Executive Summary (NDA 20-610/SE5-016)

DATE: 12/5/2006

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APPLICANT: Salix Pharmaceuticals, Inc.

DRUG: Colazal (balsalazide disodium)

INDICATION: Treatment of mildly to moderately active ulcerative colitis
(5 to 17 years of age)

RECOMMENDATION:

NDA 20-610/SE5-016 (Colazal) is recommended to be approved for the indication of the treatment of mildly to moderately active ulcerative colitis (UC) for patients 5-17 years of age (in addition to the adult population already approved) at a dose of 3 capsules three times per day (6.75 grams/ day) and 1 capsule three times per day (2.25 grams/ day) for up to 8 weeks. To get approval, the sponsor should incorporate the Division's labeling recommendations.

Since the weight range and severity of disease for the intended patient population (ages 5-17 years) will be quite variable, approval of both doses will provide clinicians an alternative choice of regimens.

There are no Phase 4 commitment, request or risk management steps recommended.

CLINICAL EVALUATION:

Efficacy:

Only one study report was included in this NDA. This was a multi-center, randomized, double-blind, parallel-group study of 2 dosage regimens of Colazal in 68 subjects who were 5 to 17 years of age with a diagnosis of mild-to-moderate active UC. Patients were randomized to receive either 6.75 g/day or 2.25 g/day of Colazal. Daily doses were administered 3 times a day (TID), approximately 8 hours apart, for a total of 8 weeks of treatment. The pre-specified primary efficacy endpoint for this study was the proportion of subjects with clinical improvement, defined as a reduction from baseline to Week 8 of the Modified Sutherland Ulcerative Colitis index (MUCAI) total score by at least 3 points.

The study indicated that 15 subjects (45%) in the Colazal 6.75 g/day group and 13 subjects (37%) in the Colazal 2.25 g/day group showed clinical improvement, with a difference in proportions of 8% and the p-value for this difference was 0.6227.

The study indicated that the high-dose population had consistently better numerical scores than the low-dose population for rectal bleeding (64% vs. 54%) and mucosal appearance (61% vs. 46%); overall, both doses showed reasonable improvement for primary efficacy endpoint and secondary endpoints. For detail efficacy evaluation, please see Dr. Keith St. Amand's clinical review dated November 22, 2006.

Safety:

Of the 68 patients enrolled in the study, no deaths occurred in this study. Four serious adverse events (SAEs) were reported. These events were as follows:

1) A 17-yo male on Colazal 6.75 grams was hospitalized for a **UC flare** which resolved several days later.

2) A 17-yo female with a history of depression since 2004 started Colazal 6.75 grams/ day on 5 Jan 06. On (b)(4) the subject reported increased **depression**. The study medication was interrupted and she was hospitalized for depression. The event was considered resolved on (b)(4).

3) A 5-yo female started Colazal 2.25 grams/ day on 10 May 05. On 13 May 05 the subject had a **UC flare** and the study medication was permanently stopped. On (b)(4) the subject had **pyrexia, abdominal pain, hematochezia, decreased albumin at 2.0 g/dL (normal= 4-5.3 g/dL), and decreased Hct at 27.7% (normal= 31.6-40.4%).** Hospitalization was required and these SAEs were considered unresolved at the time of the subject's withdrawal from the study on 17 May 05.

4) 14-yo female started Colazal on 9 Nov 05. On (b)(4) the subject was diagnosed with a **clostridial infection**. She was hospitalized and the event was considered resolved on (b)(4).

Four dropouts due to adverse events occurred (one in the high-dose group and three in the low-dose group). These adverse events were: abdominal pain and urticaria (hives), frequent bowel movements, and 2 cases of rectal hemorrhage.

The most common adverse events associated with Colazal administration were headache (15% of patients in the study), upper abdominal pain (13%), abdominal pain (12%), vomiting (10%), and diarrhea (9%). With the exception of abdominal pain and headache, these adverse events occurred to a **greater** extent in the low-dose group.

When investigator-determined **drug-related** adverse events were analyzed, the percentages for the most common events are as follows (low-dose group listed first):

vomiting (11% vs. 0%), headache (9% vs. 3%), abdominal pain upper (9% vs. 3%), abdominal pain (3% vs. 6%), and nausea (6% vs. 0%). The overall rate of drug-related adverse events was higher in the low-dose group (26% of subjects) than in the high-dose group (21% of subjects). It may be due to the lack of efficacy in the lower dose group.

In summary, both doses showed a reasonable safety profile, but the high-dose group's profile was slightly better in that it showed **less overall dropouts due to adverse events** and **less drug-related adverse events** than the lower-dose group.

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/s/

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