CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-301

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-301	*Submission Date(s)*	December 21, 2007 June 8, 2008 June 13, 2008 July 25, 2008
Brand Name		TRADE NAME (to-be-determined)	
Generic Name		Mesalamine	
PDUFA goal date		October 31, 2008	
Reviewer		Insook Kim, Ph.D.	
Team Leader		Sue-Chih Lee, Ph.D.	
OCP Division		Division of Clinical Pharmacology III	
OND Division		Division of Gastroenterology Products and In-Born Errors of Metabolism	
Sponsor		Salix Pharmaceuticals, Inc.	
Relevant IND(s)		IND 62,113	
Submission Type; Code		Original	505(b)(2)
Formulation; Strengths; Regimen		• Oral capsule dosage form contains 0.375 g of mesalamine (5-aminosalicylic acid, 5-ASA) • Four TRADE NAME capsules once daily (1.5 g/day) with or without food	
Indication		Maintenance of remission of ulcerative colitis in patients 18 years of age and older	

Optional Intra-divisional briefing was held on September 29, 2008 in presence of Dr. Dennis Bashaw and Dr. Hae-Young Ahn.

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1 Executive Summary

1.1 Recommendations

The Division of Clinical Pharmacology 3 has reviewed the clinical pharmacology and biopharmaceutics information submitted to NDA 22-301 and found it acceptable from clinical pharmacology standpoint provided a mutual agreement regarding the label language can be reached between the sponsor and the Agency.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Overview of Clinical Pharmacology and Biopharmaceutics program

In support of NDA 22-301, submitted were final study reports of 11 phase 1/2 clinical trials, three phase 3 trials (MPPK 3003, MPPK 3004, MPPK3005) and one in vitro study for drug interaction. Of 11 submitted studies, three of them were most relevant: a relative BA study evaluating mesalamine granules BID and QD and Asacol BID (MPPK 1001), a food effect study (MPPK 1002) and single dose and multiple dose PK study (MPPK1003). All other studies were supportive and conducted using different formulations from the to-be-marketed formulation. Most of the supportive studies were relative BA or food effect study for formulations in development and one PK study were conducted in pediatric patients with inflammatory bowel disease.

In the clinical pharmacology and biopharmaceutics program, the sponsor used mesalamine granules (MG) in different dosage forms, in sachet (sMG) or in capsules (eMG: TRADE NAME). The to-be-marketed product is a capsule containing mesalamine granules which was used in phase 3 clinical trials (MPPK 3003, MPPK 3004, and MPPK3005) and one phase 1 PK study (MPPK1003). The food effect and relative BA studies (MPPK1001 and MPPK1002) were conducted using mesalamine granules (of the same formulation as that in capsule) in sachet. Theses two products were equivalent based on an in vitro comparative dissolution study (please, also see CMC review by Dr. Gene W. Holbert).

Other than sMG or eMG, several supportive studies including one 12 month phase 3 trial were conducted using FMG (Dr.Falk mesalamine granules in sachet). The FMG was different in formulation from MG and manufactured in Europe while MG was manufactured in the US. The difference in manufacturing site for modified release products is considered the level 3 change in manufacturing site and normally requires a BE study for adequate bridging. Because two products were not compared in an in vivo BE study, we do not consider that two products were sufficiently bridged. Therefore, the studies conducted using FMG product are considered only supportive. The supportive studies pertinent to clinical pharmacology and biopharmaceutics were not reviewed for this NDA. However, one study BIO/SAG-16 conducted with radiolabeled FMG was reviewed because of a labeling claim based on the study.

Pharmacokinetic characteristics

The pharmacokinetics of mesalamine (5-ASA) and its metabolite, N-Ac-5-ASA, were studied after single dose and multiple oral doses of 1.5 g TRADE NAME (QD, 4 x 375 mg capsules) in 24 healthy

subjects under fasting condition. After a single dose administration of 1.5 g TRADENAME, the peak plasma concentrations of mesalamine were observed at about 4 hours post dose and the half-life was about 9 hours. The mean pharmacokinetic parameters of mesalamine and N-Ac-5-ASA are in Table 1.

Table 1: Mean (±SD) plasma pharmacokinetic parameters of mesalamine (5-ASA) and N-Ac-5-ASA after a single dose and multiple dose administration of 1.5 g TADE NAME in Healthy Volunteers

	Single Dose (%CV) (n=24)	Multiple Doses[b] (%CV) (n=24)
Mesalamine (5-ASA)		
AUC_{0-24} (µg*h/mL)	10.96 ± 4.52 (41.3)	16.90 ±5.70 (33.7)
AUC_{0-inf} (µg*h/mL)	13.57 ± 5.44 (39.8)	26.60 ± 14.82 (55.7)
C_{max} (µg/mL)	2.13 ± 1.10 (51.4)	2.72 ± 1.14 (41.8)
T_{max} (h)[a]	4 (2, 16)	4 (2, 8)
$t_{½}$ (h)	9.2 ± 7.1 (59.3)	10.1 ± 8.1 (68.5)
N-Ac-5-ASA		
AUC_{0-24} (µg*h/mL)	25.55 ± 5.52 (21.6)(	37.00 ± 8.90 (24)
AUC_{0-inf} (µg*h/mL)	50.62± 23.06 (45.6)	86.06 ±52.48 (61)
C_{max} (µg/mL)	2.78 ± 0.85 (30.5)	3.40± 0.90 (26.3)
T_{max} (h)[a]	4 (4, 12)	5 (2, 8)
$t_{½}$ (h)	12.4 ± 10.8 (11.6)	13.6± 10.2 (77.8)

[a]: median (min, max)
[b]: 7 days of treatment: Steady-state was achieved on Day 6

In the multiple-dose period, each subject received TRADENAME 1.5 g every 24 hours (QD) for 7 consecutive days. Steady state was achieved on day 6 and mean Cmax was about 22-25% higher for 5-ASA and N-Ac-5-ASA at steady state compared to that after a single dose administration. At steady state, moderate increases (1.5-fold and 1.7-fold) in systemic exposure (AUC_{0-24}) to 5-ASA (47.5% CV) and N-Ac-5-ASA (27.4% CV) were observed when compared with a single-dose of TRADE NAME.

In a separate study, after a single-dose of 1.6 g mesalamine granule in sachet (sMG, 2X800mg) under fasting condition about 31.6 ±10.6% (mean ± SD) of the administered dose was systemically absorbed based on the mean combined cumulative urinary excretion of mesalamine and N-Ac-5-ASA. The metabolite, N-Ac-5-ASA was predominant in urine consisting of 30 % of administered dose and approximately 2% was excreted unchanged in urine.

Food effect

Effect of a high fat meal on absorption of mesalamine was studied in 30 healthy subjects receiving 1.6 g of MG in sachet (2 x 0.8 g) (Study MPPK1002). Under fed condition, t_{max} for mesalamine and N-Ac-5-ASA was prolonged by 4 and 2 hours, respectively. There was a moderate increase in absorption of mesalamine (11-16% increase in AUC) while Cmax of mesalamine was similar with or without food. Nevertheless, overall absorption of administered dose was not affected by a high fat meal, based on the combined cumulative urinary excretion of mesalamine and N-Ac-5-ASA. Therefore, sMG can be taken without regard to food. Although the food effect study was conducted using sMG, the food effect study results can be extended to the TRADENAME (eMG) since the release-controlling portion of the products remains the same and the equivalence between sMG and TRADENAME was demonstrated. In addition, the phase 3 trials conducted with eMG, the drug was taken without regard to food intake. Therefore TRADENAME can be taken without regard to food intake.

Mesalamine (5-ASA) and N-Ac-5-ASA did not inhibit the major CYP enzymes evaluated.

The final study report of an in vitro drug interaction study (XT0055039) was submitted previously as NDA 20-610, SLR017 dated May 3, 2007 and reviewed by Dr. Abimbola Adelowale of the Division of Clinical Pharmacology 3. The concentration range studied in the in vitro study e.g. 0.1-100 µM sufficiently covered the mean Cmax for 5-ASA (17 µM) and N-Ac-5-ASA (35 µM) at steady state with TRADE NAME. There was no significant inhibition of CYP enzymes (Cyp1A2, Cyp2C9, Cyp2C19, Cyp2D6, and Cyp3A4/5) by 5-ASA and its major metabolite N-Ac-5-ASA. Therefore, the study report XT0055039 was not further reviewed this time.

Relative Bioavailability

The bioavailability of 5-AS and N-Ac-5-ASA after 4 day administration of sMG by dosage regimen of 0.8 g BID was compared to the dosage regimen of 1.6 g QD. It was also compared to AUC and Cmax after administration of Asacol 0.8 g (2 x 400 mg) BID for 4 days in 30 healthy subjects (Study MPPK1001).

The systemic exposure to 5-ASA and N-Ac-5-ASA was higher after sMG 0.8 g BID and 1.6 g QD than Asacol 0.8 g BID. Higher variability (72-128% CV) was observed in PK parameters after Asacol treatment compared to after the sMG treatments (33-55%). The median tmax of 5-ASA and N-Ac-5-ASA after sMG QD was about 3 hours and it was about 16 hours for sMG BID and Asacol BID indicating a carryover effect from the first dose. The mean AUC and Cmax of 5-ASA and N-Ac-5-ASA after sMG 0.8g BID and sMG 1.6 QD treatments were higher than those for Asacol 0.8 g BID treatment. The sponsor concluded that PK parameters for Asacol treatment were unreliable because intact or partially intact tablets were recovered from stool samples of 50% of subjects after Asacol treatment. Because the safety and efficacy of 1.5g eMG once daily dosing were evaluated in two placebo-controlled phase 3 clinical trials and one open-label long-term safety trial, the comparison of BA of TRADENAME to Asacol 400 mg tablet is not considered critical to this NDA.

The ratio of mean Cmax after sMG 0.8 g BID to after sMG 1.6g QD was 153% for 5-ASA and 118% for N-Ac-5-ASA while the AUC was similar between two treatments. However, attainment of the steady-state is uncertain as sMG was administered once daily or twice daily for 4 days only.

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