CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-908s005

PHARMACOLOGY REVIEW(S)

PHARMACOLOGIST'S REVIEW OF NDA 21-908 (Prior Approval Supplement, Sequence 0029 dated June 29, 2007).

Sponsor and Address: Sucampo Pharmaceuticals, Inc., Bethesda, MD.

Date of Submission: June 29, 2007

Date of HFD-180 Receipt: June 29, 2007 (electronic submission)

Date of Review: April 18, 2008

Drug: Amitiza (lubiprostone) Capsules

Category: Prostaglandin analog

Submission contents: In the prior approval supplement, the sponsor is seeking approval of Amitiza (8 μg) Capsules for treatment of patients with constipation-predominant irritable bowel syndrome (IBS-C). The sponsor did not submit any new nonclinical studies with lubiprostone, except one published Pharmacology study (Moser at al. Am J Physiol Gastrointest Liver Physiol 292: G647-G656, 2007).

Background: Amitiza Capsules (24 μg) is currently approved for the treatment of chronic idiopathic constipation. The sponsor submitted the current Prior Approval Supplement seeking approval of low dose lubiproptone (8 μg BID) for the treatment of patients with IBS-C.

PHARMACOLOGY:

The sponsor submitted the following published pharmacology study with lubiprostone.

Recovery of Mucosal Barrier Function in Ischemic Porcine Ileum and Colon is Stumulated by Novel Agonist of the CIC-2 Chloride Channel, Lubiprostone (Moser at al. Am J Physiol Gastrointest Liver Physiol 292: G647-G656, 2007).

The objective of the study was to directly investigate the role of CIC-2 chloride channel in mucosal repair by evaluating the mucosal recovery in ischemia-injured intestinal mucosa treated with lubiprostone, a selective CIC-2 agonist. Intestinal ischemia is an important mechanism of intestinal barrier injury. Ischemic injury causes disruption of the tight junction (TJ) protein complexes and enhances epithelial permeability, permitting transmigration of luminal bacterial toxins and antigens into subepithelial tissues and the circulation. Ischemia-injured porcine ileal mucosa was used in the study. After a 45 minute ischemic period, the tissues were harvested from the pigs, and the mucosa was stripped from the seromuscular layer. The mucosa was mounted in

the Ussing chamber, and short-circuit current (Isc) and transepithelianl electrical resistance (TER) were measured in response to lubiprostone.

Application of 0.01 to 1 μM lubiprostone to ischemia-injured mucosa induced concentration-dependent increases in TER, with 1 μM lubiprostone stimulating a two-fold increase in TER. However, luboprostone (1 μM) stimulated higher elevations in TER despite lower Isc responses compared with the nonselective secretory agonist, PGE_2 (1 μM). In addition, lubiprostone significantly ($p<.05$) reduced mucosal to serosal fluxes of ^3H-labeled mannitol to levels comparable to those of normal control tissues and restored occluding localization to tight junctions. Activation of CIC-2 by lubiprostone stimulated elevations of TER and reductions of mannitol flux in ischemia-injured pig intestine associated with structural changes in tight junctions.

Thus, lubiprostone may provide a novel pharmacological mechanism of accelerating recovery of acutely injured intestine.

Summary and Evaluation:

Amitiza Capsules (24 μg) is currently approved for the treatment of chronic idiopathic constipation in adult subjects. The sponsor submitted the current Prior Approval Supplement seeking approval of a low dose lubiproptone (8 μg BID) for treatment of patients with IBS-C. No new nonclinical studies, except a published pharmacology study with lubiprostone, were submitted in this submission.

In the published pharmacology study, ischemia-injured pig intestinal mucosa was mounted in the Ussing chamber, and short-circuit current (Isc) and transepithelianl electrical resistance (TER) were measured in response to lubiprostone.
Application of 0.01 to 1 μM lubiprostone to ischemia-injured mucosa induced concentration-dependent increases in TER, with 1 μM lubiprostone stimulating a two-fold increase in TER. In addition, lubiprostone significantly ($p<.05$) reduced mucosal to serosal fluxes of ^3H-labeled mannitol to levels comparable to those of normal control tissues and restored occluding localization to tight junctions. Thus, activation of CIC-2 by lubiprostone stimulated elevations of TER and reductions of mannitol flux in ischemia-injured pig intestine associated with structural changes in tight junctions.

LABELING:

The sponsor's proposed labeling is acceptable. However, since lubiprostone had significant effects on implantation and live fetuses in the Segment I reproductive toxicity study in rats, this information should be included in Section 13.1 (Nonclinical toxicology) of the label. The recommended changes for this section are provided below:

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Two 2-year oral (gavage) carcinogenicity studies (one in Crl:B6C3F1 mice and one in Sprague-Dawley rats) were conducted with lubiprostone. In the 2-year carcinogenicity study in mice, lubiprostone doses of 25, 75, 200, and 500 mcg/kg/day (approximately 2, 6, 17, and 42 times the highest recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, lubiprostone doses of 20, 100, and 400 mcg/kg/day (approximately 3, 17, and 68 times the highest recommended human dose, respectively, based on body surface area) were used. In the mouse carcinogenicity study, there was no significant increase in any tumor incidences. There was a significant increase in the incidence of interstitial cell adenoma of the testes in male rats at the 400 mcg/kg/day dose. In female rats, treatment with lubiprostone produced hepatocellular adenoma at the 400 mcg/kg/day dose.

Mutagenesis

Lubiprostone was not genotoxic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma (L5178Y $TK^{+/-}$) forward mutation assay, the *in vitro* Chinese hamster lung (CHL/IU) chromosomal aberration assay, and the *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

Lubiprostone, at oral doses of up to 1000 mcg/kg/day, had no effect on the fertility and reproductive function of male and female rats. However, the number of implantation sites and live embryos were significantly reduced in rats at the 1000 mcg/kg dose as compared to control (b) (4). The number of dead or resorbed embryos (b) (4) but was not statistically significant. The 1000 mcg/kg/day dose in rats is approximately 166 times the highest recommended human dose of 48 mcg/day, based on body surface area.

Sushanta Chakder, Ph. D. Date

Pharmacologist, HFD-180

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NDA

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