CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-301

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 29, 2008
From	John E. Hyde, Ph.D., M.D., Clinical Team Leader, DGP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 22-301 N000, Original NDA
Applicant	Salix Pharmaceuticals, Inc.
Date of Submission	December 21, 2007; Received December 31, 2007
PDUFA Goal Date	October 31, 2008
Proprietary Name / **Established (USAN) names**	APRISO Mesalamine
Dosage forms / Strength	Extended-release capsules for oral administration; each capsule contains 0.375 g mesalamine.
Proposed Indication	Maintenance of remission of ulcerative colitis in patients 18 year of age and older.
Recommended:	Approval

1. Introduction

This application, received December 31, 2007, is an original NDA submission for a new oral formulation of mesalamine, also known as 5-aminosalicylic acid, or 5-ASA. The product is a gelatin capsule containing granules of mesalamine coated with excipients to give it both delayed-release and extended-release characteristics. Each capsule contains 0.375 g mesalamine.

The proposed indication is "the maintenance of remission of ulcerative colitis in patients 18 years of age and older," with proposed dosing of four capsules (1.5 g) once daily with or without food. The Applicant proposed labeling with a contraindication for hypersensitivity to salicylates, and with warnings about acute intolerance syndrome, renal toxicity, use in hepatic impairment, use in patients with [ ] and use in patients with phenylketonuria. b(4)

This application is not for a new molecular entity. Mesalamine was first approved in a rectal suppository for ulcerative colitis in 1987. Subsequently, several oral formulations of mesalamine have been approved for treating ulcerative colitis.

Because the Applicant did not conduct all of the preclinical studies being relied upon, this was submitted as a 505B(2) application. The Applicant referenced preclinical information from studies conducted by Proctor & Gamble Pharmaceuticals for NDA 19-651 (Asacol) and by Axcan Scandipharm, Inc., for NDA 21-252 (Canasa).

2. Background

General Background

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown etiology. Peak age of onset is in the early twenties, but age of onset can vary widely. UC is more common in whites vs. non-whites and in women vs. men. The disease is manifest as mucosal inflammation and mucosal ulceration that occurs in the colon in a continuous segment beginning with the rectum. Extent of involvement varies, but it can include the entire colon. Involved areas classically show inflammatory changes that are limited to the mucosa, and, depending on severity, there may be extensive, broad-based ulceration. Clinically, UC presents as a chronic relapsing disease with variable-length bouts of bloody mucoid diarrhea and lower abdominal pain, but there may be long quiescent periods between attacks. There may also be systemic manifestations of the disease, with involvement of joints, eyes, skin, or the hepatobiliary system. Potential serious complications include severe bleeding, toxic megacolon, and perforation. There is a very significant risk of colon cancer with longstanding disease, such that pancolitis of 10 years duration or longer has a 20- to 30-fold increased risk of cancer compared to the general population.

Approved therapies for UC include corticosteroids to "tide the patient over a critical period" of UC, and aminosalicylates, which are available in rectal formulations (Canasa and Rowasa [mesalamine]) and oral formulations (Azulfadine [sulfasalazine]; Asacol, Pentasa, and Lialda [mesalamine]; Dipentum [olsalazine]; and Colazal [balsalazide]) as limited-term therapy to treat mildly or moderately active UC. Azulfadine, Asacol, and Dipentum are also approved as chronic therapy to maintain remission in UC. The safety and effectiveness of oral mesalamine products for pediatric ulcerative colitis have not been established, although balsalazide (Colazal) is approved for pediatric use in patients 5 years and older. Also used, but unapproved, therapies for ulcerative colitis include azathioprine and 6-mercaptopurine, and, less commonly, cyclosporine. Use of any of the preceding has come to be considered part of "conventional therapy." Remicade (infliximab), a TNF blocker, is approved for induction and maintenance of remission in moderately to severely active UC with inadequate response to conventional therapy.

Mesalamine's specific mechanism of action is unknown, but it is thought to act primarily topically in the colon by blocking cyclooxygenase and 5-lipoxygenase, thereby inhibiting production of arachidonic acid metabolites and diminishing inflammation. Mesalamine may also act as a reactive oxygen metabolite scavenger. Oral formulations of mesalamine are designed to have delayed- and/or extended-release characteristics in an attempt to target delivery to the presumed site of action. Typically, a third or less of orally administered mesalamine products is systemically absorbed. Preclinical studies identified the kidney and GI tract as targets of toxicity when given in high doses.

Approved oral mesalamine products contain a warning for an adverse reaction that can look like exacerbation of ulcerative colitis, and they also contain a warning for the potential to cause renal impairment. Postmarketing reports of renal injury have been uncommon, and it appears to be an idiopathic reaction to mesalamine when given to humans in the therapeutic dose range. The approved dose of oral mesalamine to treat active UC ranges from 2.4 to

4.8 g/day, in single or divided doses, depending on formulation. The approved dose for maintenance of remission (Asacol only) is 1.6 g/day divided into BID dosing.

Presubmission Communications between FDA and the IND Sponsors

The Applicant held a pre-IND meeting with the Division on August 20, 2003. At that meeting, the Applicant was advised that a 505B(2) application could be used to support the new formulation, but that it should include comprehensive summaries of the referenced studies, and that additional preclinical studies would be needed for the excipient [ ] The Applicant was also advised that it would be acceptable to pursue an application for maintenance of remission [ ] The IND submission was received on October 30, 2003, and studies were allowed to proceed. b(4)

An End-of-Phase-2 meeting was held on October 6, 2004. The Applicant proposed to conduct two identically designed, placebo-controlled, six-month studies of maintenance for remission in ulcerative colitis. Remission was defined as absence of blood in the stools and an endoscopy score of 1 or less based on the Sutherland Index endoscopy criteria. The Division agreed that the proposed studies should suffice for supporting the indication of maintenance, but the Division requested that the endoscopy criteria be modified so that remission required absence of friability; the Applicant agreed. The Division stated that the six-month study duration was adequate. The Applicant also had data on a similar formulation manufactured by Dr. Falk Pharma and inquired about the acceptability of using that data for the safety database. The Division responded that those data would be considered only as supportive and stated that the safety would largely be dependent on data from patients treated with the Applicant's formulation. The Division advised that about 100 patients treated for one year with the to-be-marketed formulation would be needed. The Division remarked that a PK study in pediatric patients would not be sufficient to fulfill the pediatric requirement, and requested that a pediatric plan be included at the time of NDA submission. The Division requested that the Applicant conduct Segment I and Segment III reproductive toxicity studies for [ ] in rats in addition to the their proposed six-month non-rodent oral toxicity studies and genotoxicity studies. The Applicant stated they did not believe Segment I and III studies were necessary and planned to provide FDA with additional information. The Division stated the studies to support clinical pharmacology and pharmacokinetics appeared acceptable. b(4)

A pre-NDA meeting was held October 29, 2007. The Division stated that the proposed safety database appeared adequate, but that its adequacy would be a review issue. The Agency asked that the submission clearly identify the formulation used in each PK study and recommended that the Applicant conduct a dissolution comparison of the Dr. Falk Pharma product to help assess the acceptability of data obtained using that product. The Division stated the toxicology package for [ ] appeared adequate. The Division did not agree that a pediatric waiver was appropriate, and the Division advised the Applicant to submit a plan or a request for deferral in the NDA submission. b(4)

Submission and Review

The NDA was dated December 21, 2007, and was received on December 31, 2007. It was given Standard review priority with an action date of October 31, 2008. The Application was submitted as paper copies. In the course of the filing review, problems were identified with the table of contents, indexing and tabbing of jackets, and completeness of the safety data as it pertained to postmarketing experience with other mesalamine products. The Division and Applicant agreed on a plan to correct the deficiencies, and the application was filed with the Applicant's commitment to provide additional safety information and new review jackets to resolve the organization problems.

Shortly after submitting the application, the Applicant decided to withdraw the proposed trade name of '[ ] and replaced it with "APRISO." b(4)

No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines have all written review documents. The primary review documents relied upon are the following:

Clinical Review by A. Peterson, dated 10/29/08.
Statistical Review and Evaluation by S. Farr, dated 9/29/08.
Office of Clinical Pharmacology Review by I. Kim, dated 10/7/08.
Pharmacology/Toxicology Review and Evaluation by S. Chakder, dated 9/25/08.
Chemistry Review by G. Holbert, dated 10/28/08.
Clinical Inspection Summary by K Malek, dated 8/28/08.
Proprietary Name, Label and Labeling Review by M. Griffis, dated 10/9/08.
DDMAC Labeling Comments by K. Klemm, dated 10/15/08.

The following review OSE review documents were completed for other applications but have relevance to the current application and are referenced in the Clinical Review:

Pericardial Effusion safety review for mesalamine by A. Mackey, dated 2/25/08, archived under NDAs 19-651, 19-618, 19-919, 20-049, 21-252, and 22-000.
Renal Impairment safety review for mesalamine by A. Mackey, dated 3/19/08, archived under NDAs 19-651, 19-618, 19-919, 20-049, 21-252, and 22-000.

The reviews should be consulted for more specific details of the application and review conclusions. This memorandum summarizes selected information from the primary review documents.

3. CMC

See the Chemistry Review by G. Holbert dated 10/28/08 for complete information.

General product quality considerations
The product consists of a polymer matrix mesalamine core granule with — coatings designed to resist dissolution in the stomach but to dissolve at pH ≥ 6. The granules are filled into a hard gelatin capsule. Each capsule contains 0.375 g mesalamine. The drug substance is manufactured by [ ] and the drug product is manufactured by Catalent Pharma in Winchester, KY. b(4)

The Chemistry Reviewer concluded that the NDA provided sufficient information to assure the identity, strength, purity, and quality of the product, and that there was adequate information on controls, process, specifications, and container/closure to support approval. Stability data were provided to support expiration dating of 36 months.

Facilities review/inspection
The Establishment Evaluation Reports of the drug substance manufacturer, drug product manufacturer, finished dosage packers, and finished dosage stability tester were all acceptable. An overall recommendation of Acceptable was issued 8/4/08.

Other issues
This formulation has both delayed-release and extended-release characteristics. There is no FDA-accepted dosage form designation that includes both properties. In the labeling review, the Chemistry Reviewer recommended that the dosage form designation be "extended-release capsules."

Because this also is a delayed-release formulation, which relies on pH-dependent dissolution to obtain its delayed-release property, the Chemistry Reviewer also recommended that labeling instruct that the product is not to be taken with antacids.

The labels had adequate information as required.

Conclusions and Recommendations
The Chemistry Reviewer recommended the NDA for approval. He recommended labeling changes as described above. No Phase 4 commitments, agreements, or risk management steps were recommended.

4. Nonclinical Pharmacology/Toxicology

See the Pharmacology/Toxicology Review and Evaluation by S. Chakder dated 9/25/08 for complete information.

This application falls under Section 505B(2) of the FD&C Act because it relies on pharmacology and toxicology data for which the Applicant does not have right of reference. The Applicant made reference to a six-month repeat-dose rat study, a 12-month repeated-

dose dog study, and mouse and rat carcinogenicity studies that were previously reviewed under NDA 19-651 (Asacol, Proctor & Gamble), and to a mouse lymphoma assay reviewed under NDA 21-252 (Canasa, Axcan Scandipharm, Inc.). The Applicant conducted and submitted four-week and 26-week oral toxicity studies with [ ] which is a component of the Applicant's formulation. The Applicant also provided publications on the pharmacodynamics of mesalamine. b(4)

General nonclinical pharmacology/toxicology considerations.
The kidney and GI tract were target organs of toxicity for mesalamine in acute studies in rats and mice. In repeat-dose studies in rats and dogs, the kidney was the target organ, with findings at high doses of regions of cortical and papillary necrosis and tubular changes. Other findings in chronic studies were stomach ulceration, gastric mucosal hemorrhage with mucosal/submucosal fibrosis, and urinary bladder inflammation in rats. Chronic nephritis was seen in chronic studies in dogs.

In a 26-week oral toxicity study in dogs using [ ] up to 250 mg/kg/day, target organs were gall bladder, spleen, and urinary bladder. The 250 mg/day dose was a tolerated dose. b(4)

Carcinogenicity
Mesalamine was negative in genotoxicity assays. Mesalamine was not carcinogenic in rats at doses up to 480 mg/kg/day or in mice up to 2000 mg/kg/day.

Reproductive toxicology
Mesalamine had no effect on fertility or reproduction in male and female rats at oral doses up to 480 mg/kg/day, and it was not teratogenic in rats and rabbits at oral doses up to 480 mg/kg/day.

Other issues
The Reviewer recommended changes to labeling sections 8.1 (Pregnancy), 13.1 (Carcinogenesis), and 13.2 (Animal Toxicology) to insert or correct scaling factors relating the animal doses to the recommended human doses. See the Pharmacology/ Toxicology review document for details.

Conclusions and Recommendations
The Pharmacology/Toxicology Reviewer recommended that the application was approvable with changes to the labeling. The Reviewer did not recommend any Phase 4 commitments.

5. Clinical Pharmacology/Biopharmaceutics

See the Office of Clinical Pharmacology Review by I. Kim dated 10/7/08 for complete information.

General clinical pharmacology/biopharmaceutics.
The major metabolite of mesalamine is N-acetyl mesalamine (N-Ac-5-ASA), which is formed by N-acetyltransferase activity in the liver and intestinal mucosa. When Apriso is

administered under fasting conditions, about 32% ± 11% (SD) of the mesalamine is absorbed. With repeated dosing, the T_{max} is 4 hours for mesalamine and 5 hours for N-Ac-5-ASA. The $t_{½}$ is about 10 hours for mesalamine and 14 hours for N-Ac-5-ASA. Most of the drug is eliminated unabsorbed in the feces. Of the 32% that is absorbed, 2% is excreted in the urine as mesalamine, and 30% is excreted as N-Ac-5-ASA.

The food effect was evaluated using the mesalamine granules in a sachet (rather than in a gelatin capsule), a formulation that was demonstrated to be equivalent to the commercial product in an *in vitro* comparative dissolution study. The Clinical Pharmacology Reviewer noted that administration with food produced a lengthening of T_{max} but similar C_{max} compared to fasted administration. The Reviewer concluded that Apriso can be taken without regard to food.

Drug-drug interactions

From an *in vitro* study reviewed under a supplement to NDA 20-610 (Colazal [balsalazide]), mesalamine and its N-acetyl metabolite were shown not to inhibit CYP1A2, CYP2C0, CYP2C19, CYP2D6, and CYP3A4/5. Therefore, mesalamine is not expected to inhibit the metabolism of other drugs that are substrates of those CYP enzymes. No direct human *in vivo* drug-drug interaction studies were conducted with Apriso.

Critical intrinsic factors potentially affecting elimination

No investigations were conducted on the effect of intrinsic factors such as age, gender, hepatic insufficiency, or renal impairment on drug elimination.

Demographic interactions/special populations

No studies were done to evaluation the effects of demographic or special populations on the pharmacokinetics of Apriso.

Thorough QT study or other QT assessment

No thorough QT study or other QT assessment was performed. See comments under Other Relevant Regulatory Issues, below.

Other issues

The Applicant presented a scintographic study using radiolabeled mesalamine granules formulated by Dr. Falk Pharma and claimed that it showed approximately 80% of the orally administered dose was available in the colon. The Clinical Pharmacology Reviewer did not feel that the claim was substantiated, because the analysis could not distinguish between released and unreleased mesalamine and because the limited absorption at the target region in the intestine may not parallel availability in the target region.

The Clinical Pharmacology Reviewer recommended that labeling include multiple-dose PK results, that PK results be presented in a tabular format, that fecal excretion results be deleted, and that the *in vitro* drug-interaction study results be included in the Pharmacokinetics section.

Conclusions

The Clinical Pharmacology Reviewer found the information in the NDA acceptable provided agreement could be reached regarding the recommended labeling changes.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Apriso is not an antimicrobial agent.

7. Clinical/Statistical- Efficacy

The reader is referred to the Clinical Review by A. Peterson dated 10/29/08 and the Statistical Review by S. Farr dated 9/29/08 for complete information.

The substantial evidence for efficacy in this application came from the Applicant's two pivotal studies of maintenance of remission in UC. They were essentially identical in design and are described together below.

Phase 3 Studies – MPUC3003 and MPUC3004 (Study 3 and Study 4)

Both of these Phase 3 studies were randomized, double-blind, placebo-controlled, multicenter studies in patients with UC in remission. The sites were in the U.S. and Russia. Study MPUC3003 (herein identified as "Study 3" for convenience) enrolled 305 patients and Study MPUC3004 (Study 4) enrolled 257. Patients were randomized to Apriso 1.5 g/day or placebo. The studies were designed to have a treatment period of six months. Patients who completed either study could be entered into the long-term, open-label study, MPUC3005 (Study 5).

Eligibility, treatment, and assessments

To be eligible, patients needed to be adults with an historically confirmed diagnosis of UC in remission for at least one month but with at least one flair in the past 12 months. Current remission was defined as a rectal bleeding score of 0 (no bleeding) and an endoscopy score of 0 or 1 using the Sutherland Index criteria (but endoscopic criteria were modified so that presence of friability required assigning a score of at least 2). Patients were excluded for history of bowel surgery other than appendectomy, abnormally elevated creatinine, liver enzyme or bilirubin elevation more than twice normal, other disease of the GI tract, significant medical conditions, allergy to salicylates, or phenylketonuria. Patients could not have received immunosuppressants or corticosteroids (oral, IV, or topical rectal) within 30 days of screening. See the Clinical Review for details of the eligibility criteria.

In both studies, patients were randomized 2:1 to be treated with oral dosing of either Apriso 1.5 g/day or placebo. Study drug was to be taken once daily in the morning for six months. In both studies, concomitant therapy could not include immunosuppressants, alternative UC therapy, systemic or topical corticosteroids, diarrhea preparations, or intestinal regulators. NSAIDs could not be used for longer than six weeks except for low-dose aspirin. Oral antibiotics were not allowed except for 7- to 10-day courses of metronidazole or ciprofloxacin.

In-office study visits were conducted at Month 1, Month 3 and Month 6. At these visits patients had a physical exam, routine blood tests, and urinalysis. Sutherland Index, excluding endoscopy score, was collected at the Month 1 and 3 visits. At Month 6, patients had a repeat endoscopy for assessment of remission status. Patients who presented with symptoms of UC relapse had stool cultures performed and were treated with antimicrobial therapy if positive. If cultures were negative, patients underwent endoscopy to determine relapse status. Patients who discontinued the study for any reason prior to Month 6 were to have all of the Month 6 assessments performed, including endoscopy.

Endpoints

The primary endpoint in both studies was maintenance of clinical remission through Month 6; with relapse from remission defined as a rectal bleeding score of ≥ 1 *and* an endoscopy score of ≥ 2 (note that this is not the complement of the remission criteria used to determine study eligibility). In the initial protocols, patients who discontinued were to be counted as relapses. Late in the studies, the analysis plans were amended to change this definition so that discontinuations were to be counted as relapses only if the discontinuations were for lack of efficacy or for a UC-related adverse event. See the Statistical Review and Evaluation for discussion of the details and timing of these amendments.

Protocol-specified major secondary endpoints were: 1) change in rectal bleeding score, 2) change in mucosal appearance score, 3) change in physician's rating of disease activity, 4) proportion with DAI ≤ 2 and with all components ≤ 1 and no rectal bleeding, 5) mean change in DAI, 6) relapse-free duration, and 7) change in stool frequency score. Secondary endpoints were to be analyzed in the ITT population with LOCF imputation. To control for multiplicity, the endpoints were to be analyzed in sequence. If statistical significance was not achieved, all subsequent endpoint analyses were to be considered exploratory.

Results

A total of 305 patients from 42 centers participated in Study 3, and 257 patients from 37 centers participated in Study 4. The median age was 46 years in both studies, percent male was 48% and 47% (values are cited for Study 3 and Study 4, respectively), percent Caucasian was 90% and 96%, and percent from U.S. sites was 52% and 40%. The percent with baseline Sutherland Index score of 0 was 34% and 43%; approximately 80% of all patients had baseline score ≤ 1 (using the modified endoscopy scoring).

The tables below present the principal efficacy results for maintenance of relapse-free status for Studies 3 and 4. The first table presents results of the Applicant's primary analysis according the statistical plan in the final protocol amendments. (By that analysis, early discontinuations without endoscopy are counted as relapses only if the discontinuation was for lack of efficacy or for a UC-related adverse reaction.) The second table presents the results counting all early discontinuations as relapses.

Percentage of Patients Relapse-Free through 6 Months in Maintenance Studies
Applicant's Primary Analysis*

	APRISO 1.5 g/day % (# no relapse/N)	Placebo % (# no relapse/N)	Difference (95% C.I.)	P-value
Study 3	**79%** (165/209)	**58%** (56/96)	**21%** (9.5%, 32%)	<0.001
Study 4	**80%** (131/164)	**68%** (63/93)	**12%** (1.1%, 24%)	0.029

* Early dropouts counted as relapse only if lack of efficacy or if UC-related adverse event occurred.

Percentage of Patients Relapse-Free through 6 Months in Maintenance Studies
All Dropouts Counted as Relapse

	APRISO 1.5 g/day % (# no relapse/N)	Placebo % (# no relapse/N)	Difference (95% C.I.)	P-value
Study 3	**68%** (143/209)	**51%** (49/96)	**17%** (5.5%, 29.2%)	<0.001
Study 4	**71%** (117/164)	**59%** (55/93)	**12%** (0%, 24.5%)	0.046

Subgroup analyses of the primary outcomes in the pooled studies were conducted by country, gender, age group, race, baseline disease severity, and baseline remission duration. There were too few non-whites and too few patients over 65 years to provide meaningful conclusions about those groups, although the estimated treatment effect was at least as large in non-whites, but little effect was seen in patients over 65. For the other subgroup analyses, the observed treatment effects were generally in the same range as the overall effect, and nominal statistical significance for each subgroup was seen in the pooled analysis. See the Statistical and Clinical Reviews for details.

Secondary endpoints analyses found a greater increase from baseline in rectal bleeding for placebo in Study 3 compared to Apriso (p=0.01), but there was not a statistically significant difference for the second secondary endpoint of change in mucosal appearance (p=0.41). By the hierarchical analysis plan, none of the other secondary endpoints in Study 3 were deemed to show statistically significant differences. In Study 4 the change in rectal bleeding score did not show a statistically significant difference (p=0.38), so that none of the differences in secondary endpoints in that study were deemed statistically significant.

The Statistical Reviewer noted that the imputation strategy for the primary endpoint and the hierarchical testing order for the secondary endpoints were changed in late-stage protocol amendments after study completion. The Statistical Reviewer also noted that the sample size for Study 4 was revised downward from 300 to 250 in an amendment dated 8/9/07, which is one day after the stated Study 4 completion date. The Applicant stated the amendment occurred prior to breaking the study blind.

Conclusions and Recommendations
The Statistical Reviewer concluded that the results reported in the submission supported the conclusion that Apriso is efficacious for maintenance of remission of UC. She felt that the evidence from Study 3 was clearer and that Study 4 should only be considered as supportive due to the late-stage study design changes and lack of secondary endpoint efficacy.

The Clinical Reviewer concluded that both pivotal studies demonstrated Apriso is effective in maintenance of remission from ulcerative colitis, and that the efficacy profile was the same between genders and nationalities. She felt that the limited enrollment of non-whites and patients over 65 made conclusions about those subgroups difficult, but that it was appropriate to extrapolate efficacy to them. The Clinical Reviewer recommended that the information in the application supported approval for the maintenance of remission of ulcerative colitis in patients 18 years of age and older.

8. Safety

In addition to the two six-month efficacy studies described above, the Applicant conducted an open-label extension study, Study 5. The study accepted patients who completed Study 3 or Study 4, provided they were in remission, had not withdrawn for a drug-related adverse reaction, and had acceptable compliance with taking study medication. Study 5 also accepted additional patients in remission from UC who had not participated in the Phase 3 efficacy trials; eligibility criteria were similar to those of the efficacy studies. Patients were treated with Apriso 1.5 g/day once daily in the morning. Treatment duration could be up to two years. Monitoring visits that included vital signs and laboratory testing occurred every three months after starting treatment, and there was an additional visit at Month 1. There was also telephone contact at Months 2, 4, and 5. At the time of the NDA submission, 365 patients had enrolled; the number increased to 387 by the time of the cutoff for the 120-day safety update.

The safety data base used for labeling was comprised of 557 patients treated with Apriso, of whom 354 had been exposed for at least six months and 250 for at least a year. A total of 367 patients came from the two placebo-controlled studies and an additional 190 from the open-label extension study. In addition, the Applicant provided safety information for studies conducted using a mesalamine formulation made by Dr. Falk Pharma. That product is similar to Apriso but is manufactured at a different site (in Europe). Although dissolution profiles of the two products are similar, there has not been adequate evaluation to determine if they can be considered bioequivalent. While the safety data from the Dr. Falk Pharma product were evaluated during the NDA review, the review team considered them as secondary safety data. [redacted] b(4)

There were no deaths in the clinical studies with Apriso. (However the safety update report for Dr. Falk Pharma mesalamine formulations covering the period of January 2002 to February 2008 described three deaths, one of which involved anaphylactic shock and was considered possibly related to the product.) Serious adverse events occurred at an overall rate of 1.4% in the Apriso randomized controlled studies. Four serious adverse events were

seen with Apriso: distal esophagitis, UC flare, pancreatitis, and second degree AV block with worsening LV function. None of these led to study medication discontinuation directly, although the patient with UC flare had already discontinued due to preceding symptoms. Of the non-serious adverse reactions, most were mild or moderate. Severe reactions occurred at a rate of 6% for Apriso and 5% for placebo. Discontinuations due to adverse reactions were 11% for Apriso and 17% for placebo; these were mostly recurrence of UC symptoms. The Clinical Reviewer provided recommendations for a table of common adverse reactions to include in labeling, as well as recommendations for adverse reactions to be included in the listing of less common events of significance.

Mesalamine products have been the subject of recent reviews of postmarketing data by OSE. The Clinical Reviewer also requested selected reports from the postmarketing database regarding hepatic adverse reaction. The Clinical Reviewer examined postmarketing adverse event reports for mesalamine products and found several cases of worsening of pre-existing liver disease associated with mesalamine use. She recommended that the labeling include a warning cautioning about use with patients with liver disease. See Section 7.1.17 of the Clinical Review for further information.

Conclusions

The Clinical Reviewer concluded that, overall, Apriso appears to have a safety profile comparable to other mesalamine products when used at the recommended dose of 1.5 g/day. The Reviewer provided recommendations for the safety section of the labeling and recommended that the labeling include a hepatic failure warning for patients with previous liver disease.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

Because the adult indication is otherwise ready to be approved, the requirement for pediatric studies is eligible for deferral. Due to the low incidence of ulcerative colitis in pediatric patients below age 5 years, the Division has previously waived requirements for pediatric studies of ulcerative colitis treatment for that age group. The Division also has taken that positional that there is sufficient similarity between adult and pediatric ulcerative colitis that efficacy in pediatrics can be extrapolated from adult findings, but that there is still a need for dose finding and for assessment of effectiveness and safety in pediatric populations.

The Clinical Reviewer recommended that the Applicant be required to evaluate safety, effectiveness, and pharmacokinetics of at least two dosing regimens in pediatric patients age 5 years and older who are in remission of ulcerative colitis, but that the PREA requirement for studies in patients under 5 years could be waived.

The application was presented to the Pediatric Research Committee (PeRC) on August 27, 2008, and the committee agreed with the proposals for partial waiver and deferral. An acceptable timeline for the pediatric development program was negotiated with the Applicant.

11. Other Relevant Regulatory Issues

Standard of Evidence for Efficacy

Although both the Clinical Reviewer and the Statistical Reviewer concluded that the data in the application support the conclusion that Apriso is efficacious for maintenance of remission in ulcerative colitis, the Statistical Reviewer expressed reservations about the strength of evidence provided by Study 4. Because of concerns about the late-stage design changes and lack of any secondary endpoint efficacy, she felt Study 4 should be considered supportive and not showing substantial efficacy.

It is important to note for this application that Study 3 was a large, multicenter trial that provided a clear and statistically very persuasive result, with $p < 0.001$ by either analysis presented in Section 7 above. That is comparable to the level of statistical evidence provided by two studies with $p < 0.05$. Also, there were reasonably consistent findings across the subgroups examined. It could be argued that Study 3 might be able to stand by itself as substantial evidence of efficacy. In addition, Study 4 provided results similar to those of Study 3, and with p-values less than 0.05, although the Statistical Reviewer expressed some difficult in interpreting them. Taken as a whole, the evidence for efficacy in the application can be considered substantially equivalent to that provided by two adequate and well-controlled studies, so that there is adequate evidence of efficacy to support approval.

Length of the Efficacy Studies

In recent years the Division has been advising IND sponsors at End-of-Phase-2 (EOP2) meetings to conduct pivotal maintenance studies in ulcerative colitis for a duration of one year; this is consistent with recommendations also being given by the European Union. However, at the time that the EOP2 meeting was held for this product (October 2004), the Division agreed that a study duration of six months would be adequate for the NDA. Because there is no new substantial scientific issue essential to determining the safety or effectiveness of the drug that would require concluding that a duration of six months is not acceptable, the agreement at the EOP2 meeting should stand. The length of the pivotal studies should not be an issue in the approval decision for this particular application.

Given that the Division accepted six months as an adequate duration for demonstrating efficacy in maintenance, and that safety data were collected for treatment well beyond six months, there is no need either to instruct or imply that treatment should not extend beyond six months. However, it would be reasonable for the labeling to include an explicit statement concerning the limitations of the clinical trials on which the approval is based. This TL Reviewer recommends that such a statement appear in the Clinical Studies section of the labeling.

Lack of QT Evaluation
There was no thorough QT assessment for this product and the clinical studies did not incorporate collection of ECG data. Mesalamine products have been approved and marketed since 1987. Preclinical studies have not pointed to any problems with QT prolongation due to mesalamine, and postmarketing experience with several marketed products similar to the present one have not identified a concern regarding QT prolongation. This TL Reviewer recommends that QT evaluation need not be required for approval of this application.

Division of Scientific Investigations (DSI) audits
Clinical site inspections were conducted at three Russian sites (City Polyclinic #38 in St. Petersburg and two sites at the Saratov State Medical University in Saratov) and two U.S. sites (Mexico, MO and Bristol CT). Minor protocol violations were found at two of the Russian sites, but DSI concluded that the data from all of the inspected sites can be used in support of the NDA.

Patent issues
The Applicant made the required 505B(2) patent certifications, and the application was cleared for approval by the OND Immediate Office and the Office of Chief Council.

12. Labeling

Proprietary name
In the review dated 10/9/08, the Division of Medication Error Prevention and Analysis (DMEPA) concluded the proprietary name of "Apriso" was acceptable.

Division of Drug Marketing, Advertising, and Communications (DDMAC) comments
DDMAC made several recommendations regarding labeling. Refer to the DDMAC labeling review dated 10/15/08 for details. The review team decided to adopt some of the recommendations, but the team felt that the descriptions of the dosing form and interaction data (items 4 and 7) were appropriate to retain in the labeling, and that the lack of strict parallels with labeling of other mesalamine products (items 3, 5, and 6) did not raise significant concerns.

Patient labeling/medication guide
The reviewers did not recommend that the product needed patient labeling or a Medication Guide.

Specific labeling issues

- Phenylketonuria (PKU)
  Apriso contains aspartame, and the Applicant [redacted] With the usual adult dosing, patients would consume an amount of aspartame equivalent to about 2.2 mg/day phenylalanine (Phe). In light of the fact that Phe-restricted diets for PKU patients may still contain several hundred mg of Phe, the clinical review team [redacted] but that the information should be included under patient counseling information so that PKU patients could take the Phe content into account in managing

b(4)

their diets. The information was provided under a separate numbered subheading so that it would appear in the labeling highlights.

- Hepatic warning
  Currently approved mesalamine products have warnings for renal effects, exacerbation of UC, hypersensitivity, and pyloric stenosis. The Applicant initially proposed labeling that [redacted] In the Clinical Reviewer's evaluation of postmarketing reports for other mesalamine-containing products, she noted several cases in which patients with pre-existing hepatic insufficiency developed liver failure while taking mesalamine. She recommended that the hepatic warning be included for this product with a modification to describe the observation of apparent precipitation of liver failure in cases of pre-existing liver disease. The need to ask for a similar warning for currently marketed oral mesalamine products is being considered. b(4)

- [redacted] b(4)

- Administration with antacids
  The Labeling and Nomenclature Committee has established a policy that any product with delayed-release characteristics must include a statement in labeling that the product should not be administered with antacids, because the delayed-release property is dependent on pH.

- Morning administration
  In the clinical studies, Apriso was administered once in the morning. [redacted] The review team requested that the labeling recommend dosing as it was studied in clinical trials, because there was no information to support that dosing at other times, such as at bedtime, would have the same effect. b(4)

- Presentation of clinical study results
  The Division requested that the originally designated endpoint, in which discontinuations of any kind were treated as relapses, be presented in the labeling. The review team felt that counting discontinuations for possibly drug-related adverse reactions as success presented an anti-conservative representation of the drug's effect. Further, this is the way inflammatory bowel disease maintenance outcome data have been presented in recently approved labelings.

- Adverse reaction data
  [redacted] The review team b(4)

noted the Dr. Falk Pharma product is manufactured at a different site than Apriso and, while similar, has not undergone an evaluation that would allow a determination of bioequivalence. The review team elected to include information about adverse reactions with the Dr. Falk Pharma product in the labeling as adverse reaction data from other sources, which also included postmarketing experience with other mesalamine products.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
The recommended action is approval with changes to labeling as negotiated with the Applicant. All the primary review disciplines recommended the product for approval.

Risk Benefit Assessment
The risk and benefit characteristics appear similar to those of already approved and marketed oral mesalamine products for treatment of ulcerative colitis.

Recommendation for Postmarketing Risk Management Activities
No special postmarketing risk management activities are recommended for this Application.

Recommendation for other Postmarketing Study Commitments or Requirements
Pediatric studies should be required under PREA for pediatric patients aged 5 to 17 years. See Section 10 above (Pediatrics) for additional details.

None of the primary review disciplines had recommendations for additional postmarketing commitments or requirements.

Recommended Comments to Applicant
There are no recommended comments to the Applicant.

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/s/

John Hyde
10/29/2008 04:51:18 PM
MEDICAL OFFICER