyperparasitemia, pulmonary edema or renal failure. Patients with severe, malaria are not candidates for oral therapy. In the event of recrudescence of *P. falciparum* infections after treatment with Fansidar or failure of chemoprophylaxis with Fansidar, patients should be treated with a different blood schizonticide.

- c. The last sentence of the *General* subsection was revised to read:

Excessive sun exposure should be avoided. Excessive exposure to the sun must be strictly avoided.

- d. The following bullets were added to the *Information for the Patient* subsection, and ordered as follows:

Patients also should be advised:

- That malaria can be a life-threatening infection in the traveler;
- That Fansidar is being prescribed to help prevent or treat this serious infection;
- That no chemoprophylactic regimen is 100% effective and protective clothing, insect repellents, and bednets are important components of malaria prophylaxis;
- To seek medical attention for any febrile illness that occurs after return from a malarious area and inform their physician that they may have been exposed to malaria;
- That in a small percentage of cases, patients are unable to take this medication because of side effects, and it may be necessary to change medications;
- That when used as prophylaxis, the first dose of Fansidar should be taken 1 or 2 days prior to arrival in an endemic area;
- That if the patient experiences any symptom that may affect the patient's ability to take this drug as prescribed, the physician should be contacted and alternative antimalarial medication should be considered.

- d. The *Laboratory Tests* subsection was revised to read:

Regularly scheduled complete blood counts, and liver enzyme tests and analysis of urine for crystalluria should be performed whenever Fansidar is administered for more than three months.

- e. The last sentence in the second paragraph of the *Drug Interactions* subsection was revised to read:

When recovery of depressed platelets or white blood cell counts in patients with drug-induced folic acid deficiency is too slow, folinic acid (leucovorin) may be administered in doses of 5 –15 mg intramuscularly daily for 3 days or longer. Folinic acid (leucovorin) may be administered in doses of 5 mg to 15 mg intramuscularly daily, for 3 days or longer, for depressed platelet or white blood

~~cell counts in patients with drug-induced folic acid deficiency when recovery is too slow.~~

6. The **ADVERSE REACTIONS** section was revised as follows:

a. The *Skin and Miscellaneous Sites Reactions* subsection should be renamed *Skin and Miscellaneous Sites Allergic Reactions*:

b. The *Respiratory Reactions* subsection should be revised to read:

Pulmonary infiltrates resembling eosinophilic or allergic alveolitis.

c. The following subsection should be added before *Miscellaneous Reactions*:

*Genitourinary: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, and crystalluria.*

d. The *Miscellaneous Reactions* subsection should be revised to read:

Drug fever, chills, ~~and toxic nephrosis with oliguria and anuria~~ periarthritis nodosa and LE phenomenon have occurred.

7. The **DOSAGE AND ADMINISTRATION** section was revised to read:

*The ~~dosage tablets~~ should be swallowed whole, and not chewed, with plenty of fluids after a meal.*

(a) *Treatment of Acute Malaria*

Adults \_\_\_\_\_ 2 to 3 tablets taken as a single dose.

Pediatric patients \_\_\_\_\_ The dosage for treatment of malaria in  
(2 months-18 years) \_\_\_\_\_ children is based upon body weight:

<u>Weight (Kg)</u>	<u>Number of tablets taken as a single dose</u>
<u>&gt;45</u>	<u>3</u>
<u>31-45</u>	<u>2</u>
<u>21-30</u>	<u>1 ½</u>
<u>11-20</u>	<u>1</u>
<u>5-10</u>	<u>½</u>

~~A single dose of the following number of Fansidar Tablets is used in sequence with quinine or alone:~~

~~Adults \_\_\_\_\_ 2 to 3 tablets~~  
~~9 to 14 years \_\_\_\_\_ 2 tablets~~

4 to 8 years	1 tablet
Under 4 years	1/2 tablet

*(b) Treatment of Complicated Malaria*

Standard treatment of severe or cerebral malaria consists of quinine over 7 to 10 days. The therapy with quinine is conveniently reduced to 2 to 3 days by adding a single dose of Fansidar after quinine therapy. Furthermore, sequential quinine and Fansidar therapy effectively prevents relapses which are common with quinine monotherapy.

e) (b) *Prevention of Malaria*

The malaria risk must be carefully weighed against the risk of serious adverse drug reactions (see INDICATIONS and USAGE). If Fansidar is prescribed for prophylaxis, it is important that the physician inquires about sulfonamide intolerance and points out the risk and the need for immediate drug withdrawal if skin reactions do occur.

The first dose of Fansidar should be taken 1 or 2 days before arrival in an endemic area; administration should be continued during the stay and for 4 to 6 weeks after return.

	<u>Once Weekly</u>	<u>Once Every 2 Weeks</u>
Adults	1 tablet	2 tablets
9 to 14 years	3/4 tablet	1 1/2 tablets
4 to 8 years	1/2 tablet	1 tablet
Under 4 years	1/4 tablet	1/2 tablet

Pediatric patients                      The dosage for prevention of malaria  
(>2 months-18 years) in children is based upon body weight:

<u>Weight (Kg)</u>	<u>Number of Tablets Taken Once Weekly</u>
<u>&gt;45</u>	<u>1 1/2</u>
<u>31-45</u>	<u>1</u>
<u>21-30</u>	<u>3/4</u>
<u>11-20</u>	<u>1/2</u>
<u>5-10</u>	<u>1/4</u>

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text (enclosed).

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission

should be designated "FPL for approved supplement NDA 18-557/S-015." Approval of this submission by FDA is not required before the labeling is used.

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 reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kristen Miller, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and  
Immunologic Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/

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Renata Albrecht  
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