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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

Appears This Way
On Original

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

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