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APPLICATION NUMBER:
022205Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader (CDTL) Review Memo

Date	February 3, 2012
From	Robert P. Fiorentino M.D., M.P.H. Clinical Team Leader Division of Gastroenterology & Inborn Errors, FDA/ CDER
Subject	Cross-Discipline Team Leader Review
NDA#	NDA 22-205 / N-000
Applicant	Salix Pharmaceuticals, Inc.
Date of Submission	August 3, 2011 [Original NDA submission July 16, 2007]
PDUFA Goal Date	February 3, 2012
Proprietary Name	GIAZO
Established (USAN) names	Balsalazide disodium
Dosage forms / Strength	Tablet for oral administration; each tablet contains 1.1 g balsalazide disodium
Proposed Indication	GIAZO is a locally acting aminosalicylate indicated for the treatment of mildly to moderately active ulcerative colitis in male patients 18 years of age and older
Recommended Action:	Approval

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1 Introduction & Background

The current submission, received August 3, 2011, is the third resubmission (i.e., fourth review cycle) for this NDA. It was submitted in response to a Complete Response (CR) letter issued by the FDA on April 27, 2010. This application is for a new oral formulation of balsalazide disodium for the treatment of ulcerative colitis.

The product is a tablet containing 1.1 g balsalazide disodium. The Applicant proposes the following indication:

GIAZO is a locally acting aminosalicylate indicated for the treatment of mildly to moderately active ulcerative colitis in male patients 18 years of age and older.

The proposed dosing is three tablets twice daily (b) (4) (for a total daily dose of 6.6 g) for up to eight weeks.

In the previous review cycle, failure to pass inspection at the Nexgen Pharma, Inc. facility led to a Withhold recommendation from the Office of Compliance, resulting in the Complete Response dated April 27, 2010. However, at the time of the CR, all review disciplines deemed the application to be otherwise approvable apart from the facility inspection issue. Labeling had also been negotiated with the Applicant and was determined to be finalized as of April 26, 2010.

The sponsor had resolved the manufacturing issue that led to the CR and submitted their response on August 3, 2011. However, during this review cycle the CMC reviewer noted a change in one of the 3 drug substance data master files (DMFs) that ultimately resulted in withdraw of two of the 3 manufacturing sites for the drug substance. This is further discussed in the CMC section of this review. From the ONDQA perspective the CMC issues have been resolved and this NDA may be Approved.

Selected sections of the CDTL Review by John Hyde dated April 27, 2010 from the previous review cycle are summarized or reproduced in condensed form. The reader is referred to the previous CDTL review appended at the end of this memo and previously submitted electronically to file (DAARTS).

New issues identified during this review cycle, including determination that PREA was not applicable to this approval, are discussed in this review and contrasted to prior recommendations. An additional Clinical Pharmacology review this cycle prompted changes to label agreed to in the previous review cycle.

CDTL Comment

Balsalazide disodium is currently available as Colazal in capsules containing 750mg balsalazide sodium and indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older.

2 CMC

Refer to Marie Kowblansky's chemistry (CMC) review submitted during this review cycle and dated January 09, 2012.

As noted previously, the applicant has resolved the manufacturing issue that led to the CR and submitted their response on August 3, 2011. However, during this review cycle it was noted by the CMC reviewer that a manufacturing change (updated specifications) was made to one of the 3 drug substance DMFs [REDACTED] (b) (4) a change which ONDQA deemed to improve the manufacturing quality.

FDA had a teleconference with Salix on November 22, 2011 during which the sponsor decided that they would withdraw the other two manufacturers (that had not updated their specifications) from the submission and rely solely on the manufacturer with the updated DMF.

As a result, two of the three drug substance manufacturing sites identified in previous submissions were withdrawn from this submission, leaving [REDACTED] (b) (4) [REDACTED] (b) (4) as the sole supplier. DMF [REDACTED] (b) (4) was reviewed in connection with this submission and found to be acceptable by ONDQA.

The Office of Compliance has issued an overall recommendation of ACCEPTABLE for all facilities involved in the manufacture of this product (EES report appended in CMC review). As per ONDQA, the new information submitted to this NDA provides assurance that the commercial product will have the required identity, strength, purity, and quality. From a CMC standpoint, the labeling has not been revised since the last submission and continues to be acceptable. Consequently, from the ONDQA perspective this NDA may be Approved.

3 Nonclinical Pharmacology/Toxicology

There were no new Pharmacology/Toxicology data in the resubmission, and no additional review of nonclinical data was performed in this (or the previous) review cycle. The reader is referred to the Pharmacology/Toxicology review by K. Zhang, dated 1/10/08, from the initial review cycle, as well as the CDTL review by J. Hyde dated April 27, 2010 (attached in Appendix A).

4 Clinical Pharmacology

There were no new Clinical Pharmacology data in the resubmission; however, Clinical Pharmacology provided a labeling review this cycle that proposed new changes to the labeling. As noted in Insook Kim's review (signed January 20, 2012), food effect studies have demonstrated that the presence of food reduced peak concentrations and AUC of balsalazide and its metabolites, 5-ASA and N-Ac-5-ASA.

the product was administered in the phase 3 trial without regard to food intake.

Presently, Clinical Pharmacology recommends that the dosage administration be *without* regard to food, because 1) the product was taken without regard to food in phase 3 trials which established efficacy and, 2) the systemic exposures [of active metabolites] are likely to be reflective of the availability of drug in the intestine. Based on the mechanism by which mesalamine is released by microflora in the colon, the lower systemic absorption may be secondarily due to lower local availability of mesalamine (preceding absorption).

In addition to Clinical Pharmacology's reasoning, I also note that Colazal, which contains the same active ingredient in capsular form, is currently labeled to take "with or without food" in both adult and pediatric dosing.

It is not possible to determine if potential safety concerns associated with higher exposures to balsalazide or its active metabolites when taken *without* food would be "balanced" by improved efficacy due to greater exposures in the colon (or *vice versa* for concomitant administration *with* food). At this time, there is insufficient clinical data available to provide definitive recommendations restricting the administration of Giaso to either approach.

For further discussion of additional Clinical Pharmacology issues discussed in previous review cycles, the reader is referred to the CDTL review by J. Hyde dated April 27, 2010 (attached in Appendix A).

5 Clinical/Statistical Efficacy

There were no new clinical data in the resubmission, and no additional review of clinical data was performed in this review cycle. The reader is referred to the CDTL review by J. Hyde dated April 27, 2010 (attached in Appendix A) for a review of findings from previous review cycles.

6 Safety

The previous review cycle included negotiations with the sponsor regarding the presentation of adverse reaction information in the labeling (resulting in Table 1 of the proposed label).

7 Advisory Committee Meeting

This application was not presented to an Advisory Committee.

8 Pediatrics

The applicability of the Pediatric Research Equity Act (PREA) to Giazos approval as well as the design of pediatric post marketing studies was revisited during this review cycle. Current recommendations contrast with those in the previous CDTL and medical officer review memos and are discussed herein.

Applicability of PREA

Balsalazide disodium (trade name: Colazal) was designated as an Orphan Drug Product on August 12, 2005 for the “treatment of pediatric patients with ulcerative colitis” and has the following Approved Orphan Indication:

Treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older. Safety and Effectiveness of Colazal beyond 8 weeks in children (ages 5-17) and 12 weeks in adults have not been established.

Because the Giazos NDA was submitted on July 16, 2007 and since Giazos contains the same active ingredient/moiety and is made by the same company (Salix), the Orphan designation for balsalazide disodium applies to Giazos. This was confirmed during a series of discussions between DGIEP staff and the Office of Orphan Drug Products (including medical officer, Henry (b) (6) Startzman) and Pediatric & Maternal Health Staff (PMHS).

The relevance of the pediatric Orphan designation of balsalazide disodium to the applicability of PREA related post-market requirements does not appear to have been discussed in the previous review cycle.

The Pediatric Research Equity Act specifically discusses the applicability of the Act to orphan drugs and is found in Section 505B(k) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. § 35513(k)]:

Orphan drugs. Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526 [21 USC § 360bb].

As a related historical precedent, DGIEP has had recent experience with a separate BLA application (Remicade, BLA#103772) in which OCC interpreted the Act to mean that PREA does not apply to adult approvals in which the same indication has orphan designation in pediatrics. During the review of the pediatric study for Remicade in UC (conducted under the assumption that PREA applied), the Office of Chief Counsel (OCC) provided DGIEP a memorandum (dated August 18, 2011) noting that, “per section 505B(k) of the Act, PREA was not triggered and there should not have been a required PREA PMR” at the time of the adult approval.

Because this current NDA application is similarly for an adult indication (UC) for which the same drug (balsalazide disodium) carries a pediatric orphan designation for the same indication

(also UC), it appears that PREA does not apply as per the OCC interpretation of Section 505B(k) of the Federal Food, Drug, and Cosmetic Act.

Development of Pediatric PMC (outside of PREA)

Despite PREA not being applicable, DGIEP reconsidered the objectives of the prior PMC agreed to by the applicant for pediatric studies. I note from the prior CDTL review that the applicant had agreed to a PK study in pediatric patients ages 12 through 17 on 4/02/10.

The Sponsor had initially requested a waiver for pediatric studies (initially assumed to be required under PREA). On October 29, 2008, this recommendation for full waiver of pediatric studies was presented by the Division to PERC. According to the most recent medical officer review (Dr. Leptak, dated April 27, 2010), the outcome of the PERC discussion was the following: 1) full waiver of studies for pediatric UC patients under 12 years of age, 2) should the product be approved, the label should include information for adolescent UC patients between 12 and 17 years of age, and 3) the Division has the discretion to determine if additional studies are required to adequately label balsalazide disodium for this adolescent UC patient population.

In the previous review cycle, a second PERC committee meeting was held on April 08, 2010. The outcome of that discussion was consistent with the prior PERC recommendations with the following suggestion for the Division's consideration: labeling of the product for children under the age of twelve for those patients able to swallow the adult tablet formulation.

The above recommendations for pediatric studies were revisited during this cycle and discussed both internally within DGIEP and with PMHS. Although I support further studies in pediatric patients down to 12 years of age, I doubt the utility of pursuing studies outside of PREA that would support the approval of Giazio tablets in ages younger than 12.

Although not explicitly discussed in prior review cycles, a significant proportion of children <12 years of age may not be able to swallow the Giazio tablet (up to 6 times per day). According to the sponsor, the dimensions of the oval-shaped Giazio 1.1g tablet are 0.370" x 0.748" (approximately 10mm x 20mm). I note that according to European CHMP guidelines, the Giazio pill would be considered too big to be acceptable to children <12 years of age¹ without supportive data on its ability to be swallowed. There is not a similar FDA guidance but this highlights that tablets of the size of Giazio could present a challenge for younger pediatric patients who could otherwise take the same active drug TID in a smaller pill form (i.e., Colazal) that is approved down to 5 years of age. I agree with the previous medical officer's review that the advantage of BID Giazio would only apply to patients who can swallow the tablet and I further believe that there could be a subset of children older than 12 who are able to swallow the tablet and who may benefit from BID dosing. If PK data demonstrates that the exposures in patients who are 12 to 17 years old (and who are able to swallow the tablet) are comparable to adults, then extrapolation of efficacy may be possible. However, because data from pediatric studies in Colazal suggest higher exposures to balsalazide and lower exposures to the active metabolites compared to adults, there could be a potential for age-dependent differences in prodrug conversion and absorption. In addition, observed gender differences in the Giazio

¹ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/06/WC500107908.pdf (last accessed February 01, 2012).

program with respect to efficacy also suggest the potential for gender related differences in efficacy. Given these findings, the review team this cycle discussed with the applicant the need for pediatric studies to also assess pharmacodynamic exposure-response (ER) in addition to PK. An ER relationship would provide more robust data to be able to conclude that the response to treatment in pediatric patients will be comparable to adults and could also be used to inform appropriate pediatric dosing. If the pediatric study in Giazio cannot establish comparable exposures or a similar ER relationship between the 12 to 17 age group and adults, then the company may have to perform further studies in order to extend the indication down to the pediatric age group.

These discussions have been incorporated into the pediatric PMC agreed to by the applicant.

9 Other Relevant Regulatory Issues

A Proprietary Name Review was performed by the Division of Medication Error Prevention and Analysis (review dated January 16, 2012) during this cycle and the name, Giazio, was found to be acceptable.

The reader is referred to the CDTL review by J. Hyde dated April 27, 2010 (attached in Appendix A) for a review of findings from previous review cycles Standard of Evidence for Efficacy.

10 Labeling

During this review cycle Study Endpoints and Labeling Division (SEALD) was provided the opportunity to review the final label, as they were not consulted in previous review cycles. Jeanne Delasko and Ann Marie Trentacosti provided comments that were incorporated into the final label sent to the sponsor for concurrence.

After reviewing DGIEP's suggested label revisions, the sponsor provided a revised label that was being reviewed at the time of the finalization of this memo.

11 Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I recommend Approval. The CMC issues that led to the previous CR have been resolved. The Office of Compliance has issued an overall recommendation of ACCEPTABLE for all facilities involved in the manufacture of this product.

Risk Benefit Assessment

The risk:benefit assessment has not changed from the prior CDTL review. The reader is referred to the CDTL review by J. Hyde dated April 27, 2010 (attached in Appendix A) and to the separate DGIEP Division Director memorandums.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

In concordance with prior reviews, no special postmarketing risk evaluation and management strategies (REMS) are recommended for this Application.

Recommendation for other Postmarketing Study Commitments or Requirements

During the previous review cycle, the Clinical Reviewer, CDTL and Division Director recommended a postmarketing commitment to conduct a study to evaluate efficacy in female patients, and the Clinical Reviewer and Clinical Pharmacology Reviewer recommended a commitment to conduct a study of antibiotic interaction.

Because of the orphan designation granted to balsalazide disodium in 2005 for pediatric patients with UC, the previous recommendation for a PK study in pediatric patients ages 12 through 17 cannot be made a PREA requirement. Although the Applicant agreed to such a study on 4/2/10, the sponsor was informed that PREA did not apply. Despite this, the sponsor has agreed to a PMC to study PK/PD in pediatric patients (male and female) with UC; the inclusion of females being that pediatric data (PK/PD & safety) could be used to extrapolate efficacy (b) (4)

As noted in the previous CDTL memo (J. Hyde), there are phase 4 PMCs for Colazal (NDA 20-610) that remain outstanding. The prior review team considered whether similar commitments should be attached to the approval for Giazio as a means to providing a timeline for the commitments. The prior team concluded that it would not be necessary to restate the same commitments for Giazio, however they did apparently feel that a drug-interaction study to investigate the effect of antibiotic therapy was of value, given the dependence of balsalazide metabolism on gut flora. Since the previous drug interaction commitment for Colazal did not address this concern directly, the prior review team felt that a commitment for an antibiotic interaction study was appropriate for Giazio. I endorse this recommendation.

Subsequent to the most recent Complete Response, the sponsor has submitted an annual report (dated Sept. 16, 2011) for Colazal that provides status reports of postmarketing study commitments. I note that there are still 3 outstanding PMCs that the sponsor describes as PENDING. These include a possible *in vivo* animal PK study and ascertainment of the need for additional human PK studies in patients with renal or hepatic impairment. The previous review team had concluded that it would not be necessary to restate the same commitments for Giazio. Although this plan is reasonable, it is possible that data from the Colazal PMC studies could ultimately prompt modifications to the Giazio label once they are reviewed.

Recommended Comments to Applicant

None.

12 Appendix A: Previous Review Cycle CDTL Memo (J. Hyde, 4/27/2010)

22 pages have been withheld in full immediately following this page as a duplicate copy of the Cross Discipline Team Leader Review for a Complete Response" dated April 27, 2010 which is located in the "Medical Review Section"

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/s/

ROBERT FIORENTINO
02/03/2012