CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-049/S006

CORRESPONDENCE

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

SEP 10 1999

Application Number: NDA 20-049/S-006

Name of Drug: Pentasa (mesalamine) Capsules

Sponsor: Roberts Laboratories, Inc.

Material Reviewed

Submission Date(s): August 6, 1999, FPL

Receipt Date(s): August 12, 1999

Background and Summary Description: NDA 20-049, which provides for Pentasa (mesalamine) Capsules at a dose of 1 gm four times daily, was approved May 10, 1993 for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

NDA 20-049/S-006, submitted November 20, 1998, provided for the following:

1. Revision of the ADVERSE REAACTIONS section to,

   a. add a Postmarketing Reports subsection, as requested in the Division's September 1, 1998 letter,

   b. add "agranulocytosis" as an additional adverse event in the **Other:** subsection, and

   c. add a statement that "Allergic reactions, which could involve eosinophilia, can be seen in connection with PENTASA therapy," in response to the Division's August 25, 1998 letter.

2. Revision of the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection to include results from 104-week feeding studies in mice and rats.

S-006 was Approvable on May 12, 1999, pending FPL with the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection revised to read,

> "In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500 mg/kg/day and it was not tumorigenic. For a 50 kg person of average height (1.46 m^2 body surface area), this represents 2.5 times the recommended human dose on a body surface area basis (2960 mg/m^2/day). In a 104-week dietary

carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose represents 1.5 times the recommended human dose on a body surface area basis.

No evidence of mutagenicity was observed in an in vitro Ames test and an in vivo mouse micronucleus test.

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.8 times the recommended human dose based on body surface area).

Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with PENTASA capsules during controlled clinical trials."

The sponsor has responded to the May 12, 1999 Approvable letter with an August 6, 1999 submission that contains FPL (package insert).

Review

The submitted insert (**coded 189 0107 002, Rev. 6/99, 50019193**) was compared to the draft insert (**coded 189 0107 002, Rev. 9/98, 50019193**)which was the basis for the Approvable action. No changes have been made, except for the revision to the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection that was requested in the Approvable letter.

Conclusions

The submitted insert is acceptable and can be considered the currently approved labeling. An approval letter should be drafted.

/S/ 9/10/99
Regulatory Health Project Manager

/S/ 9-10-99

ROBERTS PHARMACEUTICAL CORPORATION

ORIGINAL

NDA SUPPL AMEND
SLR-006 AF

August 6, 1999

08/20/99
/S/

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 12 1999
HFD-180

Lilia Talarico, M.D.
FOOD AND DRUG ADMINISTRATION
CDER, DGICDP (HFD-180)
Attn: Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

NDA 20-049: PENTASA® (mesalamine) Controlled-Release Capsules
Amendment to Supplemental Application S-006

Dear Dr. Talarico:

Please refer to our NDA 20-049 for PENTASA® (mesalamine) Controlled-Release Capsules, our supplemental application S-006 dated 11/20/98, your 5/12/99 approvable letter, and our letter dated 5/18/99 regarding final printed labeling (FPL).

As requested, we are now submitting 20 copies of the FPL, 10 of which are individually mounted on heavy paper, plus one which is highlighted in yellow to indicate the changes that were made.

If you have any questions or comments regarding this submission, please do not hesitate to communicate with Ms. Susan Elliott or me.

Sincerely,

Alvin D. Howard, Vice President
Regulatory Affairs

SE
Enclosures: FORM FDA 356h
20 FPL

PENPIFPL.DOC

FOUR INDUSTRIAL WAY WEST, EATONTOWN, NEW JERSEY 07724-2274 • TEL. (732) 676-1200 / FAX (732) 676-1300

ROBERTS PHARMACEUTICAL CORPORATION

12/03/98
/S/

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED

November 20, 1998

NDA NO. 20049 REF. NO. 006
NDA SUPPL FOR SLR

CENTER FOR DRUG
REC'D
NOV 23 1998
HFD-180
EVALUATION AND RESEARCH

05/11/99
It is acceptable to add the agranulocytosis to the Adverse Reactions Section of the labeling.
/S/
/S/

Lilia Talarico, M.D.
FOOD AND DRUG ADMINISTRATION
CDER, DGICDP (HFD-180)
Attn: Document Control Room 6B-45
5600 Fishers Lane
Rockville, MD 20857

NDA 20-049: PENTASA® (mesalamine) Controlled-Release Capsules
Supplement: Labeling Changes

Dear Dr. Talarico:

We refer to your letter dated September 1, 1998 requesting the addition of a new subsection in the ADVERSE REACTIONS section of the Pentasa® (mesalamine) Capsules package insert, entitled "Postmarketing Reports". We have incorporated the exact wording that you have requested in your 09/01/98 letter into our revised package insert.

However, we have taken this opportunity to make 3 additional changes to the package insert:

1) Under the section header Carcinogenesis, Mutagenesis, Impairment of Fertility, we have deleted the current sentence which states that [redacted] and replaced it with the new sentence [redacted]

   The carcinogenicity studies in rats and mice have been completed and were submitted in the Annual Reports to IND [redacted] on April 7, 1992 (Serial No. 104) for the rat study and on November 20, 1992 (Serial No. 114) for the mouse study.

2) Under the section header ADVERSE REACTIONS, we have added agranulocytosis as an additional adverse event in the subsection OTHER; the sentence in which the word "agranulocytosis" appears, begins with "Published case reports and/or spontaneous postmarketing surveillance...".

ORIGINAL

We have enclosed for your reference an explanatory statement prepared by Hoechst Marion Roussel, Inc. the former IND/NDA holder for this product to justify the addition of this adverse event to the Pentasa® Capsules package insert.

3) As requested in your letter dated August 25, 1998 regarding the inclusion of a statement pertaining to eosinophilia, we have included the following statement in the ADVERSE REACTIONS section under OTHER: "Allergic reactions, which could involve eosinophilia, can be seen in connection with PENTASA therapy".

On September 24, 1998, we had submitted documentation to the NDA that was received from [redacted] on this issue.

As per your letter of September 1, 1998, we are submitting the revised package insert as a Special Supplement-Changes Being Effected including 16 copies of the final printed labeling, 10 of which are mounted on heavy paper, plus 1 which is highlighted in yellow. We plan to implement these changes immediately unless you request further changes to the labeling.

Sincerely,

Richard J. Raffa
Associate Director,
Regulatory Affairs

Enclosure: FDA Form 356h
Revised Pentasa® Capsules Package Insert (189 0107 002) – 16 copies
Supporting documents for labeling changes

LBLCHGS

April 6, 1998

Hoechst Marion Roussel, Inc
Route 202-206 · P.O. Box 6800
Bridgewater, NJ 08807-0800

Reasoned Statement

Amendment to the "Adverse Event" section, of the U.S. Package Insert for Pentasa (mesalamine)

On the basis of cases retrieved from our database and general medical and pharmacological considerations, reasonable documentation exists which supports the addition of agranulocytosis to the adverse event section of U.S. Package Insert of Pentasa (mesalamine).

The following summarizes our review of available data regarding **Pentasa (mesalamine)** and **agranulocytosis.** Pentasa (mesalamine) is indicated for treatment of ulcerative colitis. This review came following receipt of a case of agranulocytosis reported for Pentasa early this year. The report received by our license partner [redacted] came from the French Medical Agency.

> **Case # 199810416DDC** . The patient, a 72-year-old woman, was treated with Pentasa (mesalamine) 2 g/day from 01-Sep-1996. Fifteen months later, on 02-Dec-1997 the patient developed acute agranulocytosis and leucopenia. Concomitant medication was acetylsalicylic acid (started 26 Nov 97 for unspecified indication). Pentasa (mesalamine) was discontinued due to this event. The patient improved quickly after discontinuation of both Pentasa (mesalamine) and the concomitant drug (acetylsalicylic acid).

The case was assessed as "CONDITIONAL" based on our causality algorithm.

A review of our database revealed 10 other cases of agranulocytosis received for Pentasa. Four cases of agranulocytosis were reported in 1997. These cases involved two reports assessed as "PROBABLE" based on the HMR causality algorithm. This assessment was based on two criteria: a *temporal compatibility* between adverse event onset and the dates of therapy with Pentasa and the resolution of the event following discontinuation of the medication *("positive dechallenge").* Additionally, no alternative explanation was proposed by the reporter or identified by the evaluator. These two cases are briefly summarized herewith:

> **1. Case # 199711326HMRI**: This spontaneous verbal report was received from a physician in the United States. He reports a 29 year old female who experienced angranulocytosis during Pentasa (mesalamine) therapy. The patient started receiving 2 grams of Pentasa twice daily for Crohn's Disease on 11-Mar-1996 and continued therapy until 06-Aug-1997. The physician reports that the patient had an absolute neutrophil count (ANC) of 900 on 02-Jul-1997, which dropped to 100 on 06-Aug-1997. Concomitant medications: Folic acid, birth control pills. Medical history: Cholestatic jaundice with subsequent cholecystectomy for gall stones. Pentasa was discontinued on 07 Aug 1997 and the event abated. By 18 Aug, ANC had returned to 2,300. Patient recovered without sequelae.
>
> **2. Case # 199712816DDC** This postmarketing involves a 79 year old woman who was receiving mesalazine (Pentasa) 1.5 g daily orally from August 30, 1994 to August 4, 1997 (indication not reported. Relevant concomitant medications include levothyroxine sodium (Eltroxin). On August 4, 1997 the patient developed agranulocytosis and was hospitalized. Pentasa treatment was discontinued the same day. The patient recovered without sequelae.

The following table summarizes the cases of agranulocytosis reported for Pentasa (mesalamine):

Case #	Therapy Duration	Adverse event reported	Underlying disorder concomitant medication	Treatment and Outcome
199710426DDC	8 months	Agranulocytosis, neutropenic fever, (?) bacterial endocarditis, Acute Renal Failure	Dosulepin (Prothiadin)	Discontinuation of mesalazine, antibiotics, G-CSF. Patient recovered
199710318DDC	4 months	Acute Myelocytic Leukemia. Thrombocytopenia. Neutropenia, Neut: 200		Discontinuation of Pentasa. Ongoing
199711326HMRI	5 months	Agranulocytosis, Neut: 100	Folic acid, birth control pills	Pentasa discontinued. Event abated
199712816DDC	3 years	Agranulocytosis	Levothyroxine sodium (Eltroxin	Pentasa discontinued. Patient recovered.
199713234DDC	6 months	Agranulocytosis, leukopenia, anemia. WBC: 1100; neutrophils= 3.5%	Prednisolone, furosemide	Pentasa discontinued. Patient recovered. Treatment with G-CSF
94003292	1 month	Neutropenia, decreased hematocrit, decreased hemoglobin, Neut: 418	Mercaptopurine	
95003129		Agranulocytosis		Treatment: iron. Therapy with Pentasa continued. Event abated with no sequelae.
95005185	59 days	Anemia, Leukopenia. Neut: 130	6-mercaptopurine	Pentasa and 6-mercaptopurine discontinued. Neupogen. Patient recovered. No abnormality noted after Pentasa was restarted.
96003431		Agranulocytosis. Leukopenia. "Total agranulopoia in bone marrow"	Enalapril, ranitidine, acetylsalicylic acid, furosemide, isosorbide mononitrate, angina pectoris, stomach resection due to ulcer	Mesalazine discontinued. Outcome unknown.
96004994	6 weeks	Agranulocytosis, worsened diarrhea, 78 polynuclear neutrophil	Bactrim, Myelofibrosis noted on bone marrow examination	Pentasa discontinued. Neupogen. Patient recovered

Our search included available literature articles on the subject: in a series of 49 hematological reactions suspected to be associated with mesalazine therapy, one case of agranulocytosis was noted [Current Problems in Pharmacovigilance. 21st Vol. Pages 5-6]. In a review of 70 cases of agranulocytosis by Sprikkelman A. et al of the Dept. of Hematology, University Hospital of Groningen, the Netherlands, 1 case was reported to have been due to Mesalazine. In a study conducted by the Boston Collaborative Drug Surveillance Program involving over 10,300 patients on Sulfasalazine and over 4000 patients on Mesalazine, no cases of blood disturbances was noted in patients on Mesalazine.

Current knowledge of mesalazine recognizes its hematological side effects. Meylers 13th edition, for instance, lists thrombocytopenia and leukopenia. Martindales 31st edition states "although uncommon, mesalazine-associated adverse effects on the blood have been reported, including thrombocytopenia, neutropenia and fatal aplastic anemia. By February 1994, the Committee on Safety of Medicines in the UK had been notified of 26 cases of thrombocytopenia, leucopenia, or neutropenia, and 6 cases of aplastic anemia, pancytopenia, or bone marrow depression associated with mesalazine." Drug Facts and Comparisons, 50thEdition, 1996. (P. 1949) has listed agranulocytosis as an adverse event for mesalazine.

Agranulocytosis is not listed in the U.S. Package Insert and the [redacted] Core Data Sheet for Pentasa. The following events are listed in the former: aplastic anemia and leukopenia; the latter's "Special Warnings and Special Precautions for Use" section states "Mesalamine-induced ...serious **blood dyscrasias** have rarely been reported with mesalazine. Treatment should be discontinued on suspicion or evidence of these adverse events." On the other hand, in countries where marketing of this product is licenced by [redacted] agranulocytosis is listed in the package insert approved for use. In this instance, the "adverse reaction" section reads: "There have been rare reports of leucopenia, neutropenia, **agranulocytosis**, aplastic anemia.... " and applies to the three formulation [redacted] marketed in these countries. Agranulocytosis has also been added in the U.S. package insert of our competitor product, Asacol (Proctor and Gamble Pharmaceuticals).

HMR markets Pentasa (mesalamine) in the United States and since the U.S. package insert is used as the core data sheet by the GDSP, we recommend that this adverse event be added to the U.S. package insert.

Best regards,

Dr. Byron Gesulgon
Global Drug Surveillance & Pharmacoepidemiology

enclosure

NDA 20-049/S-006

Roberts Laboratories, Inc.
Attention: Richard J. Raffa
4 Industrial Way West
Eatontown, NJ 07724-2274

Dear Mr. Raffa:

We acknowledge receipt of your labeling supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Pentasa (mesalamine) Capsules

NDA Number: 20-049

Supplement Number: S-006

Date of Supplement: November 20, 1998

Date of Receipt: November 23, 1998

This supplement proposes the following changes to the package insert:

1. Revision of the ADVERSE REACTIONS section to,

   a. add a Postmarketing Reports subsection, as requested in our September 1, 1998 letter,

   b. add "agranulocytosis" as an additional adverse event in the Other subsection, and

   c. add a statement that "Allergic reactions, which could involve eosinophilia, can be seen in connection with PENTASA therapy," as requested in our August 25, 1998 letter.

2. Revision of the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection to include results from 104-week feeding studies in mice and rats.

Your submission stated the changes would be implemented immediately.

We note that you have submitted this supplement under 21 CFR 314.70(c), 'Special Supplement - Changes Being Effected.' The proposed revision to the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection (described above) is not the kind of change permitted by regulation to be put into effect prior to approval of a supplement. An approved supplement is required for the proposed change; therefore, the revisions to both the

PRECAUTIONS and ADVERSE REACTIONS section are being reviewed under 21 CFR 314.70(b).

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 22, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/ 12-15-98 /S/ 12/15/98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-049
HFD-180/Div. Files
HFD-180/M.McNeil
HFD-180/Choudary
HFD-180/Gallo-Tores
DISTRICT OFFICE

Drafted by: mm/December 14, 1998
final: 12/15/98

SUPPLEMENT ACKNOWLEDGEMENT (AC)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINIISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 24, 1999

FROM: Pharmacology Team Leader
Division of Gastrointestinal and
Coagulation Drug Products
HFD-180

MAR 25 1999

SUBJECT: NDA 20049 (Pentasa Controlled-Release Capsules)
Supplement SLR 006 Dated November 20, 1998

TO: NDA 20049

In the above listed supplement (SLR 006, dated November 20, 1998), the sponsor is proposing to change the labeling under the "PRECAUTIONS" section, subsection "Carcinogenesis, Mutagenesis, Impairment of Fertility" to incorporate the results of the completed carcinogenicity studies in rats and mice. The present labeling for pentasa under the subsection, and sponsor's proposed revision are reproduced below. They are followed by our evaluation and the recommended version.

Current Labeling:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's Proposed Version:

[redacted]

Evaluation:

Sponsor's proposed version appears rather abrupt and the expression of the highest doses tested in the studies as multiples of human doses are confusing. The basis of the expression is not provided. Only in the following sentences the explanation is provided. The explanation should start in the beginning of the subsection. Sponsor states in the proposed version that no toxicity or carcinogenicity was observed in these studies. This statement is only partially correct. While there was no evidence for any tumorigenic effect of mesalamine in these studies, there were certainly toxicities observed in both studies as evidenced by nonneoplastic histopathology lesions in mice such as chronic interstitial nephritis, renal papillary necrosis, focal hepatocellular hyperplasia, hemorrhage and cystitis of the urinary bladder and in rats such as focal deposits of brown pigments in renal tubules. Therefore the claim of no toxicity should be denied.

Recommended Version:

"In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500 mg/kg/day and it was not tumorigenic. For a 50 kg person of average height (1.46 m^2 body surface area), this represents 2.5 times the recommended human dose on a body surface area basis (2960 mg//m^2/day). In a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose represents 1.5 times the recommended human dose on body surface area basis.

No evidence of mutagenicity was observed in an in vitro Ames test and an in vivo mouse micronucleus test.

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.8 times the recommended human dose based on body surface area).

Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine have not been seen with PENTASA capsules during controlled clinical trials."

/S/ 3/25/99
Jasti B. Choudary, B.V.Sc., Ph.D.

cc:
NDA
HFD-180
HFD-181/PM, Ms. McNeil
HFD-180/Dr. Choudary

JBC/hw/3/24/99

APPEARS THIS WAY
ON ORIGINAL

NDA 20-049/S-006

Roberts Laboratories Inc.
Attention: Richard J. Raffa
Associate Director, Regulatory Affairs
4 Industrial Way West
Eatontown, NJ 07724-2274

MAY 12 1999

Dear Mr. Raffa:

Please refer to your supplemental new drug application dated November 20, 1998, received November 23, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pentasa (mesalamine) Capsules.

This supplement proposes the following changes to the package insert:

1. Revision of the ADVERSE REACTIONS section to,

   a. add a Postmarketing Reports subsection, as requested in our September 1, 1998 letter,

   b. add "agranulocytosis" as an additional adverse event in the Other subsection, and

   c. add a statement that "Allergic reactions, which could involve eosinophilia, can be seen in connection with PENTASA therapy," as requested in our August 25, 1998 letter.

2. Revision of the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection to include results from 104-week feeding studies in mice and rats.

Your submission stated the changes would be implemented immediately.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c). However, as we notified you in our December 15, 1998 letter to this application, the proposed change to the PRECAUTIONS section is not the kind of change permitted by regulation to be put into effect prior to approval of a supplement. Therefore, the entire supplement was reviewed under 21 CFR 314.70(b).

We have completed the review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

Please revise the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection to read,

> "In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500 mg/kg/day and it was not tumorigenic. For a 50 kg person of average height (1.46 m^2 body surface area), this represents 2.5 times the recommended human dose on a body surface area basis (2960 mg/m^2/day). In a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose represents 1.5 times the recommended human dose on a body surface area basis.

No evidence of mutagenicity was observed in an in vitro Ames test and an in vivo mouse micronucleus test.

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.8 times the recommended human dose based on body surface area).

Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with PENTASA capsules during controlled clinical trials."

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

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

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 the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. 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 to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/ 5/12/99

/S/ 5-12-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-049/S-006

MAY 12 1999

Name of Drug: Pentasa (mesalamine) Capsules

Sponsor: Roberts Laboratories, Inc.

Material Reviewed

Submission Date(s): November 20, 1998; draft labeling

Receipt Date(s): November 23, 1998

Background and Summary Description: NDA 20-049, which provides for Pentasa (mesalamine) Capsules at a dose of 1 gm four times daily, was approved May 10, 1993 for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

On August 25, 1998 the Division issued a letter to the firm which described the literature report of a 37 year old female who developed Churg-Strauss syndrome, with eosinophilia, mononeuritis multiplex, mennigism, intermittent blindness and rash, after 17 months of mesalamine therapy for ulcerative colitis. The firm was asked to analyze all safety reports pertaining to eosinophilia, provide that analysis, and consider whether revision of the labeling was warranted.

On September 1, 1998 the Division issued a letter to the sponsors of all products that contain or are metabolized to mesalamine. This letter requested revision of the respective products' package inserts to include 1) a Postmarketing Reports subsection in the ADVERSE REACTIONS section and 2) specific, consistent wording in the Postmarketing Reports subsection regarding the occurrence of various forms of hepatotoxicity which have occurred in patients exposed to these products. The letter also directed sponsors to submit final printed labeling (FPL), revised as requested, in accordance with 21 CFR 314.70(c), "Special Supplement-Changes Being Effected."

On November 20, 1998 Roberts submitted supplement –006 (S-006) as "Special Supplement-Changes Being Effected" to NDA 20-049. The supplement provides for the following:

1. Revision of the ADVERSE REACTIONS section to,

   a. add a Postmarketing Reports subsection, as requested in our September 1, 1998 letter,

   b. add "agranulocytosis" as an additional adverse event in the Other subsection, and

c. add a statement that "Allergic reactions, which could involve eosinophilia, can be seen in connection with PENTASA therapy," in response to our August 25, 1998 letter.

2. Revision of the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection to include results from 104-week feeding studies in mice and rats.

In a December 15, 1998 letter the firm was informed that the change to the PRECAUTIONS section (described above) was not permitted by regulation to be put into effect prior to approval of a supplement. The firm was also informed that the revisions to both the ADVERSE REACTIONS and PRECAUTIONS sections of the insert would be reviewed under 21 CFR 314.70(b), "Supplements Requiring FDA Approval Before the Change is Made." Note: Although the firm submitted FPL with S-006, it is reviewed as draft labeling since the supplement did not qualify as submitted.

Review

The submitted insert (**coded 189 0107 002, Rev. 9/98, 50019193**) was compared to the currently approved insert (**coded 50006017, August 1995**). In addition to formatting changes and other minor editorial revisions which do not affect the meaning of the information conveyed, the following changes have been made:

1. PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility:

   This subsection has been revised as follows (throughout this review, deletions are indicated by strikethroughs, new text is represented by a double underline):

[redacted]

Note: The final study reports of the referenced 104 week studies in rats and mice were submitted to IND [redacted] on April 7 and November 20, 1992, respectively. See the March 31, 1993 pharmacology review for additional information. According to a

March 24, 1999 pharmacology review of the current submission, the sponsor's proposed revision to this portion of the insert is unacceptable. Instead, the sponsor should be directed to revise this subsection to read,

"In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500 mg/kg/day and it was not tumorigenic. For a 50 kg person of average height (1.46 m^2 body surface area), this represents 2.5 times the recommended human dose on a body surface area basis (2960 mg/m^2/day). In a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose represents 1.5 times the recommended human dose on a body surface area basis.

No evidence of mutagenicity was observed in an in vitro Ames test and an in vivo mouse micronucleus test.

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.8 times the recommended human dose based on body surface area).

Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with PENTASA capsules during controlled clinical trials."

2. ADVERSE REACTIONS section:

   a. In the Other subsection (third paragraph) the first sentence has been revised to read, "Published case reports and/or spontaneous postmarketing surveillance have described infrequent instances of pericarditis, fatal myocarditis, chest pain and T-wave abnormalities, hypersensitivity pneumonitis, pancreatitis, nephrotic syndrome, interstitial nephritis, hepatitis, aplastic anemia, pancytopenia, leukopenia, agranulocytosis, or anemia while receiving mesalamine therapy."

   The firm provided a three page "Reasoned Statement" in support of this revision. On May 11, 1999 Dr. Hugo Gallo-Torres, Medical Team Leader indicated that the submitted information is sufficient to justify the proposed change.

   b. The following sentence has been added to the end of the Other subsection: "Allergic reactions, which could involve eosinophilia, can be seen in connection with PENTASA therapy."

   In response to the Division's August 25, 1998 request, the sponsor submitted an analysis of all safety reports pertaining to eosinophilia in a September 24, 1998 correspondence. This September 24, 1998 submission was referenced in the cover

letter for S-006. On May 11, 1999 Dr. Hugo Gallo-Torres indicated that the submitted information is sufficient to justify the proposed revision.

c. A Postmarketing Reports subsection has been added. It reads as follows:

"The following events have been identified during post-approval use of products which contain (or are metabolized to) mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:
Gastrointestinal: Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome which included hepatic function changes was also reported."

This wording was requested in the September 1, 1998 letter, therefore, it is acceptable.

3. HOW SUPPLIED section:

a. The NDC numbers have been revised from [redacted] to 54902-180-81 (240-count bottle) and from [redacted] to 54092-189-80 (80-count blister pack).

This modification reflects the July 1, 1998 change of NDA ownership from Hoechst Marion Roussel, Inc. to Roberts Laboratories Inc. Therefore, this is an acceptable editorial revision.

b. The firm has made a minor change to the existing capsule imprint (they have removed the Marion Merrell Dow portion of the imprint).

According to Dr. Eric Duffy, Chemistry Team Leader, this change is in accordance with 21 CFR 314.70 (d)(9) and is, therefore, acceptable.

4. Manufacturer/Distributor Block:

This section has been revised to indicate Roberts Laboratories Inc. as the manufacturer and distributor of Pentasa Capsules.

This is an acceptable editorial revision.

Conclusions

The firm should be requested to revise the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection to read as follows:

> "In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500 mg/kg/day and it was not tumorigenic. For a 50 kg person of average height (1.46 m^2 body surface area), this represents 2.5 times the recommended human dose on a body surface area basis (2960 mg/m^2/day). In a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose represents 1.5 times the recommended human dose on a body surface area basis.
>
> No evidence of mutagenicity was observed in an in vitro Ames test and an in vivo mouse micronucleus test.
>
> No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.8 times the recommended human dose based on body surface area).
>
> Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with PENTASA capsules during controlled clinical trials."

An Approvable letter which requests FPL, revised to include this change, will be drafted.

/S/ 5/12/99
Regulatory Health Project Manager

/S/ 5-12-99

cc:
Original NDA 20-049
HFD-180/Div. Files
HFD-180/McNeil
HFD-180/Choduary
HFD-180/Gallo-Torres
HFD-180/Duffy
draft: mm/May 7, 1999
r/d Initials: JChoudary 5/10/99
EDuffy 5/11/99
HGallo-Torres 5/11/99
LTalarico 5/11/99
final: May 12, 1999
CSO REVIEW

APPEARS THIS WAY
ON ORIGINAL