CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-557 / S -015

Trade Name: Fansidar

Generic Name: (sulfadoxine and pyrimethamine)

Sponsor: Hoffman-La Roche Inc.

Approval Date: April 30, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-557 / S -015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-557 / S -015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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 recrudescent 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 recrudescent *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~~ periarteritis 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 (2 months-18 years)	The dosage for treatment of malaria in children is based upon body weight:

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

~~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 — ½ 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.~~

~~c)~~ (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.

	Once Weekly	Once Every 2 Weeks
Adults	1 tablet	2 tablets
~~9 to 14 years~~	~~3/4 tablet~~	~~11/2 tablets~~
~~4 to 8 years~~	~~1/2 tablet~~	~~1 tablet~~
~~Under 4 years~~	~~1/4 tablet~~	~~1/2 tablet~~

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

Weight (Kg)	Number of Tablets Taken Once Weekly
≥45	1 ½
31-45	1
21-30	¾
11-20	½
5-10	1/4

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

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

/s/

Renata Albrecht
2/26/04 07:52:27 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-557 / S -015

APPROVABLE LETTER (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-557/S-015

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

Dear Ms. DeVeñezia-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 submissions dated September 6, 2000, and November 8, 2000.

This supplemental new drug application provides for the following changes:

1. Revisions to multiple sections consistent with the worldwide safety information available on this product.

2. Addition of statements in the *Information for the Patient* subsection of **PRECAUTIONS** regarding malaria prophylaxis.

We completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, you must submit draft labeling revised as follows. Added text is noted by double underline and deleted text is noted by ~~strikethrough~~:

1. The **CLINICAL PHARMACOLOGY** section should be 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 recrudescent 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 should be 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 should be 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 should be revised to read:

[ ]

5. The **PRECAUTIONS** section should be revised as follows:

   a. Remove the numbers (1-9) preceding each subsection.

   b. The following paragraph should be added to the beginning of the *General* subsection:

   [ ]

   c. The last sentence of the *General* subsection should be revised to read:

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

   d.

   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 should be 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 should be 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 should be 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:

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:

7. The **DOSAGE AND ADMINISTRATION** section should be 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 (2 months-18 years)	The dosage for treatment of malaria in children is based upon body weight:

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

~~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 — ½ 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.~~

~~c)~~ *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.

	Once Weekly	Once Every 2 Weeks
Adults	1 tablet	2 tablets
~~9 to 14 years~~	~~3/4 tablet~~	~~11/2 tablets~~
~~4 to 8 years~~	~~1/2 tablet~~	~~1 tablet~~
~~Under 4 years~~	~~1/4 tablet~~	~~1/2 tablet~~

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

Weight (Kg)	Number of Tablets Taken Once Weekly
>45	1 ½
31-45	1
21-30	¾
11-20	½
5-10	1/4

In addition, all previous revisions as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

If you have any questions, call Kristen Miller, 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

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

/s/

Renata Albrecht
4/30/03 02:31:43 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-557 / S -015

APPROVED LABELING

Roche

FANSIDAR®

brand of

sulfadoxine and pyrimethamine

TABLETS

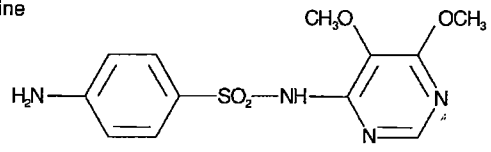
R_x only

WARNING: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF FANSIDAR HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS. FANSIDAR PROPHYLAXIS MUST BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH, IF A SIGNIFICANT REDUCTION IN THE COUNT OF ANY FORMED BLOOD ELEMENTS IS NOTED, OR UPON THE OCCURRENCE OF ACTIVE BACTERIAL OR FUNGAL INFECTIONS.

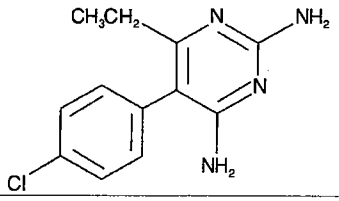
DESCRIPTION

Fansidar is an antimalarial agent, each tablet containing 500 mg N^1-(5,6-dimethoxy-4-pyrimidinyl) sulfanilamide (sulfadoxine) and 25 mg 2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine (pyrimethamine). Each tablet also contains cornstarch, gelatin, lactose, magnesium stearate and talc.

Sulfadoxine



Pyrimethamine



FANSIDAR® (sulfadoxine and pyrimethamine)

CLINICAL PHARMACOLOGY

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 recrudescent malaria that develops after prior therapy (or prophylaxis) with Fansidar.

PHARMACOKINETICS

Absorption

After administration of 1 tablet, peak plasma levels for pyrimethamine (approximately 0.2 mg/L) and for sulfadoxine (approximately 60 mg/L) are reached after about 4 hours.

Distribution

The volume of distribution for sulfadoxine and pyrimethamine is 0.14 L/kg and 2.3 L/kg, respectively.

Patients taking 1 tablet a week (recommended adult dose for malaria prophylaxis) can be expected to have mean steady state plasma concentrations of about 0.15 mg/L for pyrimethamine after about four weeks and about 98 mg/L for sulfadoxine after about seven weeks. Plasma protein binding is about 90% for both pyrimethamine and sulfadoxine. Both pyrimethamine and sulfadoxine cross the placental barrier and pass into breast milk.

Metabolism

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

Elimination

A relatively long elimination half-life is characteristic of both components. The mean values are about 100 hours for pyrimethamine and about 200 hours for sulfadoxine. Both pyrimethamine and sulfadoxine are eliminated mainly via the kidneys.

Characteristics in Patients

In malaria patients, single pharmacokinetic parameters may differ from those in healthy subjects, depending on the population concerned. In patients with renal insufficiency, delayed elimination of the components of Fansidar must be anticipated.

INDICATIONS AND USAGE

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 **CLINICAL PHARMACOLOGY: Microbiology**) may be encountered which have developed resistance to Fansidar, in which case alternative treatment should be administered.

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.

CONTRAINDICATIONS

- Repeated prophylactic use of Fansidar is contraindicated in patients with renal or hepatic failure or with blood dyscrasias;
- Hypersensitivity to pyrimethamine, 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.

FANSIDAR® (sulfadoxine and pyrimethamine)

WARNINGS

FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF FANSIDAR HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS. FANSIDAR PROPHYLAXIS MUST BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH, IF A SIGNIFICANT REDUCTION IN THE COUNT OF ANY FORMED BLOOD ELEMENTS IS NOTED, OR UPON THE OCCURRENCE OF ACTIVE BACTERIAL OR FUNGAL INFECTIONS.

Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Fansidar prophylactic regimen has been reported to cause leukopenia during a treatment of 2 months or longer. This leukopenia is generally mild and reversible.

PRECAUTIONS

General

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 recrudescent *P. falciparum* infections after treatment with Fansidar or failure of chemoprophylaxis with Fansidar, patients should be treated with a different blood schizonticide.

Fansidar should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. As with some sulfonamide drugs, in glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. Urinalysis with microscopic examination and renal function tests should be performed during therapy of those patients who have impaired renal function. Excessive sun exposure should be avoided.

Information for the Patient

Patients should be warned that at the first appearance of a skin rash, they should stop use of Fansidar and seek medical attention immediately. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation.

Patients should also be warned that the appearance of sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura, jaundice or glossitis may be early indications of serious disorders which require prophylactic treatment to be stopped and medical treatment to be sought.

Females should be cautioned against becoming pregnant and should not breastfeed their infants during Fansidar therapy or prophylactic treatment.

Patients should be warned to keep Fansidar out of reach of children.

Patients also should be advised:

- that malaria can be a life-threatening infection;
- 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.

Laboratory Tests

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

Drug Interactions

There have been reports which may indicate an increase in incidence and severity of adverse reactions when chloroquine is used with Fansidar as compared to the use of Fansidar alone. Fansidar is compatible with quinine and with antibiotics. However, antifolic drugs such as sulfonamides, trimethoprim, or trimethoprim-sulfamethoxazole combinations should not be used while the patient is receiving Fansidar for antimalarial prophylaxis. Fansidar has not been reported to interfere with antidiabetic agents.

If signs of folic acid deficiency develop, Fansidar should be discontinued. 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Pyrimethamine was not found carcinogenic in female mice or in male and female rats. The carcinogenic potential of pyrimethamine in male mice could not be assessed from the study because of markedly reduced life-span. Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totaling 200 mg to 300 mg. Pyrimethamine was not found mutagenic in the Ames test. Testicular changes have been observed in rats treated with 105 mg/kg/day of Fansidar and with 15 mg/kg/day of pyrimethamine alone. Fertility of male rats and the ability of male or female rats to mate were not adversely affected at dosages of up to 210

mg/kg/day of Fansidar. The pregnancy rate of female rats was not affected following their treatment with 10.5 mg/kg/day, but was significantly reduced at dosages of 31.5 mg/kg/day or higher, a dosage approximately 30 times the weekly human prophylactic dose or higher.

Pregnancy

Teratogenic Effects: Pregnancy Category C. Fansidar has been shown to be teratogenic in rats when given in weekly doses approximately 12 times the weekly human prophylactic dose. Teratology studies with pyrimethamine plus sulfadoxine (1:20) in rats showed the minimum oral teratogenic dose to be approximately 0.9 mg/kg pyrimethamine plus 18 mg/kg sulfadoxine. In rabbits, no teratogenic effects were noted at oral doses as high as 20 mg/kg pyrimethamine plus 400 mg/kg sulfadoxine.

There are no adequate and well-controlled studies in pregnant women. However, due to the teratogenic effect shown in animals and because pyrimethamine plus sulfadoxine may interfere with folic acid metabolism, Fansidar therapy should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential who are traveling to areas where malaria is endemic should be warned against becoming pregnant, and should be advised to practice contraception during prophylaxis with Fansidar and for three months after the last dose.

Nonteratogenic Effects

See **CONTRAINDICATIONS.**

Nursing Mothers

See **CONTRAINDICATIONS.**

Pediatric Use

Fansidar should not be given to infants less than 2 months of age because of inadequate development of the glucuronide-forming enzyme system.

Geriatric Use

Clinical studies of Fansidar did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

FANSIDAR® (sulfadoxine and pyrimethamine)

ADVERSE REACTIONS

For completeness, all major reactions to sulfonamides and to pyrimethamine are included below, even though they may not have been reported with Fansidar (see **WARNINGS** and **PRECAUTIONS: Information for the Patient**).

Hematological Changes

Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, methemoglobinemia, and eosinophilia.

Skin and Miscellaneous Sites Allergic Reactions

Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, toxic epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia, allergic myocarditis, slight hair loss, Lyell's syndrome, and allergic pericarditis.

Gastrointestinal Reactions

Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pancreatitis, feeling of fullness, and transient rise of liver enzymes.

Central Nervous System Reactions

Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness, nervousness, and polyneuritis.

Respiratory Reactions

Pulmonary infiltrates resembling eosinophilic or allergic alveolitis.

Genitourinary

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

Miscellaneous Reactions

Drug fever, chills, periarteritis nodosa and LE phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

FANSIDAR® (sulfadoxine and pyrimethamine)

OVERDOSAGE

Acute intoxication may be manifested by headache, nausea, anorexia, vomiting and central nervous system stimulation (including convulsions), followed by megaloblastic anemia, leukopenia, thrombocytopenia, glossitis and crystalluria. In acute intoxication, emesis and gastric lavage followed by purges may be of benefit. The patient should be adequately hydrated to prevent renal damage. The renal, hepatic, and hematopoietic systems should be monitored for at least 1 month after an overdosage. If the patient is having convulsions, the use of parenteral diazepam or a barbiturate is indicated. For depressed platelet or white blood cell counts, folinic acid (leucovorin) should be administered in a dosage of 5 mg to 15 mg intramuscularly daily for 3 days or longer.

DOSAGE AND ADMINISTRATION (See INDICATIONS AND USAGE)

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

Treatment of Acute Malaria

Adults	2 to 3 tablets taken as a single dose.
Pediatric patients (>2 months to 18 years)	The dosage for treatment of malaria in children is based upon body weight:

Weight (kg)	Number of Tablets Taken as a Single Dose
>45	3
31 to 45	2
21 to 30	1 ½
11 to 20	1
5 to 10	½

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.

FANSIDAR® (sulfadoxine and pyrimethamine)

	Once Weekly	Once Every 2 Weeks
Adults	1 tablet	2 tablets

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

Weight (kg)	Number of Tablets Taken Once Weekly
>45	1 ½
31 to 45	1
21 to 30	¾
11 to 20	½
5 to 10	¼

Prophylaxis with Fansidar should not be continued for more than two years, since no experience of more prolonged administration is available to date.

HOW SUPPLIED

Scored tablets, containing 500 mg sulfadoxine and 25 mg pyrimethamine — unit dose packages of 25 (NDC-0004-0161-03). Imprint on tablets: FANSIDAR ((ROCHE LOGO)) ROCHE.

Manufactured by:
F. Hoffmann-La Roche Ltd.
Basel, Switzerland

Distributed by:

Roche **Pharmaceuticals**

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

XXXXXXXX

Revised: XXXX XXXX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-557 / S -015

MEDICAL REVIEW

Medical Officer's Review
Of Labeling Supplement: (Serial Number SLR 015) to NDA No. 18,557
Fansidar® (sulfadoxine and pyrimethamine) tablets
for the treatment treatment and prophylaxis of *P. falciparum* malaria

Date Submitted:	7/27/99
Date Received:	7/28/99
Date Assigned:	7/29/99
Date Completed	8/30/99 **updated 4/30/03 (see addendum at end of review)**

SPONSOR: Hoffman – La Roche Pharmaceuticals Corporation
340 Kingsland Street
Nutley, NJ 07110-1199
(973)-562-5539
Contact person: Lynn DeVenecia-Tobias
Program Manager
Drug Regulatory Affairs
973-562-5539

DRUG IDENTIFICATION: Fansidar® (500 mg sulfadoxine, 25 mg pyrimethamine) oral antimalarial tablet

RELATED IND/NDA: —

MATERIAL REVIEWED: NDA 18, 557, SLR 015
Lariam® (NDA 19,591,mefloquine hydrochloride), Daraprim® (NDA 78,578, pyrimethamine) and Malarone® (NDA 21,078, atovaquone-proguanil) final printed labels

SUBMISSIONS RECEIVED:

18-557 SLR 015 Revised draft labeling

This labeling supplement contains package insert revisions consistent with the worldwide safety information available for the drug Fansidar® (sulfadoxine-pyrimethamine), as well as new statements in the Information for Patient subsection of PRECAUTIONS. The latter revisions are in accordance with the Agency's suggested label changes relevant to malaria prophylaxis, incorporated in the NDA 19-591, Mefloquine hydrochloride (Lariam®) Tablets.

The submission consisted of one jacket that contained the annotated draft label, a normal text version of the proposed label, and 11 annotated references that serve as basis for the proposed labeling revisions. The references consist of a 1995 Roche Drug Safety core report that reviews the worldwide adverse events associated with Fansidar® for the last 20 years (1974-1994), World Health and USP reports, AHFS drug information and 6 published articles. No new clinical trial information accompanied this submission.

REVIEW METHOD, CONTENT AND ORGANIZATION:

This review will summarize key features of the proposed label, the basis for the proposals and a final recommendation. The proposed changes to the label were reviewed in the sequence they appear in the label.

The basis for the proposed change was reviewed by examining

a) the information provided in the annotated references (attached to the draft label, provided at the end of the review as Attachment 1
b) additional relevant literature, generated from a Medline search on Fansidar® worldwide resistance, pharmacokinetics, safety and efficacy in pregnancy and pediatrics.

c) To augment the data from the 1995 sponsor report, the FDA AERS safety database was also queried (Attachment 2) regarding the drug's safe use in pregnancy, the incidence of crystalluria, photosensitivity, and hepatic toxicity.

d) Finally, the currently approved labels for mefloquine (Lariam®), pyrimethamine (Daraprim®) and atovaquone-proguanil (Malarone®) were reviewed to provide perspective, and assure consistency in labeling of antimalarials.

Medical Officer comments are limited to substantive, non-editorial changes proposed by the sponsor and precede the FDA-revised version of the label. Sections of the label will be CAPITALIZED, subsections underlined and Medical Officer comments will be *italicized.* The CLINICAL PHARMACOLOGY sections, separately reviewed by Houda Mahayni and Shukal Bala, summarizes their recommendations in the relevant section of the label.

BACKGROUND AND REGULATORY HISTORY:

Fansidar®, (sulfadoxine 500mg and pyrimethamine 25 mg per tablet) was approved in March 1981, as single dose treatment of Chloroquine-resistant *P. falciparum* malaria due to susceptible strains of plasmodia. The drug is likewise approved for prophylaxis using a weekly or biweekly regimen. Dosing recommendations for curative treatment of malaria in children are based on age, including dose recommendations for children below a year of age.

Since Fansidar® was approved in 1981, several other drugs have been approved for the treatment of *P. falciparum* malaria. These include Mefloquine (1989), IV Quinidine (1991), Halofantrine (1992) and most recently Malarone (atovaquone-proguanil, 2000). Additionally, Mefloquine and Malarone have been approved for prophylaxis.

Current resistance to Fansidar® appears to vary significantly by geographic location (see Table 1). Despite the known emergence of resistance to the drug, Fansidar® remains on the antimalarial formulary of many countries in Africa. The sponsor's database confirms that worldwide sales for the drug in malaria endemic countries continues to rise, whereas in industrialized countries, the use of the drug has declined following the introduction of mefloquine. Although Fansidar® is not currently listed by the Centers for Disease Control as a prophylactic option for travel to malaria endemic countries, it is recommended for presumptive treatment of malaria in travelers. (CDC Health Information for International Travel 1996-97, Table 14 a and b, updated 07/25/2002, URL: http://www.cdc.gov/travel /yellowbk/page128.htm)

REVIEW OF PROPOSED CHANGES:

1. CLINICAL PHARMACOLOGY:

Medical Officer's Comments: This section of the label needs to be organized in accordance with current antimalarial labels, into two subsections: Microbiology and Pharmacokinetics.

A. MICROBIOLOGY:

Medical Officer comments: Dr. Shukal Bala further suggests that the Microbiology subsection be organized into these subheadings: Mechanism of Action, Activity in Vitro and Drug Resistance. The following text incorporates her recommended changes:

FDA Revised Draft

"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 *P. falciparum.* Fansidar® is 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 vivo or in vitro.

B. PHARMACOKINETICS:

Medical Officer comments: Please refer also to the Biopharmaceutical Review by Houda Mahayni, PhD. This section of the label has been revised extensively. In format, it resembles the labels of mefloquine and atovaquone proguanil. The data, cited from published literature as well as a report of sponsors internal research, as presented in this section appears to be accurate, although largely supported by studies on the pharmacokinetics of I

Except for a report on the pharmacokinetics of Fansidar® in children with non-severe malaria (Winstanley et al 1992. Br. J Clin Pharmac 33:143-148.The disposition of oral and intramuscular pyrimthemine/sulfadoxine in Kenyan children with high parasitemia but clinically non-severe Falciparum malaria.), the doses utilized in the annotated literature are the prophylactic doses of Fansidar®. There is no information provided for chronic dosing, drug interaction, as well as pharmacokinetics in pediatric and geriatric patients and patients with renal or hepatic insufficiency

2. INDICATIONS AND USAGE:

Medical Officer comment: Appropriate statements on the prophylactic use of Fansidar® and the emergence of Fansidar® resistance are incorporated in this section of the proposed label. Consistent with the organization of the indications and usage sections of the current labels of mefloquine and atovaquone-proguanil, the Fansidar® label should likewise organize this section into two subsections: treatment and prophylaxis:
The statement on the risk of Fansidar® resistance should immediately follow the treatment indication since failure of treatment (due to resistance) poses a more immediate and serious risk than failure of prophylaxis.

FDA Revised Draft:
"INDICATIONS AND USAGE:
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.
Prevention of Malaria:

3. CONTRAINDICATIONS: This section was reformatted to include bullets and is very effectively re-written.
Medical Officer comment: The current label contraindicates "repeated use of the drug", whereas the revised label expands this to '. Because of the prolonged half lives of both pyrimethamine and sulfadoxine in patients with hepatic and renal failure, and the risk of drug accumulation and toxicity in these patients, the sponsor should provide better guidelines for what would be considered "prolonged " therapy. In the absence of such guidelines, consideration should be made to contraindicating the use of Fansidar in these patients regardless of duration of treatment.
In addition to hypersensitivity to pyrimethamine and or sulfadoxine, hypersensitivity to the other components of Fansidar® is contraindicated. These include corn starch, gelatin, lactose, magnesium stearate and talc. This wording parallels similar wording in the Malarone label .
Fansidar use is also contraindicated in the pregnant patients at term and during the nursing period because of the theoretical risk of kernicterus from the exposure of the neonate to the sulfa drug. This contraindication is consistent with the current label for trimethoprim-sulfamethoxazole. None of the other antimalarial labels are

contraindicated in pregnancy or in the nursing period. A review of the 202 spontaneous reports of pregnant patients exposed to Fansidar® in the sponsor's database reveals that all but 2 of these cases received the drug prophylactically , with no reports of kernicterus. A review of the relevant literature, (see table 2) on the use of the drug in pregnancy, documents its beneficial effect without revealing an excess of abortions, teratogenicity nor kernicterus. Nevertheless most of the use of Fansidar® in these reports propose the use of a 2 dose regimen of pyrimethamine sulfadoxine during pregnancy as the a cost-effective and practical strategy for reducing fetal transmission of malaria , and improving the health of pregnant women and their offspring. Most of the regimens utilized a dose in early pregnancy , as well as a second dose in the last trimester. Contraindicating Fansidar for treatment of acute infection in the pregnant patient may restrict the usefulness of this drug in the population most likely to benefit from its use, while overstating the risk of single dose treatment. Nevertheless, none of the other antimalarials are contraindated in the prophylactic use of the drug in pregnancy therefore they provide alternatives to Fansidar for malaria prevention.

FDA Revised Draft:
CONTRAINDICATIONS:

- Prophylactic use of Fansidar® is contraindicated in patients with renal or hepatic failure or with blood dyscrasias
- Hypersensitivity to pyrimethamine, 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

4. PRECAUTIONS:

Medical Officer comment:

In the General subsection : MO proposes adding a comment on the use of Fansidar® in severe malaria and the use of Fansidar® after previous treatment or prophylaxis with the same drug (see below).

The statement " Excessive exposure to sun must be strictly avoided " is added to general precautions (underscoring MO's). In the sponsor's database 15 patients of 300 million patient exposures (0.00005%) developed photosensitivity. These patients had taken the drug prophylactically for travel to the tropics and had been exposed to "heavy unaccustomed sun." Five of these 15 had taken chloroquine concomitantly. In the AERS database, only one case of photosensitivity was reported of a total of 317 reported adverse events. Given that the rate of photosensitivity is miniscule, that Fansidar® use occurs in the tropics where malaria is endemic and where sun exposure is significant, inclusion of this statement appears to be out of proportion to the overall risk. Furthermore, the episodes of photosensitivity all occurred with the prophylactic use of the drug whereas this statement could discourage its use for treatment of acute malaria. Since patients with acute malaria are often too sick for any outdoor activities this risk would be overstated when the drug is used for the more beneficial indication. Although other severe cutaneous reactions are known to occur with Fansidar®, these are generally allergic in nature (Steven's Johnson, erythema multiforme, Lyell's syndrome, bullous reactions), and the role of sun exposure as a risk for these reactions is unclear. MO suggests removing the words "must" and "strictly", and reword as follows "Excessive sun exposure should be avoided."

FDA Revised Draft:
"PRECAUTIONS:

General: 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 recrudescent *P falciparum* infections after treatment with Fansidar® or failure of chemoprophylaxis with Fansidar®, patients should be treated with a different blood schizonticide.

Fansidar® should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. As with some sulfonamide drugs, in glucose-6- ——— dehydrogenase-deficient individuals, hemolysis may occur. Urinalysis with microscopic examination and renal function tests should be performed during therapy of those patients who have impaired renal function. Excessive sun exposure should be avoided.

Medical Officer comment: In the Information for the Patient subsection, suggest reorganizing the information in the order of their clinical importance. In the first item, the word "for the traveler" be stricken out, as malaria can be a life-threatening infection even for the non-traveler.

FDA Revised Draft:

Patients also should be advised:

- That malaria can be a life-threatening infection
- 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;

Medical Officer comments:

In the Laboratory tests section, would include testing for liver enzymes (new information added by sponsor in adverse event section). Hepatic adverse events were the second most frequent overall adverse events in the sponsor's database (17%), second only to the skin disorders (31%) (Table 5 of sponsor's Drug safety report)). Likewise, hepatic adverse events were the second most frequent serious adverse event, second only to the severe cutaneous reactions. Eighty of the 116 serious hepatic adverse events (69%) required hospitalization, although there was only one attributable death in the sponsor's analysis. The rise of liver enzymes has been reported to peak on the 10th week, consistent with the timing of blood tests suggested in the label.

There is no information provided on the development of crystalluria associated specifically with the use of Fansidar®, although specific information on testing for crystalluria is incorporated in the new label. Neither the sponsor's database (to 1994, nor the AERS report from DDMAC (to 2000), lists crystalluria as an adverse event. It is conceivable that the basis for this recommendation is the crystalluria that has been reported to occur with sulfadiazine when used to treat Toxoplasma encephalitis. (Molina JM, Belenfant X, Doco-Lecompte T, Idatte JM, Modai J. AIDS 1991 May. 5:587-9.) The recommended dose for sulfadiazine for toxoplasmosis is a 4 grams initial dose to a maximum of 8 grams a day for a minimum of three weeks. These are far greater (on a mg/kg basis), than those recommended with the prophylactic or therapeutic use of Fansidar®. Whether prolonged (>3 months) use of Fansidar® is associated with crystalluria at antimalarial doses of the drug, is not known, and is not substantiated. Given that hepatic adverse events are known to occur, and that crystalluria is a theoretical risk, would prefer to replace the latter test with the former, as follows:

FDA Revised Draft:

Laboratory Tests: Regular blood counts, and liver enzyme tests should be performed whenever Fansidar ® is administered for more than three months.

5. DRUG INTERACTIONS:

a. Drug Interactions

Medical Officer comments: Suggest re-state the last sentence in the second paragraph as follows

FDA Revised Draft:

"Drug Interactions:...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.

b. Pregnancy

Medical Officer comment: MO agrees with the addition of the clause on contraception during prophylaxis and treatment with Fansidar®. While no data accompanied the recommendation to extend contraception to 3 months after the use of the drug, this duration is consistent with the pharmacokinetics of Fansidar®.

FDA Revised Draft:

Pregnancy..... Women of childbearing potential who are traveling to areas where malaria is endemic should be warned against becoming pregnant, and should be advised to practice contraception during prophylaxis with Fansidar® and for three months after the last dose.

c. Pediatrics

Medical Officer comment: No clinical data on the safety and efficacy of Fansidar® in pediatric patients accompanied this submission. Nevertheless, there is a substantial worldwide experience with the use of Fansidar® in pediatrics. Based on the sponsor's database, pediatric patients comprised 10% of the accumulated 9.3 million users in industrialized countries compared to 50% of 323.6 million users in malarious areas. Taken together, a total of 162.7 million children have received Fansidar® to date. In the sponsor's safety database report, of 965 cases of adverse events in the drug database, 45 (4.7%) were under 19 years of age, probably reflecting a reporting bias. Nevertheless, the drug appears to be safe and effective when used within clinical trial context, as can be gleaned from the published literature to date (Table 3).

FDA Revised Draft:

"Pediatric Use: Fansidar® should not be given to infants less than 2 months of age because of inadequate development of the glucuronide-forming enzyme system."

6. ADVERSE REACTIONS:

Medical Officer comments: The adverse events added to the existing label are relatively minor. In the sponsors' report, the adverse events rates have declined progressively since 1985, following the introduction of mefloquine and its increased use for prophylaxis in industrialized countries.

A review of the AERS database which more likely reflects prophylactic rather than treatment use of Fansidar® reveals a total of 317 AE reports from the years 1982-2000. Over half of these are local reports (160/317 US). The adverse events most frequently reported (>1% of total) that are not listed in the draft label include: hypersensitivity (7.26%), sepsis (4.73%), congenital abnormalities (4.42%), leucopenia (3.79%), pneumonia (2.84%), anorexia (2.52%), pulmonary eosinophilia(2.52%), vasculitis (2.52%), asthenia, cough, infection, malaise, myalgia, pruritus, vision abnormalities, (all 1.89%). Of these, consequences of leucopenia such as sepsis, and infection need inclusion consistent with the black box warning referring to their occurrence. On the other hand, "Hypersensitivity" is an all encompassing term, represented by the term "anaphylactoid reactions" and the individual symptoms of which are adequately represented in the Skin and Miscellaneous Sites Reactions" subsection.

FDA Revised Draft:

"ADVERSE REACTIONS: For completeness, all major reactions to sulfonamides and to pyrimethamine are included below, even though they may not have been reported with Fansidar®. See WARNINGS and PRECAUTIONS: *Information for the Patient.*

Hematological Changes: Agranulocytosis, aplastic anemia, megaloblastic anemia, trgom0ocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, methemoglobinemia, and eosinophilia.

Skin and Miscellaneous Sites Allergic Reactions: Erythema multiforme, Stevens-Johnson syndrome, generahzed skin eruptions, toxic epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia, and allergic myocarditis, slight hair loss, Lyell's syndrome, and allergic pericarditis.

Gastrointestinal Reactions: Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, and pancreatitis, feeling of fullness, and transient rise of liver enzymes.

Central Nervous System Reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness, and nervousness, and polyneuritis.

Respiratory Reactions: Pulmonary infiltrates and eosinophilia.

Miscellaneous Reactions: Drug fever, chills, sepsis and infections, periarteritis nodosa and LE phenomenon have occurred.

The preamble to the section states that all major reactions to sulfonamides and pyrimethamine have been included, even if they may have not been reported with Fansidar®. If so, "crystalluria" must also be added as follows:

FDA Revised Draft:

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

7. DOSAGE AND ADMINISTRATION

Medical Officer comments: There are several clinical issues pertinent to this section of the label:

1. *Under "Treatment of Acute [redacted]", the original label refers to the use of Fansidar® alone or in sequence with quinine. Other than for trimethoprim (DARAPRIM), no other antimalarial bears a note on combination treatment in the DOSAGE AND ADMINISTRATION section of the label.*

Further, in the sub-section on "Treatment of Complicated Malaria", reference is made to a World Health Organization Scientific Group Technical Report (section 6.6.1.4.page 40, Practical Chemotherapy of Malaria, Technical Report Series 805, Item 10 in sponsor's appendix) that cites reducing the duration of quinine therapy by the addition of Fansidar®. [redacted] In addition, this section goes against earlier statements on oral therapy for severe malaria, and would therefore exclude this sub-section all together.

The existing label citing combination treatment with quinine for acute non-complicated malaria is the subject of prior negotiation and therefore may stand as written. Nevertheless, consideration should be made for appropriate statements on drug combinations and their utility in malaria therapy in the appropriate section of the label.

2. Pediatric dose: Basis for dosing in children: TREATMENT

The clinical data submitted to the original NDA on May 15, 1980 and reviewed by Edgar J Martin, MD (see Orignial NDA Medical Officer's Review, March 1981, in Divisional files) contained no efficacy and pharmacokinetic data in children. Nevertheless the doses approved in the original NDA have not been revised in this draft label. Furthermore, the currently labeled lower limit of age in the pediatric age group for which a dose is recommended, is 0 years. This is inconsistent with the statement in the CONTRAINDICATIONS section of the label against the use of Fansidar® in infants less than 2 months of age. Furthermore, there is no pediatric formulation available for use other than the tablet form. It is suggested that the tablet be swallowed whole, making it difficult to administer to very young infants. Lastly, the Centers for Disease Control , (URL:http://www.cdc.gov/travel/yellowbk /page128.htm) has the following treatment (but not prophylactic) dosage recommendations in children that are based on a body weight, rather than age

"CDC recommendations for Fansidar® Treatment

Weight (Kg)	Pediatric dose (# of tablets)
5-10	½

11-20	1
21-30	1 ½
31-45	2
>45	3"

Medical Officer comment: Basing dosage recommendations on body weight may result in more precise dosing in children, as it allows for dosing between children of the same age with varying body masses. Furthermore, since the mean body weight of 2 month old infants in the United States currently stands at 2 kg (The Harriet Lane Handbook: A Manual for Pediatric House Officers, Barone, MA, Ed. 14th Edition, June 1996, page 735), the lower limit of 5 Kg in the CDC dosage scheme based on weight is consistent with the CONTRAINDICATIONS section of the draft label.

Basis for dosing in children: PROPHYLAXIS.
Under the current dosage in the label, the treatment and prophylaxis total daily dose (in Tablets), translate into the following Total Daily Doses:

Prophylaxis **Treatment**

[redacted]

Based on pediatric patient weights, therefore, using the 0.5 ratio for prophylaxis to treatment doses, the corresponding doses for prophylaxis in the CDC weight-based dosing regimen in pediatric patients should be as follows:

Weight (Kg)	Pediatric PROPHYLACTIC once a week dose (# of tablets)	Pediatric TREATMENT single dose (# of tablets)
>45	1 ½	3
31-45	1	2
21-30	¾	1 ½
11-20	½	1
5-10	1/4	½

Medical Officer comment: The sponsor has been requested to provide pharmacokinetic information to substantiate pediatric dosing. This is more crucial for treatment rather than prophylaxis, given that the drug's limited utility as a prophylactic agent. In the likelihood that they are unable to do so, it must be acknowledged that the basis for the above recommendations is partly from extrapolations from the adult dosage, expert opinion and limited validation studies.

FDA revised draft:
"DOSAGE AND ADMINISTRATION (See INDICATIONS AND USAGE):

The tablets should be swallowed whole with plenty of fluids after a meal

(a) *Treatment of Acute Malaria*

Adults — 2 to 3 tablets taken as a single dose.

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

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

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.

	Once Weekly	Once Every 2 Weeks
Adults	1 tablet	2 tablets

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

Weight (Kg)	Once Weekly
>45	1 ½
31-45	1
21-30	¾
11-20	½
5-10	1/4

Prophylaxis with Fansidar® should not be continued for more than two years, since no experience of more prolonged administration is available to date.

GENERAL SUMMARY AND RECOMMENDATIONS

The sponsor has been requested to substantiate the basis for their proposed label by providing the following:

1) pharmacokinetic information in pediatric patients that would allow dose recommendations on a per kilogram basis for both treatment and prophylaxis
2.) an analysis of AE rates when Fansidar® was used alone or in combination with chloroquine or quinine
3.) adverse event rates in pregnancy, particularly as they relate to age of gestation.
4) The overdosage section of the label (page 7, upper right hand corner) suggests monitoring of renal, hepatic, and hematopoietic systems without specifying the unit of time required. The unit of time referred to must be provided as well as the basis for the recommendation.

Eileen Navarro, MD
Medical Officer, HFD 590

Concurrence:
HFD590/MTL/RocaR
HFD590MO/MeyerhoffA
cc:
HFD590/Div Dir/GoldbergerM
HFD590/PM/Franke E
HFD590/PM/Jensen V

4/30/03 Addendum to MO Review:
The above questions were forwarded to the sponsor in a telefacsimile in June, 2000 and again on August 14, 2000. The sponsor has been unable to provide a basis for the proposed doses for pediatric patients. There are several challenges to providing information for pediatric dosing in the label for a drug such as Fansidar®, which has been in the market for years and is widely used in the developing world, but not in the USA.
These include the difficulty of obtaining pharmacokinetic data to support dose recommendations and the lack of a pediatric formulation. While the sponsor is unable to provide data to support the weight based doses proposed by the CDC and which have been proposed by the FDA as an alternative, recent literature validates the limitations of the age-based Fansidar® dosage schema (Terlouw DJ, Courval JM, Kolczac MS, Rosenberg OS, Oloo AJ et al Treatment History and Treatment Dose are important determinants of sulfadoxine-pyrimethamine efficacy in children with uncomplicated Malaria in West Kenya, J of Infect Dis 2003:187:467-76). This study retrospectively studied determinants of Fansidar® efficacy in 2869 episodes of uncomplicated malaria treated with Fansidar® in 1072 Kenyan children under 5 years. This study found that treatment history and treatment dose were the relevant determinants for Fansidar® clinical efficacy, and showed that a threshold concentration of **27.5/1.375 mg of sulfadoxine/pyrimethamine Fansidar®/kg body weight** best correlated with the likelihood of treatment success. This study also found a trend to increased failures with increasing age, attributed to underdosing of the older child using age based Fansidar® doses.

Weight (Kg)	Pediatric PROPHYLACTIC once a week dose (# of tablets)	Sulfadoxine/ pyrimethamine Dose /kg/ DAY	Pediatric TREATMENT single dose (# of tablets)	Sulfadoxine/ pyrimethamine Dose /kg/DAY
>45	1 ½	16.7/0.83	3	33.3/1.6*
31-45	1	11.1/0.55	2	22.2/1.1
21-30	¾	12.5/0.625	1 ½	25/1.25
11-20	½	12.5/0.625	1	25/1.25
5-10	1/4	12.5/0.625	½	25/1.25

*based on the upper end of the range , to determine if the recommended dose is likely to fall below the suggested efficacious target, except for the first category which is based on the minimum 45 kg

MO comment: The doses proposed by the Agency in the label generally approximate the cutoffs levels found efficacious in the cited CDC-WHO study. Nonetheless, because Fansidar® is available only as tablets, preparing slightly larger doses to exceed the cutoffs is difficult, and the proposed doses may be the more practical approach to dosing for children. The basis for smaller prophylactic doses is not well supported in malaria and has the theoretical potential of contributing to resistance. However, given the regulatory precedent similar doses are proposed in the label for prophylaxis.

Eileen Navarro, M.D.

Table 1 Worldwide Fansidar® Resistance As Reported In Current Malaria Literature

Failure Rate (%)		Level of Resistance(%)			Study Site	Reference	Date Reported
RX	PX	RI	RII	RIII			
1		X	X		Mali	Diourte Y. et al. AJTMH 60:475-8.	Mar 1999
6					Columbia	Osorio LE et al. AJTMH 61:968-72	Dec 1999
0.2					Zambia	Mulenga M. et al. Clin Ther 21(5):841-52	May 1999
0.3			3	17	Zambia	Barat LM et al. Trop Med Intl Hlth 3:535-42.	July 1998
d 7 1.5 d10 10					Gambia	Bojang KA et al. TransR SocTropMedHyg 92:73-6.	Jan 1998.
d3 6.6 d15 2.3					Gabon	von Seidlein L et al. Am J Trop Med Hyg 58:638-44	May 1998
31					Myanmar	Lell B et al. Am J Trop Med Hyg 58:619-24	May 1998
d14 47 d28 67					Kenya	SmithiusFMetal. Trans R Soc TropMedHyg 91:468	July 1997
0					Tanzania	Falaschi F et al. East Afr Med J 74:275-7.	May 1997
0 (28% in vivo)					Malawi	Edoh D et al. Am J Trop Med Hyg 57:342-7	Sept 1997
9.9					Malawi	Verhoeff FH etal. AnnTrop MedParasitol 91:133-40.	Mar 1997
			2		Uganda	Ndyomugyenyi R. Acta Trop 10:137-43	Sept 1997
0					Tanzania	Wakibara JV et al. East Afr Med J 74:69-71.	Feb 1997

Legend:
RX – Treatment of acute malaria
PX- Prophylaxis for malaria
d- day

TABLE 2 EFFICACY and SAFETY of Fansidar in Pregnancy Citation	location / design	Findings
Shulman CE. Malaria in pregnancy: its relevance to safe-motherhood programmes. Ann Trop Med Parasitol **1999 Dec**. 93 :S59-66	Kenya /prospective	2 doses of Fansidar reduced anaemia and improved birthweight, policy in Kenya
Verhoeff FH; et al. Malaria in pregnancy : its consequences for the infant in rural Malawi. Ann Trop Med Parasitol **1999 Dec** 93 :S25-33	Malawi/cross-sectional	A 2nd treatment course with Fansidar reduced LBW , anemia, post neonatal mortality
Okereke CS. Management of HIV-infected pregnant patients in malaria-endemic areas. Clin Ther **1999 Sep**; 21:1456-96;	-------/ Review	In developing countries w/ high birth rates, malaria, and HIV, prophylaxis against both diseases during pregnancy is a challenge.
Goodman CA; Coleman PG; Mills AJ. Cost-effectiveness of malaria control in sub-Saharan Africa. Lancet **1999 Jul** 354:378-85	SubSaharan Africa, mathematic modelling.	In a very-low-income country, the cost per disability adjusted life year effectiveness **for intermittent Fansida treatment of pregnant women $4-29**.
Verhoeff FH; et al.. Trop Med Int Health **1999** Jan;4(1):5-12	Malawi/ Descriptive x-sectional	2 doses of Fansidar were inadequate to clear parasitaemia. Late pregnancy re-infections explain the high prevalence at delivery following Fansidar treatment at 28-34 wks.
Shulman CE; et al.. Intermittent sulphadoxine-pyrimethamine to prevent severe anaemia secondary to malaria in pregnancy: a randomised placebo-controlled trial. Lancet **1999 Feb** 20. 353:632-6	Kilifi, Kenya/ RDBPC	Between 1/ 96- 4/97, 1264 primigravids randomly assigned to placebo (624) or **one, two, or three doses** of Fansidar(640). 1ry outcome = anaemia and parasitaemia, at 34 wks of AOG. ITT at 34 wks showed a protective efficacy of 85% for parasitemia ([95% CI 78-90], p<0.0001) and 39% for aneamia. [95%CI 22-52], p<0.0001). 5.3% in the Fansidar group and 35.3% in the placebo group had parasitaemia , 14.5% and 23.7% had anaemia respectively. Even women w/ 1 dose benefited.
Parise ME; et al. Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. Am J Trop Med Hyg **1998 Nov**; 59(5):813-22	Kenya, RCT, fever case management (FCM) vs 2dose (2D) vs monthly (M) Fansidar in HIV +/-	FCM / 2D / M Parasitemia 27% / 12% / 9% Lowbirthweigh 14% / 8% / 8% HIV negative / HIV positive Placental malaria 2D 7% / 25% Placental malaria M / 7% AE <2%, no signif difference between HIV + and HIV -.
Phillips-Howard PA, et al. Safety of mefloquine and other antimalarial agents in the **1st trimester** of pregnancy. J Travel Med **1998 Sep**; 5(3):121-6	Prospective cohort	Traveler cohort(n=19): 0% spontaneous abortions 0% congenital anomalies, Pharmaceutical database(n=153): 2.6% spontaneous abortions,7.8% congenital anomalies
Verhoeff FH; Brabin BJ; Chimsuku L; Kazembe P; Russell WB; Broadhead RL An evaluation of the effects of intermittent sulfadoxine-pyrimethamine treatment in pregnancy on parasite clearance and risk of low birthweight in rural Malawi. Ann Trop Med Parasitol 1998 Mar;92(2):141-50.	Malawi/ prospective cohort	At delivery, no signif difference in parasitemia between 1 or 2 doses of SP. BW was lower in 1 dose of SP vs 2 or 3 doses. SP was not associated with maternal or perinatal complications. This is observed even when parasite prevalence is high due to in late re-infections. Reduction in parasitemia earlier in pregnancy from SPleads to improved foetal growth.

TABLE 3 EFFICACY and SAFETY of Fansidar in Pediatric Patients Citation	location / design	Findings
Doherty JF; et al. A randomized safety and tolerability trial of artesunate plus sulfadoxine--pyrimethamine versus sulfadoxine-pyrimethamine alone for the treatment of uncomplicated malaria in Gambian **children.** Trans R Soc Trop Med Hyg 1999 Sep-Oct;93(5):543-	Gambia/RCT	40 Gambian children with acute uncomplicated malaria. The addition of artesunate resulted in a higher proportion of afebrile children and children with a negative blood film on Day 2, and a reduction in the proportion of gametocyte carriers, when compared to sulfadoxine-pyrimethamine alone No numbers on efficacy
Goodman CA; Coleman PG; Mills AJ . Cost-effectiveness of malaria control in sub-Saharan Africa Lancet 1999 Jul 31;354(9176):378-85	Mathematical models/ treatment cost based on assumption of an existing health program	cost-effectiveness range US$ /DALY averted insecticide treatment of nets $ 4-10 provision of nets+insecticide treatment $19-85; residual spraying (two rounds / year) $32-58; **chemoprophylaxis for children** $ 3-12 intermittent treatment in pregnancy $ 4-29 improvement in case management $ 1-8 "Although some interventions are inexpensive, achieving high coverage with an intervention to prevent childhood malaria would use a high proportion of current health-care expenditure".
Bojang KA; Schneider G; Forck S; Obaro SK; Jaffar S; Pinder M; Rowley J; Greenwood BM. A trial of Fansidar plus chloroquine or Fansidar alone for the treatment of uncomplicated malaria in Gambian children. Trans R Soc Trop Med Hyg 1998 Jan-Feb;92(1):73-6	Gambia/RCT	day 7 parasite failure Fansidar 3/198 (1.5%), Fansidar plus chloroquine 3/201 (1.5%). da28 parasite failure rateFansidar 15/150 10.0% Fansidar plus chloroquine group (7/141; 5.0%) combination more effective **symptomatic** treatment than Fansidar given alone (F19/203 vs.FC 2/202; P < 0.001
von Seidlein L; et al. A randomized controlled trial of artemether/benflumetol, a new antimalarial and pyrimethamine/sulfadoxine in the treatment of uncomplicated falciparum malaria in African children. Am J Trop Med Hyg 1998 May;58(5):638-44	Gambia/RCT	d3 parasitemia success 133 (100%) CGP56697- (P = 0.003). 128 **(93.4%) of P/S** day **15 cure rate** 93.3% for CGP56697 **97.7% for P/S** (P = 0.13). Wk3-4 20 relapses CGP56697 vs 1 P/S (P < 0.0001). (19 of 23 [82.6%]) of these were new infections, WK2 **28.9% of the P/S treated children but none of the CGP56697-treated children carried gametocytes (P < 0.0001).** This study showed that CGP56697 is safe in African children with acute uncomplicated falciparum malaria, clears parasites more rapidly than P/S, and results in fewer gametocyte carriers. More frequent new infections within the third and fourth week following treatment with CGP56697 than treatment with P/S are likely to be due to the short prophylactic effect of CGP56697
Smithuis FM; et al. Plasmodium falciparum: sensitivity in vivo to chloroquine, pyrimethamine/sulfadoxine and mefloquine in	Myanmar/ open, age	Chloroquine rapid clinical recovery (P = 0.03), cure rates were worse than for PS treatment;

western Myanmar. Trans R Soc Trop Med Hyg 1997 Jul-Aug;91(4):468-72	stratified comparative	14 d parasitemia failures 72% (102/141) CQ vs 47% (69/148) PS (P < 0.0001, adjusted for age. day 28 parasitemia failures 82% (116/141) CQ vs 67% (99/148) PS group (P = 0.003). treatment failure was significantly higher in children under 15 years old than in adults for both CQ (relative risk [RR] = 2.6; 95% confidence interval [95% CI] 1.3-5.2) and PS (RR = 2.2; 95% CI 1.4-3.3).
Falaschi F; Ansaloni L . Chloroquine versus pyrimethamine/sulphadoxine in the treatment of uncomplicated P. falciparum malaria in northern Kenya. East Afr Med J **1997** May;74(5):275-7	Kenya/RCT	in two age groups (children < 10 years, adults > 10 years). . Parasites were significantly (p < 0.001) more resistant to CQ (18/38, 47.4%) than PSD (0/27, 0%). 22 were in CQ group and five were found positive (22.7%), while the **35 patients in PSD group all tested negative (p = 0.006)**. The resistance to CQ in the children group was 25% (p = 0.05) and 20% in the adult group (p = 0.13).
Verhoeff FH; et al. Parasitological and haematological responses to treatment of Plasmodium falciparum malaria with sulphadoxine-pyrimethamine in southern Malawi. Ann Trop Med Parasitol **1997** Mar;91(2):133-40	Malawi/observational	Children, aged 6-59 months, with uncomplicated infections of P. falciparum Of 107 children enrolled, 84 children (78.5%) were followed for 14 days or **until clinical failure**. The parasitological success rate amongst the latter was **90.5% (76/84).** A 14-day follow-up increased the detection of parasitological failure by 7.2%.
Falade Co et al. Comparative efficacy of halofantrine, chloroquine and sulfadoxine-pyrimethamine for treatment of acute uncomplicated falciparum malaria in Nigerian children Trans R Soc Trop Med Hyg 1997 Jan-Feb;91(1):58-62	Nigeria/RCT	110 children aged 6 mo- 11 yr randomly treated with halofantrine (HF), S-P) or CQ) for acute uncomplicated Plasmodium falciparum malaria fever clearance: HF, PS, CQ= 1.9 d, **1.6 d** , 1-7d parasite clearance: HF, PS, CQ= 3.4, 4.4, 4.1 d cure d7 : HF, PS, CQ= 92.3%,**72.7%** , 39.5% recrudescenced14: HF, PS,CQ=11%, 8%, 13%, The 3 drugs were well tolerated.
Ronn AM; Msangeni HA; Mhina J; Wernsdorfer WH; Bygbjerg IC High level of resistance of Plasmodium falciparum to sulfadoxine-pyrimethamine in children in TanzaniaTrans R Soc Trop Med Hyg 1996 Mar-Apr;90(2):179-	Tanzania/OL	Single dose 0.8-1.4 mg pyrimethamine/kg to 38 children 1-10 years of age. On day 7, 10 (26%) showed an S/RI response, 26 an RII response, and 2 an RIII response. Older children had lower pre-treatment parasitaemia and a better therapeutic response than younger children. poor therapeutic result in prophylactic dapsone-pyrimethamine
Anabwani et al. A randomised controlled trial to assess the relative efficacy of chloroquine, amodiaquine, halofantrine and Fansidar in the treatment of uncomplicated malaria in children. East Afr Med J 1996 Mar;73(3):155-8	Kenya/RCT	N=188 Halofantrine 82% cure, PS 62% cure Amodiaquine 55%cure, chloroqione 67% cure RIII only in Chloroquine
Muller O et al. A randomized trial of chloroquine,		1.25/25mg/kg PS treatment dose employed. Symptomatic failure at day 3: PS, CQ, AQ=17%

amodiaquine and pyrimethamine-sulphadoxine in Gambian children with uncomplicated malaria. Trop Med Int Health 1996 Feb;1(1):124-32	RCT/Gambia	7%(P = 0.03) 3%,(P = 0.001) Five of these patients had a generalized convulsion (1 from the AQ group, **4 from the PS group), of whom 4 developed cerebral** malaria. Parasitemia at D7, CQ vs AQ (25 vs 7%, P = 0.0009) **or PS (25 vs 4%,** P = 0.0001) Parasitemia at D28, the cumulative parasitological failures CQ vs the AQ (65 vs 35%, P = 0.0001), AQ vs **PS group** (35 vs **14%,** P = 0.001).-These results suggest that **PS acts more slowly than 4-aminoquinolines in controlling the clinical features of malaria,** and that AQ can be considered as an alternative to CQ in African areas of high CQ resistance
Wolday D; Kibreab T; Bukenya D; Hodes R. Sensitivity of Plasmodium falciparum in vivo to chloroquine and pyrimethamine-sulfadoxine in Rwandan patients in a refugee camp in ZaireTrans R Soc Trop Med Hyg 1995 Nov-Dec;89(6):654-6	Zaire/RCT	38 individuals receiving pyrimethamine-sulfadoxine, 13 (34.2%) showed sensitive or RI (delayed) responses, and 25 (65.%) showed resistance at RI (26.3%), RII (36.8%) and RIII (2.6%) levels. PS reduced parasite counts within 2 d of treatment.
Metzger W; et al. PG Sulfadoxine/pyrimethamine or chloroquine/clindamycin treatment of Gabonese school children infected with chloroquine resistant malaria.: J Antimicrob Chemother 1995 Oct;36(4):723-8	Gabon/RCT	ChloroquineI 32% cure Chloro/Clinda >90% cure PS > 90% cure

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/s/

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4/30/03 02:48:58 PM
MEDICAL OFFICER

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5/12/03 03:35:26 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-557 / S -015

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	18-557
Serial No:	SLR-015
Generic	Sulfadoxine and pyrimethamine
(Brand®)	Fansidar
Submission Date:	July 27, 1999
Sponsor:	Hoffmann-La Roche Inc.
Type of Submission:	Labeling Supplement
Reviewer:	Houda Mahayni

Submission

SLR-015

The sponsor is submitting a labeling supplement that contains package insert revisions consistent with the worldwide safety information that is available on this product. In addition, the sponsor is incorporating new statements in the *Information for the Patient* subsection of PRECAUTIONS to be consistent with points about malaria prophylaxis that were suggested by the Agency in the label for NDA 19-591 -Lariam® (mefloquine hydrochloride) tablets.

Reviewer's Comments

Clinical Pharmacology **(Text that should be deleted is strikethrough, text that should be added contains a double underline).**

Metabolism section should read as follows:

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

DOSAGE AND ADMINISTRATION section:

Recommendations

For supplement (SLR-015), please ask the sponsor to adopt the above modifications to the package insert.

Comments (to be sent to firm)

Please pass the modified version of the label to the sponsor.

Houda Mahayni, R.Ph., Ph.D.

Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

FT/RD initialed by Funmi Ajayi, Ph.D., Team Leader

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/s/

Houda Mahayni
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BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-557 / S -015

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Division of Special Pathogen and Immunologic Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 18-557/SLR-015

Name of Drug: Fansidar (sulfadoxine and pyrimethamine) Tablets, 500 mg/25 mg

Applicant: Hoffmann-La Roche Inc.

Material Reviewed:

NDA 18-557:

SLR	Date submitted	Date received
015	July 27, 1999	July 28, 1999

Amendments:

SLR	Date submitted	Date received
015	May 13, 2003	May 14, 2003
015	November 14, 2003	November 17, 2003

Background and Summary

NDA 18-557 was originally approved on October 28, 1981. The last labeling change for this NDA was approved on April 27, 2003.

On July 27, 1999, Roche submitted this labeling supplement proposing revisions consistent with the worldwide safety information available on the product. On April 30, 2003, we issued an approvable letter. On November 14, 2003, Roche submitted draft labeling in response to our April 30, 2003 approvable letter. Roche agreed to the revisions listed in the approvable letter, however, they counterproposed the following:

1. Under CONTRAINDICATIONS, add the word "Repeated" to the beginning of the sentence "Prophylactic use of Fansidar is contraindicated in patients with renal or hepatic failure or with blood dyscrasias".

2. Add the word "Oral" to the beginning of the sentence "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," in the General subsection of the PRECAUTIONS section.

3. Revise the Respiratory Reactions subsection of the ADVERSE REACTIONS section from "Pulmonary infiltrates and eosinophilia" to read "Pulmonary infiltrates resembling eosinophilic or allergic alveolitis."

4. Remove renal failure, interstitial nephritis, BUN and serum creatinine elevation, and crystalluria from the *Genitourinary* subsection and sepsis and infections from the *Miscellaneous Reactions* subsection of the ADVERSE REACTIONS section.

In a discussion with Roche on December 8, 2003, it was conveyed that the Review Team agreed to accept #1 – 3, however, based on class effects, the Review Team insisted that the adverse reactions be listed in the *Genitourinary* subsection. The Review Team did agree that sepsis and infections did not need to be added to the *Miscellaneous Reactions* subsection of the ADVERSE REACTIONS section. Roche agreed to these decisions. They also said that they do not routinely use [redacted] after the first reference in the package insert. The Review Team accepted this.

Review of S-015:

I incorporated the changes discussed on December 8, 2003 into the draft labeling submitted on November 14, 2003. This was electronically compared to the approved Fansidar label dated April 27, 2003. The following changes were found:

Double Underline = added text
~~Strikethrough~~ = deleted text

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 recrudescent 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 recrudescent *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 was renamed *Skin and Miscellaneous Sites Allergic Reactions:*

b. The *Respiratory Reactions* subsection was revised to read:

Pulmonary infiltrates resembling eosinophilic or allergic alveolitis.

c. The following subsection was 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 was revised to read:

Drug fever, chills, ~~and toxic nephrosis with oliguria and anuria~~ periarteritis 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 (2 months-18 years)	The dosage for treatment of malaria in children is based upon body weight:

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

~~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.~~

~~c)~~ (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.

	Once Weekly	Once Every 2 Weeks
Adults	1 tablet	2 tablets
~~9 to 14 years~~	~~3/4 tablet~~	~~11/2 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:

Weight (Kg)	Number of Tablets Taken Once Weekly
>45	1 ½
31-45	1
21-30	¾
11-20	½
5-10	1/4

Conclusions

The proposed labeling changes for S-015 are acceptable based on the review by Rigoberto Roca, M.D. This supplement should be approved and final printed labeling (PFL) requested.

Kristen Miller, Pharm.D
Regulatory Project Manager

Supervisory Comment/Concurrence:

Ellen Molinaro, R.Ph.
Chief, Project Management Staff

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

/s/

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