CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-301

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	October 31, 2008
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA	22-301
Applicant Name	Salix Pharmaceuticals
Date of Submission	December 21, 2007
PDUFA Goal Date	October 31, 2008
Proprietary Name / Established (USAN) Name	APRISO Mesalamine
Dosage Forms / Strength	0.375 g extended release capsule for oral administration
Proposed Indication	Maintenance of remission of ulcerative colitis
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Aisha Peterson, MD/John Hyde, MD
Statistical Review	Shahla Farr, MS/Mike Welch, Ph.D.
Pharmacology Toxicology Review	Sushanta Chakder, Ph.D.
CMC Review/OBP Review	Gene Holbert, Ph.D.
Clinical Pharmacology Review	Insook Kim, Ph.D./Sue-Chih Lee, Ph.D.
DDMAC	Kathleen Klemm, Pharm.D.
DSI	Khairy Malek, MD/Constance Lewin, MD, MPH
CDTL Review	John Hyde, MD
OSE/DMEPA	Melina Griffis, R.Ph./Kellie Taylor, PharmD, MPH/Carol Holquist, R.Ph.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

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Division Director Review

1. Introduction

This NDA submission is a 505(b)(2) application. The applicant did not conduct all the nonclinical studies relied upon to support approval. The reference listed drugs are Canasa and Asacol. This review summarizes the salient findings of the FDA reviewers. Please refer to the Cross Disciplinary Team Leader review written by Dr. John Hyde for a comprehensive presentation of the issues identified during the review of this application, a description of the FDA reviewers' analyses, and a discussion of the review team's risk/benefit decision.

2. Background

The regulatory history of this application is clearly summarized in Dr. John Hyde's Cross Disciplinary Team Leader review. Although two major studies were submitted in this application to establish the efficacy of the mesalamine product Apriso, the biostatistical reviewer, Shahla Farr, MS, stated in her review that she believes that one of the studies can only be viewed as supportive evidence of efficacy. She expressed concern about the late changes in the statistical analysis plan of the study and the lack of statistically significant supportive evidence of efficacy in its secondary efficacy endpoints. Dr. Aisha Peterson, MD, the primary clinical reviewer, concluded, however, that both studies established the effectiveness of Apriso. Dr. John Hyde addresses this variation in opinion among the reviewers regarding the strength of evidence of effectiveness demonstrated by the second study in Section 11.Other Relevant Regulatory Issues of his review.

3. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding issues.

The manufacturing process involves application of ———— polymer matrix mesalamine granule core. The coated granules are filled into gelatin capsules. The inner coating is designed to dissolve when exposed to pH ≥ 6, delivering mesalamine past the stomach. Although the formulation has both delayed- and extended-release characteristics, the chemistry reviewer recommended that the dosage form be designated "extended-release capsules." However, due to its delayed-release characteristics, the chemistry reviewer recommended that the product's labeling include instructions that it should not be taken with antacids.

b(4)

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval. I concur with the reviewer's recommendations regarding product labeling.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer, Dr. Insook Kim, Ph.D., that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Two major trials (Study 3003 and Study 3004) of similar design were submitted to support the effectiveness of encapsulated mesalamine granules (eMG) capsules (Apriso) in maintenance of remission of ulcerative colitis. The studies were randomized, double-blind, and placebo controlled. They enrolled patients with a history of ulcerative colitis (UC) whose disease had been in remission for at least 1 month and not more than 12 months. Remission was defined as a revised Sutherland Disease Activity Index (DAI) rectal bleeding score of 0 and mucosal appearance score of 0 or 1. Patients were treated with 1.5 g of eMG or placebo x 1 dose daily for 6 months.

The primary endpoint of the studies was the proportion of subjects relapse-free after 6 months of treatment. Relapse was defined, again using the modified Sutherland Disease Activity Index, as rectal bleeding score ≥ 1 and a mucosal appearance score ≥ 2. In the protocols' original analysis plans, patients who discontinued early were to be counted as relapses. However, late in the studies' conduct, the analysis plans were amended to count early discontinuation as relapse only if the discontinuation was deemed related to lack of efficacy or to a UC-related adverse event.

In both studies, treatment with eMG resulted in a statistically significantly higher proportion of patients who were relapse-free at 6 months. (See the table below, which has been reproduced from biostatistical reviewer Shahla Farr's review). The biostatistical reviewer, however, expressed concern about the robustness of the observed outcome in Study 3004, for the following reasons:

1) Study 3004 was stopped early. Although both studies started in December 2004, Study 3003 completed before Study 3004 in April of 2007 (with total N=305). Study 3004 was subsequently stopped by an amendment reducing its sample size, before completing its originally planned target enrollment – in August 2007 (with total N=257). When the reviewer performed a sensitivity analysis to explore the

impact of early stopping, assigning the observed placebo "success rate" in the study to the 43 subjects who would have been enrolled if the study had not been terminated early, the p value for the outcome comparison in Study 3004 shifted to p=0.06.

2) When the FDA reviewer applied the more conservative imputation strategy to account for missing data at 6 months (the original protocol plan of counting all patients who discontinued treatment early as having experienced a relapse), the p-value shifted in Study 3004 from the $p< 0.001$ observed in the applicant's analysis, to $p<0.046$. The applicant's analysis utilized a missing data imputation strategy for the primary efficacy analysis that counted only patients who were considered to have left the study early because of lack of efficacy or a UC-related adverse event as a relapse event. The results from these two analysis approaches are presented in the Table below with the more conservative strategy labeled "R_ITT" (FDA Reviewer ITT analysis) and the less conservative strategy employed by the applicant as "A_ITT" (Applicant's ITT analysis).

3) In Study 3004, the hierarchical analysis of the secondary endpoints, which was prespecified only in a protocol amendment that occurred after study enrollment completed, stopped at the first secondary endpoint tested, rectal bleeding, because it failed statistical significance.

Proportion of subjects relapse-free after 6 months of treatment

Study 3003	Mesalamine	Placebo	95% CI for Difference	P-Value
No Relapse (A_ITT)**	165/209=79%	56/96=58%	21% (9.5%, 32%)	<0.001
No Relapse (R_ITT)***	143/209=68%	49/96=51%	17% (5.5%, 29.2%)	<0.001
Study 3004				
No Relapse (S_ITT)**	131/164=80%	63/93=68%	12% (1.1%, 24%)	0.029
No Relapse (R_ITT)***	117/164=71%	55/93=59%	12% (0%, 24.5%)	0.046

**Applicant's ITT analysis (early dropouts as relapse only lack of efficacy or if UC-related AE occurred.

***FDA Reviewer's ITT analysis, all early withdrawals as relapse

Although the biostatistical reviewer expressed concern about the robustness of the results of Study 3004, she still felt that this study was supportive of the findings of Study 3003. The clinical reviewers were persuaded that both of these major studies provided evidence that established that Apriso is effective in maintaining remission from ulcerative colitis. Dr. Hyde pointed out in his Cross-Disciplinary Team Leader review that the outcome observed in Study 3003 was itself highly statistically significant (even utilizing the more conservative FDA

analysis), and could provide strong evidence of effectiveness, even as a stand alone trial. I concur with Dr. Hyde's conclusion. I also concur with the reviewers that the efficacy results presented in the product label should be those resulting from the analysis coding early discontinuations of any kind as a relapse. That analysis was the protocols' original designated analysis.

Dr. John Hyde, the Cross-Discipline Team leader, noted in his review that although the duration of treatment for performing efficacy evaluation in both the major studies was 6 months, substantial safety data were provided for product exposures beyond 6 months. Given that there was no safety issue identified associated with exposures longer than 6 months that would preclude longer drug exposures, Dr. Hyde did not recommend that the label should limit the duration of treatment to the 6 month period evaluated in the two major clinical trials. I concur with this decision.

8. Safety

Patients were randomized on a 2:1 basis in the two major randomized, controlled clinical trials of 6 months duration that support this 505(b)(2) application, Study 3003 and Study 3004. Three hundred sixty seven of those patients were treated with at least one dose of Apriso and provided safety data that could be compared to placebo control. In addition, there was an open label, single arm safety study that enrolled patients who had completed their participation in the two randomized, controlled trials, as well as patients who had not been previously exposed to Apriso. This extension study provides safety data on 190 additional patients exposed to Apriso in an open label setting. Of the total 557 patients that comprised the safety data base, 352 had been exposed to drug for at least 6 months and 250 for at least a year.

Mesalamine is not a new molecular entity and there is extensive clinical experience associated with its use. OSE reviews that were performed for other mesalamine applications were reviewed for this application. Dr. Peterson also requested mesalamine postmarketing database reports for hepatic adverse events and found cases of worsening of pre-existing liver disease in patients who had taken mesalamine. Based on her postmarketing safety review of mesalamine products in general, she recommended that product labeling include in the Warnings and Precautions section a description of the observation of onset of liver failure in individuals with pre-existing liver disease and a statement that caution should be exercised when administering Apriso to patients with liver disease. I concur with the clinical reviewers' recommendations for product labeling.

I concur with the reviewers' decision to not require a thorough QT study for approval of this application given the extensive clinical experience with mesalamine, its limited absorption and the lack of nonclinical evidence that there is a risk of QT prolongation associated with mesalamine.

9. Advisory Committee Meeting

There was no advisory committee meeting to discuss this application. The product is not a new molecular entity and the reviewers had no scientific issues that required discussion in an advisory committee.

10. Pediatrics

The application was presented to the PERC and the committee agreed with the reviewers' recommendation that the applicant be required to study at least two dosing regimens in children aged 5 years and older with ulcerative colitis in remission to assess pharmacokinetics, safety and effectiveness of this product. The PeRC concurred with a deferral of the submission of the study for this age range because the adult indication is otherwise ready to be approved. Because there are too few children below the age of 5 with ulcerative colitis to study, the PeRC concurred with a waiver of studies for that age group.

11. Other Relevant Regulatory Issues

The Division of Scientific Investigations audited two U.S. sites from each of the major efficacy studies, Studies 3003 and 3004, as well as three Russian sites. Sites were selected on the basis of their having enrolled large numbers of patients. After conducting the inspections, DSI recommended that the data from the sites could be used to support the NDA.

Dr. Peterson reviewed the financial disclosures for Studies 3003, 3004 and 3005. She identified only one investigator who had a disclosed equity interest. Because that investigator had only enrolled 4 of the 256 patients that participated in study 3004, and only 9 of 396 of the patients in Study 3005, she determined that the impact of the equity interest on the reported outcome of these studies was minimal.

12. Labeling

I concur with the labeling recommendations of the reviewers, which are thoroughly summarized in Section 12 Labeling of Dr. John Hyde's Cross-Discipline Team Leader review.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - I recommend approval of this 505(b)(2) application.
- Risk Benefit Assessment – I concur with the risk and benefit assessment of the reviewers. I concur with Dr. John Hyde that the FDA's review findings indicate that the risk and benefit characteristics of Apriso are similar to oral mesalamine products that are approved and marketed.
- Recommendation for Postmarketing Risk Management Activities – I do not recommend a REMS.
- Recommendation for other Postmarketing Study Commitments
  Pediatric studies should be required under PREA for patients aged 5 to 17 years.

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/s/

Donna Griebel
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DIRECTOR