CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-908

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-908

Letter Date: 3/31/05

Proposed Brand Name: Etreva

Generic Name: Lubiprostone

Reviewers: Suliman I. Al-Fayoumi, Ph.D.

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ORM Division: Division of Gastroenterology Products

OCPB Division: Division of Pharmaceutical Evaluation 3

Sponsor: Sucampo Pharmaceuticals

Submission Type: Original NDA (1 S)

Formulation, Strength(s): Soft gelatin capsule, 24 µg

Proposed Indication: [redacted] chronic idiopathic constipation [redacted]

Proposed Regimen: 24 µg capsule taken twice daily

1. Executive Summary

Lubiprostone is a novel locally-acting, chloride channel activator. Lubiprostone has been shown to specifically activate ClC-2 channels in the GIT, resulting in increased passage of stool and alleviating symptoms associated with chronic idiopathic constipation. The proposed indication for lubiprostone is the [redacted] chronic idiopathic constipation [redacted] The only drug currently approved in the U.S. for the treatment of chronic idiopathic constipation in patients less than 65 yrs old is Zelnorm® (tegaserod maleate, Novartis).

Lubiprostone is formulated as an immediate-release soft gelatin capsule at 24 µg dose strength and is recommended to be taken twice daily with food.

Data was submitted from three Clinical Pharmacology and Biopharmaceutics-related studies investigating among other things, mass balance, food-effect and cardiac safety (thorough QT study).

Seven Phase 2/3 clinical studies evaluated the safety and efficacy of lubiprostone in patients with chronic constipation. A total of 1612 patients have been enrolled in studies lasting up to 52 weeks in the clinical development program.

1.1 Recommendation

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, NDA 21-908 is **acceptable** provided that a satisfactory agreement is reached between the Agency and the sponsor regarding the proposed language in the package insert. See Appendix 3.2 for the package insert incorporating the Agency proposed changes to the labeling (See ***Detailed Labeling Recommendations*** on page 25).

1.2 Phase 4 Commitments

None.

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1.3 Summary of CPB Findings

Lubiprostone enhances the secretion of fluid into the abdominal lumen through the activation of chloride channels in the apical membrane of the epithelium, thus increasing passage of stool and alleviating symptoms associated with chronic idiopathic constipation.

The proposed indication for lubiprostone is the [redacted] of chronic idiopathic constipation [redacted]

Lubiprostone is formulated as an immediate-release soft gelatin capsule at 24 µg dose strength and is recommended to be taken twice daily with food.

Data was submitted from three Clinical Pharmacology and Biopharmaceutics-related studies investigating among other things, mass balance, food-effect and cardiac safety (thorough QT study).

The findings of the seven Phase 2/3 clinical studies indicate that there is no statistically significant improvement in the clinical response beyond a total daily dose of 24 µg. There also was a clear dose-related incidence of GI adverse events (i.e., nausea and diarrhea) with lubiprostone administration.

The findings of *in vitro* and *in vivo* pre-clinical studies as well a thorough QT study in healthy subjects indicate that lubiprostone is not associated with QT prolongation effects on the cardiac system.

Lubiprostone is a poorly soluble drug. However, due to lack of data on the extent of drug excretion in bile, it not possible to discern whether lubiprostone is a poorly or highly permeable drug.

There is a significant food-effect on the pharmacokinetics (PK) of radiolabeled lubiprostone, whereby Cmax of lubiprostone decreased by 55% while $AUC_{0-\infty}$ was unchanged with a high fat meal relative to administration under fasting conditions. The clinical relevance of such a finding is unclear. However, lubiprostone capsules were administered with food in the pivotal clinical trials. Hence, lubiprostone capsules should be labeled for administration with food.

Lubiprostone is not detected in plasma, urine or feces following oral administration of a radiolabeled dose of lubiprostone. Even after administration of a dose that is 3-fold higher than the proposed daily clinical dose, plasma concentrations of lubiprostone are still not detectable. The mean Cmax and AUC values of M3, a detectable active metabolite, increase in a dose-related manner. The findings of a mass balance study demonstrated that a radiolabeled oral dose of lubiprostone is primarily excreted in urine via the kidneys (63% of the administered dose), while around 32% of the radiolabeled dose was excreted in feces. The mean elimination half-life of total radioactivity in plasma was 3 hrs. A total of 18 metabolites of lubiprostone were characterized indicating extensive metabolism of lubiprostone following oral administration.

Lubiprostone is highly bound to plasma proteins (94.6%) within a concentration range of 1 to 30 ng/mL.

Lubiprostone is rapidly and extensively metabolized by 15-position reduction, α-chain β-oxidation, and ω-chain ω-oxidation. These biotransformations are not mediated by the hepatic CYP450 enzyme system but appear to be mediated by the ubiquitously expressed carbonyl reductase. *In vitro* metabolism studies in human liver microsomes and hepatocytes show that lubiprostone is unlikely to inhibit or induce CYP450 isozymes. While the results indicated that there was a possible mechanism-based inactivation of CYP2A6, such an effect is unlikely to have clinical implications given the limited contribution of CYP2A6 to hepatic metabolism of drugs.

Studies were not conducted to evaluate the effect of renal impairment on the PK of lubiprostone.

Studies were not conducted to evaluate the effect of hepatic impairment on the PK of lubiprostone.

Analysis of the findings of study 0411 (thorough QT study), which included data from 54 males and 41 females, did not reveal any significant gender-related differences in the pharmacokinetics of lubiprostone. Moreover, there were no gender-related differences on the safety or efficacy of lubiprostone in the clinical studies.

The pharmacokinetics of lubiprostone and its M3 metabolite have not been evaluated in elderly patients. There generally were no age-related differences on the safety or efficacy of lubiprostone in the clinical studies.

No pediatric patients were enrolled in any of the clinical studies as the inclusion/exclusion criteria noted that subjects had to be at least 18 years of age.

A dissolution test for lubiprostone was developed based on the USP Paddle method (Apparatus 2, USP <711>), whereby the soft gelating capsule is dissolved in 900 mL of [ ] at 37°C using a paddle speed of [ ] rpm. The proposed dissolution method specification was Q of not less than [ ] at 60 min.

The early phase 1 development was performed using [ ] filled with lubiprostone dissolved in medium-chain fatty acid triglyceride (MCT). Prior to starting the phase 2b study in the US, a soft capsule formulation was developed [ ] [ ] while keeping the same fill solution.

2. Question-Based Review

2.1 General Attributes

Chronic idiopathic constipation is generally defined by infrequent or difficult passage of stool. The symptoms associated with chronic idiopathic constipation (i.e., abdominal bloating, abdominal discomfort, straining at defecation, hard or lumpy stools) may be the result of abnormal colonic motility that can delay the transit of intestinal contents and impede the evacuation of rectal contents.

Lubiprostone (RU-0211) has been shown to specifically activate specific chloride channels (ClC-2) within the GIT. As a result, intestinal fluid secretion is increased thereby increasing intestinal motility and increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation.

The proposed clinical indication for lubiprostone is [ ] chronic idiopathic constipation [ ]

Lubiprostone is available as a soft gelatin capsule at 24 µg dose strength. The proposed dose is 24 µg capsule twice daily.

Three Clinical Pharmacology and Biopharmaceutics studies were submitted in support of this application, characterizing the mass balance (study 0011) and food effect (study 0312) as well as a thorough QT study in healthy subjects (study 0411).

Seven Phase 2/3 clinical studies evaluated the safety and efficacy of lubiprostone in patients with chronic constipation (studies SC9921, SC0131, SC0232, SC01S1, SC01S2, SC01S3 and SC02S3). A total of 1612 patients have been enrolled in studies lasting up to 52 weeks in the clinical development program.

Lubiprostone is currently not marketed anywhere in the world and as such no post-marketing experience is available.

2.2 General Clinical Pharmacology

1. Is there an Exposure/Response (E/R) relationship on safety or efficacy for lubiprostone?

The clinical study findings indicate that there is no statistically significant improvement in the clinical response beyond a total daily dose of 24 µg. There also was a dose-related incidence of GI adverse events (i.e., nausea and diarrhea) with lubiprostone administration.

Lubiprostone is thought to act by activating ClC-2 channels within the GIT, hence increasing intestinal fluid secretion and intestinal motility. Subsequently, the passage of stool is increased and the symptoms associated with chronic idiopathic constipation are alleviated.

Preclinical study findings indicate that the 15-OH metabolite of lubiprostone (M3) has pharmacological activity (intestinal fluid secretion) similar to lubiprostone while the other metabolites are devoid of effects on intestinal fluid secretion at oral doses as high as

10 µg/kg. Studies conducted to define the local activity of lubiprostone and the M3 metabolite confirmed that both lubiprostone and the M3 metabolite activate Cl channels located on the luminal (apical) side of the intestine, but not the channels located on the basolateral membrane. In addition, both lubiprostone and M3 metabolite were shown to result in dose-related increases in intestinal fluid secretion in rats following oral administration. The potency of the M3 metabolite was comparable to that of lubiprostone in rats.

Seven Phase 2/3 clinical studies evaluated the safety and efficacy of lubiprostone in patients with chronic constipation (studies SC9921, SC0131, SC0232, SC01S1, SC01S2, SC01S3 and SC02S3). A total of 1612 patients have been enrolled in studies lasting up to 52 weeks in the clinical development program.

The sponsor conducted a dose finding, double-blind, parallel-group, placebo-controlled, Phase 2b study (SC9921) to assess the safety and efficacy of 3 different doses and dosing regimens in patients with chronic idiopathic constipation. Patients (n = 127) were randomized to receive placebo (n = 33), lubiprostone 24 µg once daily (n = 29), lubiprostone 48 µg/day (24 µg BID; n = 32), or lubiprostone 72 µg/day (24 µg TID; n = 33). Following a 2-week baseline/washout period, patients received 3 weeks of double-blind medication. Patients were chosen for participation based on their need for relief of constipation, which was defined as < 3 spontaneous bowel movements (SBMs) per week. The primary efficacy variable was the daily average number of SBMs.

Overall, the efficacy results indicated that all patients who took lubiprostone experienced a noticeable improvement in the criteria used to assess chronic constipation in this study, including daily average number of SBMs, average degree of straining, average stool consistency, global assessment of constipation, and global assessment of treatment effectiveness.

It should be noted that based on the primary efficacy analysis, there was no statistically significant improvement in the clinical response beyond a total daily dose of 24 µg between treatment weeks 2-3.

Moreover, the incidence of GI adverse events (i.e., nausea and diarrhea) with lubiprostone administration is clearly dose-related. This was evident in study 0411 (definitive QT study), where single doses of lubiprostone, 24 µg and 144 µg were associated with incidence rates of GI adverse events of 15.9% and 70.6%, respectively. The incidence of GI adverse events in study SC9921 is summarized in table 1 and further illustrates the dose-related adverse events associated with lubiprostone.

Taken altogether, the safety and efficacy findings of study SC9921 appear to favor a total daily dose of 24 µg rather than 48 µg. However, the reviewing Medical Officer supports the sponsor's selection of the 24 µg BID dose as the clinical dosage based on the totality of evidence including the primary as well as secondary study endpoints.

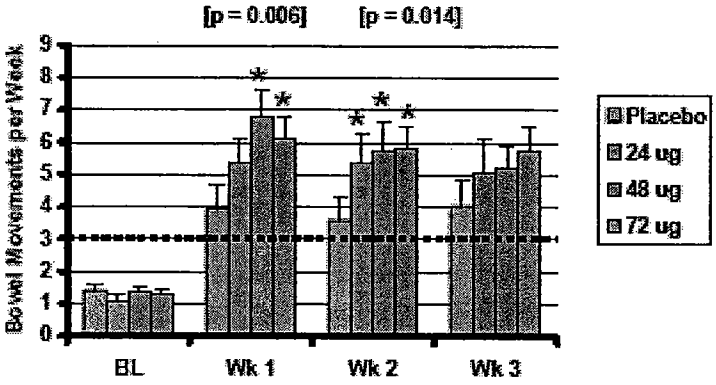

Fig. 1. Weekly average number of spontaneous bowel movements (ITT population)

Table 1. Summary of the incidence of GI adverse events with lubiprostone treatment

	Placebo	24 µg daily	48 µg daily	72 µg daily
Nausea	0%	17.2%	43.8%	36.4%
Diarrhea	0%	10.3%	6.3%	15.2%

Two pivotal clinical trials were conducted in support of the application, namely studies SC0131 and SC0232. These were multi-center, parallel-group, double-blind, placebo-controlled, Phase 3 studies with identical study designs, which were designated as the pivotal studies for the current application.

The primary objective of the two pivotal clinical trials was to assess the efficacy and safety of oral 48 µg/day lubiprostone (24 µg BID) compared to placebo for the treatment of constipation. In studies SC0131 and SC0232, respectively, 242 and 237 patients were randomized to receive placebo or lubiprostone 48 µg/day (24 µg BID). Following a 2-week baseline/washout period, patients received 4 weeks of double-blind medication; a follow-up telephone interview was conducted 2 weeks after the end of double-blind treatment. Patients were chosen for participation based on their need for relief of constipation, which was defined as, on average, < 3 SBMs per week.

In the primary efficacy analysis in each study, the mean SBM frequency during Week 1 was significantly higher ($p < 0.0001$) in the 48 µg lubiprostone group than in the placebo group. The overall treatment effect across all weeks was also significant ($p < 0.0001$) in both studies. In SC0131, the median number of SBMs at Week 1 was 3.0 in the placebo group and 5.0 in the lubiprostone 48 µg group; in SC0232, the values were 3.5 and 5.0, respectively. In both studies, the baseline median number of SBMs in both treatment groups was 1.5 (Fig. 1).

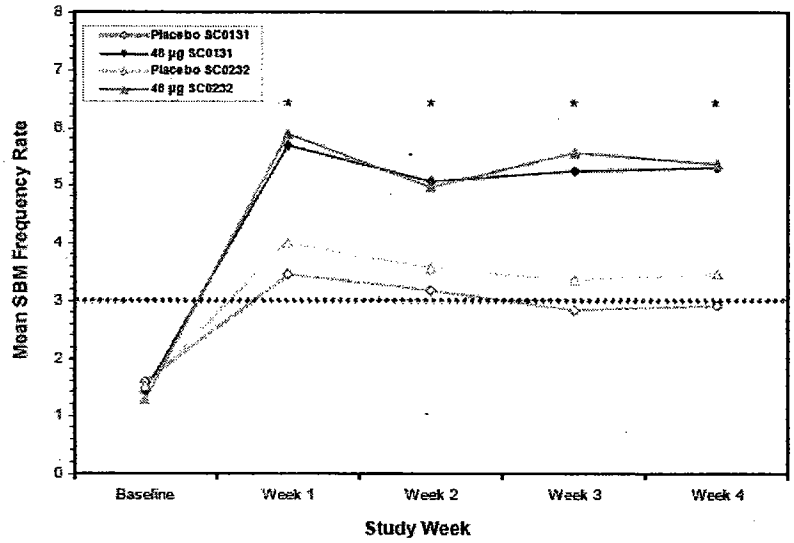

Fig. 2. Mean SBM frequency rates by pivotal study (ITT population)

2. Have the single and multiple dose pharmacokinetics of lubiprostone been adequately characterized?

Plasma concentrations of lubiprostone are not detectable even after administration of a dose that is 3-fold higher than the proposed daily clinical dose. The mean Cmax and AUC values of M3, a detectable active metabolite, increase in a dose-related manner.

The single dose PK of lubiprostone was characterized in a single study in healthy subjects (study 0411; a definitive QT study). The multiple dose PK of lubiprostone were not characterized in any of the studies submitted under this application.

In study 0411, the effect of single doses of lubiprostone (24 µg and 144 µg) on QT interval were evaluated in healthy subjects (n = 177; 41-51/treatment arm, age 18-45 years) in a randomized, single center, active (moxifloxacin) and placebo-controlled, four treatment, parallel-group study. A total of 95 subjects (54 males and 41 females) received lubiprostone treatments. Plasma samples were collected up to 24 hrs post-dose for quantitation of lubiprostone and M3, the active metabolite.

The study results indicate that lubiprostone plasma concentrations were not detectable (LOQ 10 pg/mL) even following administration of the highest lubiprostone dose utilized in the study (144 µg). The plasma concentrations of the M3 metabolite were nevertheless quantifiable. Overall, there was a dose-related increase in systemic exposure to the M3 metabolite, whereby Cmax and $AUC_{(0-t)}$ increased 3-fold and 5.5-fold, respectively with administration of lubiprostone doses of 24 µg and 144 µg.

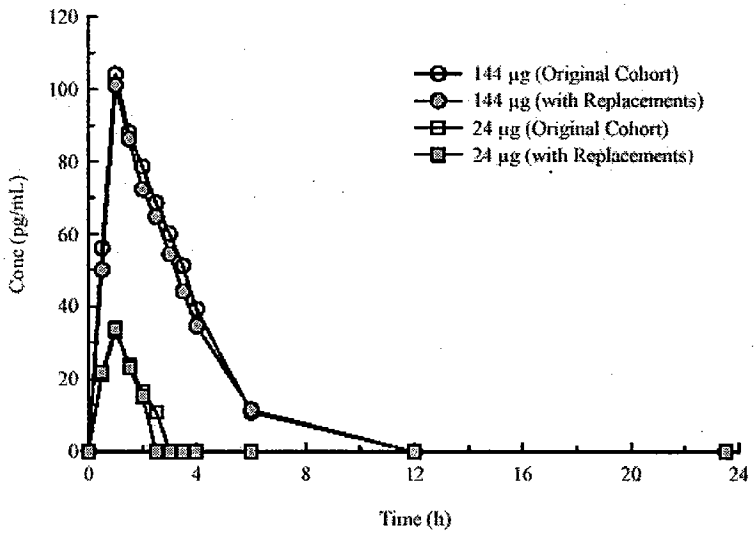

Fig 3. Mean plasma concentration-time profiles of the M3 metabolite following oral administration of single 24 or 144 µg doses of lubiprostone to healthy subjects (study 0411)

3. Does lubiprostone cause QT/QTc prolongation?

The findings of in vitro and in vivo pre-clinical studies as well a definitive QT study in healthy subjects indicate that lubiprostone is not associated with effects on the cardiac system.

The findings of *in vitro* and *in vivo* pre-clinical studies conducted to evaluate the cardiac safety of lubiprostone did not demonstrate any relevant effects of lubiprostone on the cardiac system. There were no significant effects of lubiprostone in the canine Purkinje fiber assay. In addition, lubiprostone had no effects on ECG readings, heart rate, respiration, femoral artery blood flow, or blood pressure of anesthetized dogs at doses up to 100 µg/kg administered directly into the duodenum. A dose of 1000 µg/kg produced only a transient decrease in blood pressure. Furthermore, there was no effect on QTc intervals in dogs that received repeated doses of RU-0211 for up to 39 weeks.

In order to evaluate the cardiac safety of lubiprostone, a thorough QT study (study 0411) was conducted per the ICH; E14 guidance. In study 0411, the effect of a single dose of lubiprostone on QT interval in healthy subjects (n = 177; 41-51/treatment arm, age 18-45 years) was assessed in a randomized, single center, active (moxifloxacin) and placebo-controlled, four treatment, parallel-group study. Subjects were randomly allocated to receive one of four treatments:

- lubiprostone, 24 µg (1 X 24 µg capsule)
- lubiprostone, 144 µg (6 X 24 µg capsule)
- Placebo

- Moxifloxacin, 400 mg tablet

In the study, no food was administered for at least 8 hrs pre-dose and 2 hrs post-dose.

A sample size of around 160 subjects (40 subjects/group) was selected mainly based on precedents set by similar ECG safety studies. The highest dose of lubiprostone was 3-fold higher than the total daily dose utilized in clinical trials (48 µg) and was deemed the highest feasible dose in humans by the sponsor due to associated adverse events such as nausea and diarrhea with multiple dose administration.

Plasma concentrations of lubiprostone and the M3 metabolite as well as 12-Lead ECGs were determined up to 24 hrs post-dose. Baseline ECGs were collected over a period of 24 hrs pre-dose. The primary PD variable was the mean baseline corrected QTcI (individually-determined QT correction). Secondary PD variables included mean baseline corrected QTcF and QTcB. Additionally, 95% confidence intervals for differences between each treatment and placebo were determined.

The study results indicated that lubiprostone treatment was not associated with a significant increase of QT intervals (specifically QTcI and QTcF) at single doses up to 144 µg. A mean increase in QTcB of 2 msec was observed with the highest lubiprostone dose employed in the study (144 µg). In addition, moxifloxacin, a positive control, statistically significantly prolonged the QTcI and QTcF intervals by 4 msec and 3 msec, respectively (Table 2). It should be noted that the increase in the QTc interval observed with moxifloxacin was generally lower than that traditionally observed in similar studies (around 10 msec).

Table 2. Summary of the ECG results over the 24-hr treatment period

Dose Group	Treatment A Placebo (N=41)	Treatment B 24 µg RU-0211 (N=44)	Treatment C 144 µg RU-0211 (N=51)	Treatment D Moxifloxacin (N=41)
Total N	**41**	**44**	**51**	**41**
Heart Rate in bpm*	**2**	**6**	**13**	**3**
Heart Rate tachycardic outliers N (%)	11(28%)	11(25%)	22(43%)	6(15%)
Heart Rate bradycardic outliers N (%)	1(3%)	0	0	0
PR in ms*	-3	-5	-7	-2
PR outliers N (%)	0	0	0	0
QRS in ms *	-1	-1	-2	0
QRS outliers N (%)	0	0	0	0
QT in ms*	-15	-22	-35	-5
QT new >500 ms N (%)	0	0	0	0
QTcI in ms*	**-9**	**-9**	**-7**	**4**
QTcI 95% CI - Min	**-10**	**-11**	**-10**	**2**
QTcI 95% CI - Max	**-7**	**-8**	**-5**	**6**
QTcI new >500 ms N (%)	**0**	**0**	**0**	**0**
QTcI new >450 ms N (%)	**0**	**0**	**1(2%)**	**0**
QTcI 30-60 ms inc N (%)	**1(3%)**	**0**	**2(4%)**	**4(10%)**
QTcI >60 ms inc N (%)	**0**	**0**	**0**	**0**
QTcF in ms*	-9	-11	-11	3
QTcF new >500 ms N (%)	0	0	0	0
QTcF new >450 ms N (%)	0	0	0	0
QTcF 30-60 ms inc N (%)	0	0	0	4(10%)
QTcF >60 ms inc N (%)	0	0	0	0
QTcB in ms*	-7	-5	2	7
QTcB new >500 ms N (%)	0	0	0	0
QTcB new >450 ms N (%)	0	0	0	1(2%)
QTcB 30-60 ms inc N (%)	3(8%)	2(5%)	9(18%)	13(32%)
QTcB >60 ms inc N (%)	0	0	0	0
New abnormal U waves N (%)	0	0	1(2%)	0
New ST segment depression changes N (%)	1(3%)	3(7%)	2(4%)	3(7%)
New T wave inverted N (%)	3(8%)	5(11%)	11(22%)	4(10%)
New Second & Third Degree Heart Block, Complete RBBB & LBBB, MI N (%)	0	0	0	0

* Mean change from baseline

4. What are the ADME characteristics of lubiprostone following oral administration?

4.1 Absorption

A minimum of 63% of an orally administered dose of lubiprostone is absorbed

Based on the findings of the mass balance study (study 011), at least 63% of an orally administered dose of lubiprostone is absorbed. However, lubiprostone is not detectable in plasma even after oral administration of a dose of 144 μg, which is 3-fold higher than the proposed clinical daily dose (48 μg). M3, an active metabolite of lubiprostone, is quantifiable in human plasma.

4.2 Distribution

Lubiprostone is highly bound to plasma proteins (94.6%)

The extent of protein binding of lubiprostone was determined *in vitro* using ultrafiltration at nominal concentrations ranging from 1 to 30 ng/mL, using blood from 6 male and female subjects (study AE-3391-3). The protein bound fraction of lubiprostone in plasma was 94.4-94.7%. The binding data indicate that lubiprostone is highly bound to plasma proteins.

The specific nature of plasma protein binding of lubiprostone was not explored by the sponsor

4.3 Metabolism and Excretion

The results of human and animal studies indicate that lubiprostone is rapidly and extensively metabolized by 15-position reduction, α-chain β-oxidation, and ω-chain ω-oxidation. These biotransformations are not mediated by the hepatic cytochrome P450 system but appear to be mediated by the ubiquitously expressed carbonyl reductase. In vitro metabolism studies in human liver microsomes and hepatocytes show that lubiprostone is unlikely to inhibit or induce CYP450 isozymes. Lubiprostone is not detected in plasma, urine or feces following oral administration of a radiolabeled dose of lubiprostone. The radioactive dose is primarily excreted in urine via the kidneys (63% of the administered dose), while around 32% of the radiolabeled dose was excreted in feces. The mean elimination half-life of total radioactivity in plasma was 3 hrs. A total of 18 metabolites of lubiprostone were characterized indicating extensive metabolism of lubiprostone.

Animal studies have shown that metabolism of lubiprostone rapidly occurs within the stomach and jejunum, most likely in the absence of any systemic absorption. In vitro metabolism studies using liver microsomes indicate that lubiprostone is metabolized to form 15-OH-RU-0211 (M3 metabolite) as the main metabolite. Biotransformation of

lubiprostone to the M3 metabolite is not mediated by the hepatic cytochrome P450 system but appears to be mediated by the ubiquitously expressed carbonyl reductase.

In vitro metabolism studies in human liver microsomes and hepatocytes were used to evaluate the potential inhibitory and induction effects of lubiprostone on CYP450 isozymes. (Studies SPI/SR04-009 and SPI/SR04-018). The results of study SPI/SR04-009 showed that there was no concentration-dependent inhibition of any of the studied CYP450 isozymes at lubiprostone concentrations up to 10,000 pg/mL (CYP 1A2, 2A6, 2b6, 2C9, 2C19, 2D6, 2E1 and 3A4). While the results indicated that there was a possible mechanism-based inactivation of CYP2A6, such an effect is unlikely to have clinical implications given the limited contribution of CYP2A6 to hepatic metabolism of drugs.

Study SPI/SR04-018 evaluated the potential of lubiprostone to induce CYP450 isozymes (CYPs 1A2, 2B6, 2C9 and 3A4) in primary cultures of human hepatocytes. The results of the study showed that lubiprostone is unlikely to induce any of the studied CYP450 isozymes at lubiprostone concentrations up to 1,000 pg/mL.

In an *in vivo* open-label, mass balance study (study 0011), healthy male subjects (n = 4, age 18-45 years) received single oral doses of ^{3}H-RU-0211 (lubiprostone) 72 µg (3 X 24 µg capsules). Blood, urine and feces samples were collected up to 168 hours post-dose.

The study findings indicate the following:

- Following administration of ^{3}H-RU-0211, tmax of radioactivity was noted at 2.5 hrs post-dose.
- The radioactive dose was primarily excreted in urine via the kidneys (63% of the radiolabeled dose), while around 32% of the radiolabeled dose was excreted in feces (Fig. 4). The mean elimination half-life of total radioactivity in plasma was 3 hrs.
- Lubiprostone (RU-0211) was not detected in plasma, urine or feces.
- A total of 18 metabolites of lubiprostone (M1-M18) were characterized indicating extensive metabolism of lubiprostone. M3 and M14 were the major metabolites of lubiprostone in plasma. M10 was the major metabolite identified in feces (accounted for 5.8% of the administered dose), while M14 was the major metabolite in urine (accounted for 34.6% of the administered dose).
- M3, the only pharmacologically active metabolite of lubiprostone, is formed in both humans and animals by the reduction of the carbonyl group at the 15-hydroxy moiety that consists of both α-hydroxy and β-hydroxy epimers. Overall, M3 accounts for less than 10% of an oral dose of radiolabeled lubiprostone.

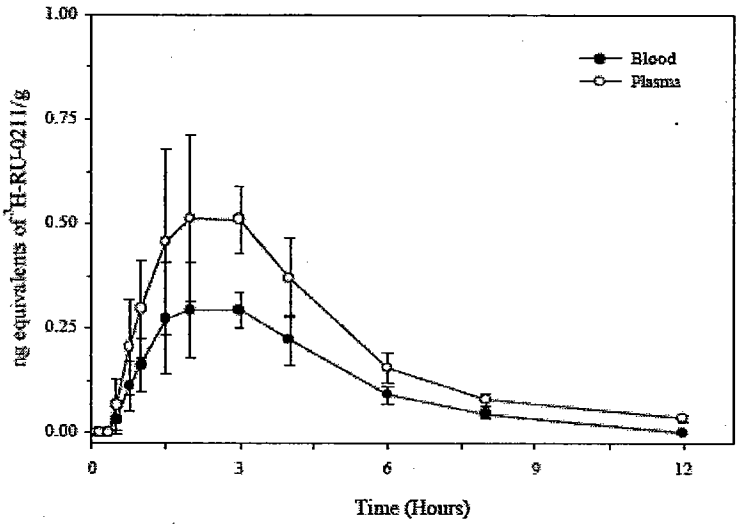

Fig. 4. Mean ^{3}H-RU-0211 concentration-time profiles in blood and plasma following administration of single oral doses of ^{3}H-RU-0211 to healthy subjects

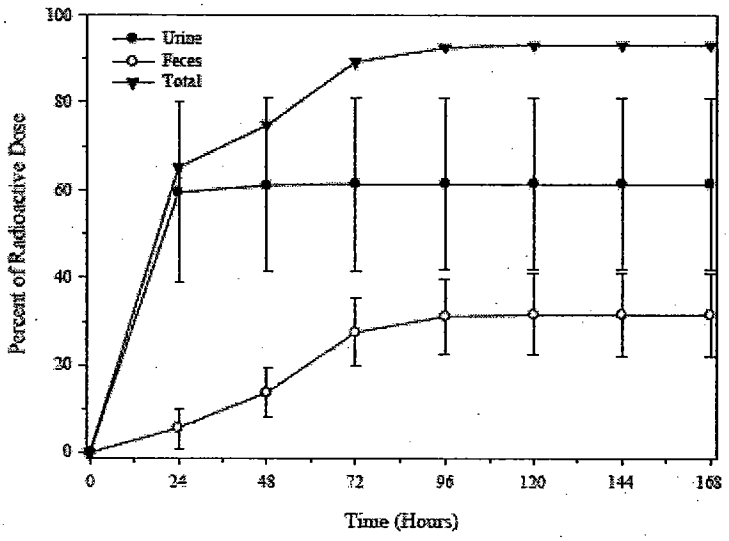

Fig. 5. Cumulative fractions of radioactivity in urine and feces following administration of single oral doses of ^{3}H-RU-0211 to healthy subjects

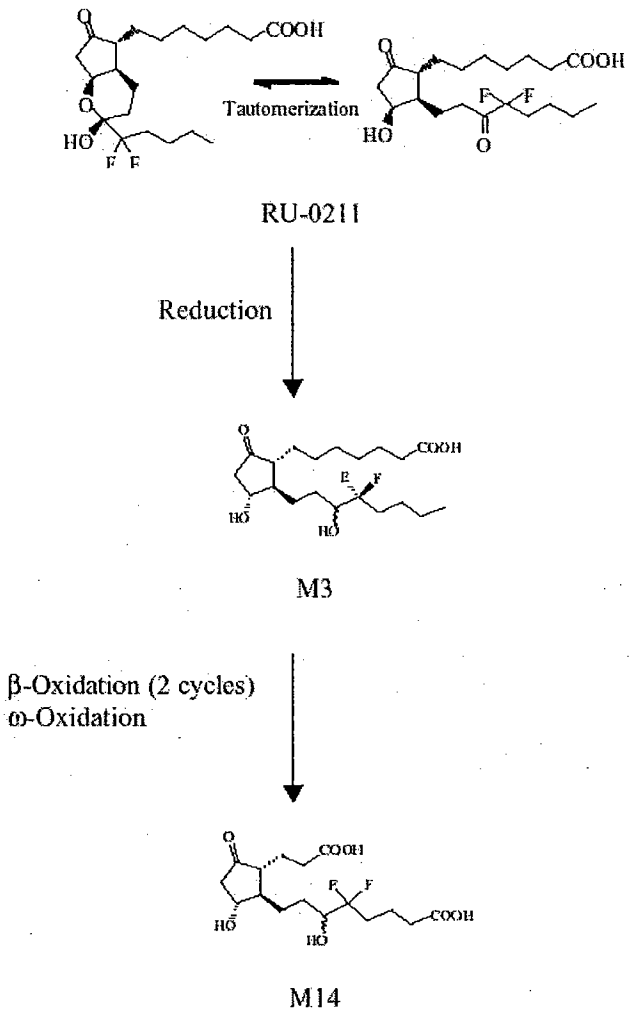

Fig. 6. The proposed metabolic pathway of RU-0211 in humans

2.3 Intrinsic Factors

1. Is there a need for dosage adjustment in special populations?

1.1 Elderly

The pharmacokinetics of lubiprostone and its M3 metabolite have not been evaluated in elderly patients.

A total of 217 geriatric patients ≥ 65 years of age were enrolled in the clinical development program, out of which 57 patients were enrolled in the well-controlled clinical studies while 160 were enrolled in long-term safety studies.

A total of 95 subjects received lubiprostone in study 0411 (definitive QT study), which evaluated the cardiac safety of lubiprostone doses of 24 µg and 144 µg. An analysis of the potential effects of age on the PK of the M3 metabolite in the study did not reveal any correlations between drug exposure and age. This is likely due to the narrow age range of subjects enrolled in the study (18-45 years).

Analysis of pooled efficacy data from well-controlled clinical trials showed that elderly patients (≥ 65 yrs) had a comparable response rate to lubiprostone 48 µg/day on SBM frequencies (primary efficacy endpoint) relative to other age subgroups. (See Fig. 7). In the active dose groups, adverse event frequencies were generally similar across age groups.

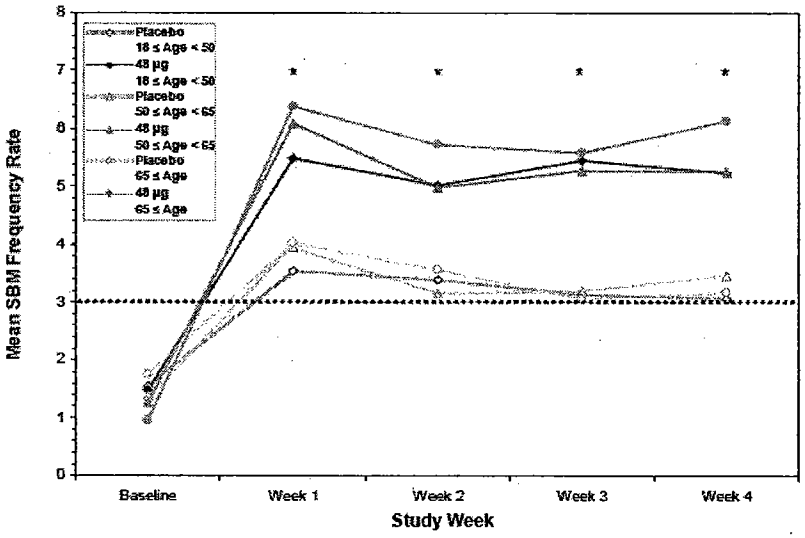

Fig. 7. Mean SBM frequency rates by age group (ITT population)

1.2 Gender

There is no need for dosage adjustment in female patients

Analysis of the findings of study 0411, which included data from 54 males and 41 females, did not reveal any significant gender-related differences in PK. In addition, analysis of pooled efficacy data from well-controlled clinical trials showed that male (n = 32) and female (n = 239) patients had similar response rates to lubiprostone 48 µg/day on SBM frequencies (primary efficacy endpoint). (See Fig. 8). In the active dose groups, adverse event frequencies were generally similar across genders.

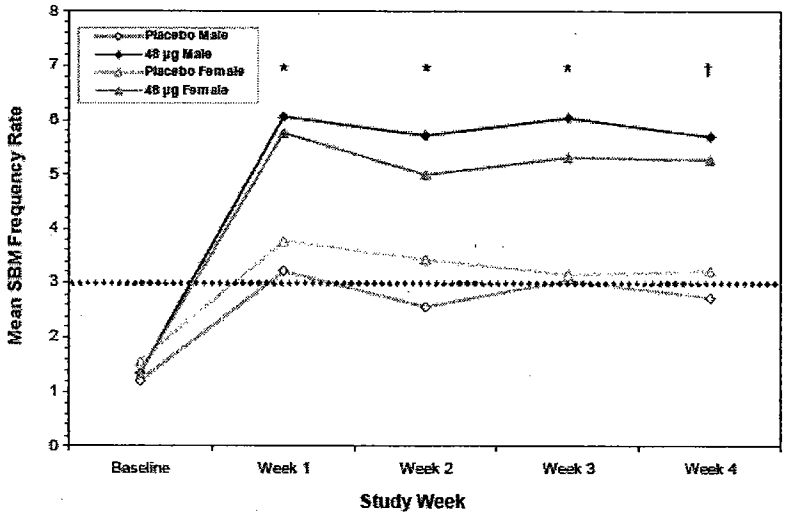

Fig. 8. Mean SBM frequency rates by gender (ITT population)

1.3 Pediatrics

No pediatric patients were enrolled in the clinical development program

There were no pediatric patients enrolled in any of the clinical studies as the inclusion/exclusion criteria noted that subjects had to be at least 18 years of age.

1.4 Hepatic Impairment

Studies were not conducted in patients with hepatic impairment

1.5 Renal Impairment

Studies were not conducted in patients with renal impairment

2.4 Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence systemic exposure and/or response and what is the impact of any differences in exposure on response?

Not applicable due to undetectable systemic exposure of lubiprostone. In addition, lubiprostone does not appear to be metabolized by CYP450 enzymes to any significant extent.

2.5 General Biopharmaceutics

1. What is the BCS classification of lubiprostone?

Lubiprostone is not a highly soluble drug. Due to the lack of data on the extent of drug excretion in bile, it not possible to discern whether lubiprostone is a poorly or highly permeable drug.

The solubility of lubiprostone ranges from [ ] at pH 1 to [ ] at pH 10. Lubiprostone is not a highly soluble drug.

Mass balance study findings indicate that around 63% of an orally administered dose of lubiprostone is excreted in urine and hence absorbed. However, due to lack of data on the extent of drug excretion in bile, it not possible to discern whether lubiprostone is truly a poorly permeable drug or a highly permeable drug.

2. Are the proposed dissolution test method and specifications for lubiprostone soft gelatin capsule acceptable?

The proposed dissolution test method and specifications for lubiprostone soft gelatin capsule are acceptable

A dissolution test method for lubiprostone was developed based on the USP Paddle method (Apparatus 2, USP <711>), whereby soft gelatin capsules are dissolved in 900 mL of [ ] at 37°C using a paddle speed of [ ] rpm. The proposed dissolution method specification was Q of not less than [ ] at 60 min.

The selection of a pH 1 was based on stability considerations as lubiprostone is more stable in acidic media relative to neutral and basic media. The selection of a [ ] for use in the dissolution medium was based on the improved dispersion and solubility of lubiprostone when using [ ]

Overall, the sponsor's proposed dissolution test method and specifications are acceptable.

3. Are the various formulations of lubiprostone used throughout the clinical development adequately linked?

Dissolution data was provided by the sponsor to link Phase 2 and Phase 3 formulations of lubiprostone

Early on in drug development, the [ ] suggested a poor possibility of developing the compound as a solid dosage form. Additionally, a low clinical dose in the µg range was anticipated based on pharmacology studies of the compound. This also suggested [ ]

The early phase 1 development was performed using [redacted] lubiprostone dissolved in medium-chain fatty acid triglyceride (MCT). Prior to starting the phase 2b study in the US, a soft capsule formulation was developed as a preferable dosage form [redacted] while keeping the same fill solution.

The soft capsule lubiprostone formulation consists of two parts; fill material in the core and gelatin preparation which surrounds the core. The fill solution is lubiprostone, 24 µg dissolved in medium chain fatty acid triglyceride (medium-chain triglycerides, MCT).

The production of lubiprostone soft gelatin capsules was conducted by [redacted] The production of soft capsules for the phase 2 clinical study was conducted by [redacted] For the clinical phase 3 studies and commercial formulation, the production was transferred to [redacted]

Dissolution data provided for the Phase 2 and Phase 3 formulations of lubiprostone indicate generally similar dissolution performance albeit no comparative dissolution testing was conducted.

Fig. 9. Side-by-side comparison of the dissolution profiles of the Phase 2 lubiprostone formulation (figure to Left) and the Phase 3 lubiprostone formulation (figure to Right)

Table 3. Composition of the lubiprostone soft gelatin capsule formulation, 24 ug

Component	Reference to quality standard	Function	Quantity per capsule
Fill solution			
RU-0211	In-house standard (R-Tech Ueno)	Active ingredient	24 µg
Medium-chain triglycerides	NF		q.s.
Total weight of fill material			
Gelatin preparation contained in capsule			
Gelatin	NF	Shell of capsule	--
FD&C Red No. 40	21 CFR part 74.340	Coloring	--
D&C Yellow No. 10	21 CFR part 74.1710	Coloring	--
Purified water	USP	Solvent	--
Total weight of Gelatin Preparation			--
Processing Agents and identification			

4. What is the effect of food on the bioavailability of lubiprostone?

There is a significant food-effect on the PK of ^{3}H-RU-0211, whereby Cmax decreased by 55% while $AUC_{0-\infty}$ was unchanged with a high fat meal relative to administration under fasting conditions. The clinical relevance of such a finding is not clear. However, lubiprostone capsules were administered with food in the pivotal clinical trials. Hence, lubiprostone capsules may be labeled for administration with food.

A single study (study 312) was conducted to evaluate the effect of food on the bioavailability of lubiprostone. Study 312 was an open-label, randomized, single-dose, two-treatment, two period, two-sequence crossover design in healthy male and female subjects (n =14). In each of the two periods, subjects received a single 72 µg (3 X 24 µg capsule) oral dose of ^{3}H-RU-0211 (lubiprostone) either under fasting conditions or within 30 min of a high-fat breakfast. The two treatment periods were separated by a 7-12 day washout period. Blood samples were collected up to 120 hrs post-dose in each treatment period for quantitation of lubiprostone and its metabolites.

Given the virtually undetectable systemic levels of lubiprostone following oral administration, the PK parameters were determined based on total orally bioavailable radioactivity. This approach is likely to confound the interpretation of the PK results as total radioactivity includes the parent compound, lubiprostone, along with numerous metabolites. Nevertheless, such a non specific approach is the only feasible one for assessing the effect of food on the PK of lubiprostone.

The results indicated that administration of ^{3}H-RU-0211 following a high-fat breakfast resulted in a decrease of the Cmax by 55% while total exposure ($AUC_{0-\infty}$) was unchanged relative to administration under fasting conditions (Table 5). The significant decrease in Cmax under fed conditions is apparently due to the delay in tmax by 5 hrs. The clinical relevance of such a finding is not clear. It should be noted that lubiprostone capsules were administered with food in the two pivotal clinical trials.

Table 4. Mass balance of total radioactivity following administration of a single oral dose of ^{3}H-RU-0211, 72 µg under fasting and fed conditions

Pharmacokinetic Parameters	Mean (SD)			
	N	Fed (T)	N	Fasted (R)
% Cumulative Excreted in Urine	14	59.7 (10.22)	13	57.2 (11.39)
% Cumulative Excreted in Feces	14	19.5 (9.15)	13	22.6 (9.35)
Total Cumulative % Excreted[a]	14	79.2 (15.06)	13	79.8 (15.82)
C_{max} (ng/g)	14	0.256 (0.0901)	13	0.560 (0.1131)
AUC_{0-t} (ng·hr/g)	14	2.83 (0.549)	13	2.69 (0.506)
$AUC_{0-\infty}$ (ng·hr/g)	10	3.24 (0.867)	13	2.86 (0.512)
$T_{1/2\beta}$ (hr)	10	6.25 (2.833)	13	3.09 (1.094)
T_{max} (hr)[b]	14	8.00 (3.00, 12.1)	13	3.00 (1.50, 4.05)

Table 5. Bioequivalence assessment summary of total radioactivity following administration of a single oral dose of ^{3}H-RU-0211, 72 µg under fasting and fed conditions

Matrix	Pharmacokinetic Parameters	Least Square Means[a] Fed N	(T)	Fasted N	(R)	Test/ Reference Ratio[b]	90% CI[c]
Plasma	ln(C_{max}) (ng/g)	14	0.244	13	0.546	44.6	(37.5, 53.1)
	ln(AUC_{0-t}) (ng·hr/g)	14	2.77	13	2.66	104	(97.8, 111)
	ln($AUC_{0-\infty}$) (ng·hr/g)	10	3.16	13	2.89	109	(101, 118)
Whole Blood	ln(C_{max}) (ng/g)	14	0.166	13	0.344	48.2	(40.8, 57.0)
	ln(AUC_{0-t}) (ng·hr/g)	14	1.84	13	1.73	106	(97.8, 115)
	ln($AUC_{0-\infty}$) (ng·hr/g)	10	2.06	12	1.86	111	(102, 121)

2.6 Analytical Section

1. Have the analytical methods been adequately validated?

Validated ( ) and LC/MS/MS analytical assay methods were developed and used to quantify lubiprostone (RU-0211) and the M3 metabolite in human plasma throughout the clinical development program.

At the time the initial pharmacokinetic studies were performed, a ( ) assay had not yet been developed. Consequently, the initial studies were conducted using ^{3}H-labeled lubiprostone. A ( ) method was then developed for the measurement of lubiprostone and an LC/MS/MS method was developed for the simultaneous measurement of the metabolite M3 (15-OH-RU-0211).

The ( ) assay was linear from ( ) pg/mL with a lower limit of quantitation (LOQ) of - pg/mL. As shown in Table 6, the between-run precision ranged from ( ) to ( )

Table 6. Between run variability of the ( ) assay for lubiprostone concentrations in human plasma

Concentration (pg/mL)	Between Run Precision (%)[1,2]
( )	( )

The LC/MS/MS assay was linear from ( ) pg/mL for each analyte with lower limits of quantitation (LOQ) of ( ) pg/mL. As shown in Table 7, the intraday precision ranged from ( ) for lubiprostone and ( ) for the M3 metabolite. The interday precisions ranged from ( ) respectively.

Table 7. Intraday and interday variability of the LC/MS/MS assay for lubiprostone and the M3 metabolite in human plasma

Concentration (pg/mL)	Intraday (%)[1]	Interday (%)[2]
RU-0211		
10		
200		
800		
15-OH-RU-0211		
10		
200		
800		

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3. Detailed Labeling Recommendations

The key CPB labeling recommendations are summarized as follows:

- Under **Food Effect** subsection of the **CLINICAL PHARMACOLOGY** section, the following statement was revised to describe the effect o food on the pharmacokinetics of lubiprostone:

[

]. Pharmacokinetic parameters of total radioactivity demonstrated that Cmax decreased by 55% while $AUC_{0-\infty}$ was unchanged when lubiprostone was administered with a high-fat meal. The clinical relevance of the effect of food on the pharmacokinetics of lubiprostone is not clear. However, lubiprostone was administered with food in the [ ] trials."

- Under the **DOSAGE AND ADMINISTRATION** section, the Dosage and administration instructions were revised to reflect the need for administration of lubiprostone with food:

"The recommended dosage for [ ] is 24 mcg taken twice daily orally with food, [ ]

Additional labeling changes may be forthcoming after discussions with the Clinical Review Team.

4. Appendices

4.1 Proposed labeling (original and Agency proposed)

4.2 OCPB Filing and Review Form

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Appendix 4.1

Proposed Package Insert

14 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

Appendix 4.2

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-908	Proposed Brand Name	[illegible]
OCPB Division (I, II, III)	III	Generic Name	Lubiprostone
Medical Division	Gastroenterology	Drug Class	Cl channel blocker
OCPB Reviewer	Suliman Al-Fayoumi	Indication(s)	Relief of chronic idiopathic constipation
OCPB Team Leader	Dennis Bashaw	Dosage Form	IR tablet
		Dosing Regimen	24 µg BID
Date of Submission	3/31/05	Route of Administration	Oral
Estimated Due Date of OCPB Review	12/1/05	Sponsor	Sucampo
PDUFA Due Date	1/31/06	Priority Classification	Standard
Estimated Division Due Date	12/31/05		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1	1	
Isozyme characterization:	X	1	1	
Blood/plasma ratio:	X	1	1	
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X	2	2	
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	1	1	
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
Population Analyses –				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**	**1**	
Dissolution:	**X**			
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**X**	**6**	**6**	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	
Comments sent to firm ?	**Not needed at this time**	
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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/s/

Suliman Alfayoumi
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Dennis Bashaw
1/5/2006 12:05:09 PM
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