

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-301**

**OTHER REVIEW(S)**

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

---

CLINICAL INSPECTION SUMMARY

DATE:                    8/28/2008

TO:                     Heather Buck, Regulatory Project Manager  
Aisha Peterson, M.D., Medical Officer  
Division of Gastroenterology Products

FROM:                  Khairy Malek, M.D.  
Good Clinical Practice Branch 1  
Division of Scientific Investigations

THROUGH:             Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch 1  
Division of Scientific Investigations

SUBJECT:              Evaluation of Clinical Inspections

NDA #                  22-301

APPLICANT:            Salix Pharmaceuticals

DRUG:                 ——— (mesalamine) Encapsulated Granules      **b(4)**

NME:                    No

THERAPEUTIC CLASSIFICATION:      Standard, 10 month

INDICATIONS:        1. Maintenance of remission in mild to moderate ulcerative colitis.

CONSULTATION REQUEST DATE: March 27, 2008

DIVISION ACTION GOAL DATE: August 30, 2008

PDUFA DATE:                    October 31, 2008

I. BACKGROUND:

Mesalamine is the agent commonly used to induce and maintain remission in mild to moderately active ulcerative colitis. Its action appears to be a topical effect, rather than systemic. The clinical efficacy of oral mesalamine compounds depends upon delivery of the intact molecule to the colonic mucosa without breakdown during digestion. This can be done

Mesalamine Pellets (MP) is a novel formulation of mesalamine which combines the advantages of both a delayed and extended release oral solid dosage form

The study drug

b(4)

The inspected sites were chosen because of enrollment of large number of subjects. The Russian sites were also chosen because of suspicion of human subject protection violation as well as reported protocol violation.

Two protocols were inspected:

1. Protocol MPUC3003 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Trial To Evaluate The Use Of Mesalamine Pellet Formulation 1.5G QD To Maintain Remission From Mild To Moderate Ulcerative Colitis"
2. Protocol MPUC3004: Same title as protocol MPUC3003

II. RESULTS (by Site):

Name of CI, Location	Protocol # and # of Subjects	Inspection Date	Final Classification
Boris Starostin, M.D. St. Petersburg, Russia	MPUC3003 30 Subjects	July 21-25, 2008	VAI
Yuri Shvartz, M.D. Saratov, Russia	MPUC3004 30 Subjects	July 28-30, 2008	VAI
Andrey Rebrov, M.D. Saratov, Russia	MPUC3003 19 subjects	July 31-August 1, 2008	VAI
Glenn Gordon, M.D. Mexico, MO, USA	MPUC3003 12 Subjects	June 26-30, 2008	NAI
Salam Zakko, M.D. Bristol, CT, USA	MPUC3004 11 Subjects	June 24-27, 2008	NAI

Key to Classifications

- NAI = No deviation from regulations.
- VAI = Deviation(s) from regulations.
- OAI = Significant deviations from regulations. Data unreliable.
- Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Boris Starostin, M.D.-Site # 572  
City Polyclinic # 38, Centre for Gastroenterology No 1  
26, Kavalergardskaya, 193015, St. Petersburg, Russia
  - a. What was inspected: The field investigator and I reviewed the records of all subjects in the study. There were no limitations to the inspection.
  - b. General observations/commentary: We found 2 protocol violations:  
  
There were 3 flares in disease activity, for subjects # 8, 11 and 30, among the 30 subjects' records reviewed. The protocol specifies that a stool sample will be sent for analysis to rule out presence of Clostridium difficile, ova or parasites in case of a flare. In the 3 cases of flare, the clinical investigator (CI) did not send a stool sample for analysis. The CI defended his action, by stating that it was more important to treat the subjects' symptoms immediately rather than to follow the unscheduled visit procedures and leave the flare subjects without treatment until the stool analysis results are back.  
  
The second protocol violation is that, for two subjects (#18 and 33), when the CI received the hematology results and these were described by the lab as samples clotted or unsuitable for analysis, the CI did not submit a second sample for analysis. In case of subject # 18, the affected hematology samples were for Visits 2 and 3. In case of subject # 33, the affected samples were for screening and Visit 1.
  - c. Assessment of data integrity: These violations would not affect the validity of the data. The data from this site can be used in support of the NDA.
2. Yuri Shvartz M.D.-Site # 566  
Saratov State Medical University, Department of Hospital Therapy, Saratov Regional Clinical Hospital, 1 Smirnovskoye Ravine, Saratov 410053, Russia
  - a. What was inspected: We reviewed the records of all subjects in the study. There were no limitations to the inspection.
  - b. General observations/commentary: The study was well conducted except that the first 6 subjects, at the beginning of the study, # 1-6, were given the preparatory medication (Fortrans) for sigmoidoscopy one day before these subjects signed informed consent documents.
  - c. Assessment of data integrity: This violation would not affect the validity of the data. The data from this site can be used in support of the NDA.

3. Andrey P. Rebrov, M.D.-Site # 565  
Saratov State Medical University, Department of Hospital Therapy, Saratov Regional Clinical Hospital, 1 Smirnovskoye Ravine, Saratov 410053, Russia.
  - a. What was inspected: We reviewed all the 19 subjects' records at this site. There were no limitations to the inspection.
  - b. General observations/commentary: At this site we found one protocol violation, in that the CI enrolled one subject, # 9, in the study for two days before discontinuing the subject after realizing that the subject's lab result was positive for Hepatitis B.
  - c. Assessment of data integrity: Apart from the above protocol violation, the study was well conducted. This violation would not affect the validity of the data. The data from this site can be used in support of the NDA.
4. Glenn Gordon, M.D.-Site # 618  
Center for Digestive and Liver Disease, Inc., 714 Medical Park Drive, Mexico, MO 65265-3726, USA
  - a. What was inspected: The field investigator reviewed the records of all 12 subjects enrolled in the study, out of which 7 completed the study and 5 had early termination. There were no limitations to the inspection.
  - b. General Observations: At this site the field investigator observed no violations.
  - c. Assessment of data integrity: The data from this site are reliable and can be used in support of the NDA.
5. Salam Zakko, M.D.-Site 419  
Connecticut Gastroenterology Institute, Brewster Road  
Bristol, CT, USA.
  - a. What was inspected: At this site the field investigator inspected the records of all 11 subjects randomized. Seven subjects completed the study and 4 had early termination, one discontinued due to an adverse event, and 3 discontinued due to lack of efficacy. There were no limitations due to the inspection
  - b. General Observations: At this site the field investigator observed no violations.
  - c. Assessment of data integrity: The data from this study can be used in support of the NDA.

**IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

The data from the 5 sites inspected are reliable and can be used in support of the NDA

**Khairy Malek, M.O.  
Good Clinical Practice Branch I  
Division of Scientific Investigations**

**CONCURRENCE:**

{See appended electronic signature page}

**Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations**

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

/s/

-----  
Constance Lewin

8/29/2008 08:47:11 AM

MEDICAL OFFICER

Entered into DFS on behalf of Dr. Khairy Malek.

## **REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)**

### **Division of Gastroenterology Products**

**Application Number:** 22-301

**Name of Drug:** — (mesalamine) Encapsulated Granules

**b(4)**

**Applicant:** Salix Pharmaceuticals, Inc

### **Material Reviewed:**

**Submission Date(s):** December 21, 2007

**Receipt Date(s):** December 31, 2007

**Submission Date of Structure Product Labeling (SPL):** December 21, 2007

**Type of Labeling Reviewed:** Word

### **Background and Summary**

We received NDA 22-301 from Salix Pharmaceuticals, Inc. on December 31, 2007. The proposed indication for this NDA is maintenance of remission of ulcerative colitis in patients 18 years of age and older. The proposed prescribing information in Structured Product Labeling (SPL) format, and the proposed package insert in Physician's Labeling Rule (PLR) format was submitted with the original NDA. We have not yet received the color carton and container labels but expect them in June, 2008.

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

## Review

The following issues/deficiencies have been identified in your proposed labeling.

### 1. Highlights

- a. Revise the “**Initial U.S. Approval**” statement to read “**Initial U.S. Approval: 1987**”
  - The labeling should reflect...”The verbatim statement “Initial U.S. Approval” followed by the four-year digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients”. [Best Practices]. The active ingredient mesalamine was first approved as Rowasa NDA 19-618 on December 24, 1987<sup>1</sup>.
- b. Change font size from 10 point type to 8 point type, and adjust margins to ½ inch on all sides. Note that these adjustments will likely reduce the section to one-half page as is required.
  - Highlights, excluding the boxed warning, must be limited in length to one-half page (e.g., would fit on one-half page if printed on 8.5” x 11 paper, single spaced, 8 point type with ½ inch margins on all sides, in a two-column format). [Best Practices].
- c. Revision Date for a new NDA should be left blank at the time of submission and will be edited to the month/year of the application or supplement approval. Date should read: “Revised: month/year”. [Best Practices].

### 2. Table of Contents

- Change 13.2 subsection title from "Animal Toxicology" to “Animal Toxicology and/or Pharmacology”. [Best Practices].
- Create subsection headings that identify the content. Avoid using the word “General”. See subsection 5.1 under the Warnings and Precautions. [Best Practices].

### 3. Full Prescribing Information

- Remove bold from body systems in subsection 6.1. All headings and subheadings must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Therefore, for other labeling information, use bold type sparingly; and use another method for emphasis such as italics or underline. [Best Practices].
- In subsection 6.1 Clinical Studies Experience, include the following statement (or appropriate modification) preceding presentation of adverse reactions from clinical trials: [

b(4)

<sup>1</sup> [http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl\\_No=019618&TABLE1=OB\\_Rx](http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=019618&TABLE1=OB_Rx)

**Recommendations**

Please address the identified deficiencies/issues and re-submit labeling by August 1, 2008. This updated version of labeling will be used for further labeling discussions.

---

Heather Buck  
Regulatory Project Manager  
Division of Gastroenterology Products

Supervisory Comment/Concurrence:

---

Brian Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff  
Division of Gastroenterology Products

Drafted: HB 3/26/08  
Revised/Initialed: BS 3/26/08  
Finalized: 3/27/08  
Filename:  
**RPM LABELING REVIEW**

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

/s/

-----  
Heather G Buck  
3/27/2008 08:23:55 AM  
CSO

Brian Strongin  
3/27/2008 09:57:48 AM  
CSO