ALVIMOPAN

0.0 OVERVIEW

• A. Alvimopan is a peripherally restricted mu-opioid receptor antagonist.

B. DOSING INFORMATION: For the treatment of opioid bowel dysfunction, oral alvimopan doses between 0.5 milligrams (mg) and 1.5 mg once daily were effective in improving bowel function without significant adverse effects or affecting analgesia. For the management of postoperative ileus, alvimopan doses of 6 mg and 12 mg twice daily are being investigated in Phase III clinical trials. The first dose of alvimopan is administered at least 90 minutes before surgery (2 hours is recommended) followed by postoperative dosing of 6 mg or 12 mg twice daily until the first bowel movement.

C. PHARMACOKINETICS: Human pharmacokinetic data are limited. For postoperative ileus, alvimopan administration at least 90 minutes before the initiation of surgery was required in order to achieve clinical benefit. In opioid bowel dysfunction patients, a maximal response was observed 4 to 7 hours after an alvimopan dose.

D. CAUTIONS: The most commonly reported adverse events include abdominal pain, loose stool, flatulence and diarrhea. In most cases the incidence of adverse events is dose related.

E. CLINICAL APPLICATIONS: Alvimopan is an investigational drug being studied for use in the prevention of postoperative ileus and the management of opioid bowel dysfunction.

1.0 DOSING INFORMATION

1.1 DOSAGE FORMS

• A. Information on specific products and dosage forms can be obtained by referring to the Product Index.

• B. SYNONYMS

1. ADL 8-2698
2. LY246736
3. Entereg

1.3 ADULT DOSAGE

1.3.1 NORMAL DOSE

• A. ORAL

1. OPIOID BOWEL DYSFUNCTION

a. Oral alvimopan doses between 0.5 milligrams (mg) and 1.5 mg once daily were effective in improving bowel function without significant adverse effects or affecting analgesia in patients treated with opioids for nonmalignant chronic pain (n=67) and patients treated with methadone for opioid withdrawal (n=34). Alvimopan doses of 3 mg resulted in severe abdominal cramping, diarrhea, nausea, and vomiting in some study subjects (Schmidt, 2001).

2. POSTOPERATIVE ILEUS

a. Based on Phase II clinical trial results, alvimopan doses of 6 milligrams (mg) and 12 mg twice daily are being investigated in Phase III clinical trials. The first dose of alvimopan is administered at least 90 minutes before surgery (2 hours is recommended) followed by postoperative dosing of 6 mg or 12 mg twice daily until the first bowel movement (Schmidt, 2004).

b. In a randomized clinical trial, a dose of 6 milligrams of oral alvimopan shortened the time to recovery of gastrointestinal (GI) function and duration of hospitalization in patients undergoing partial colectomy or total abdominal hysterectomy. Alvimopan
was administered 2 hours before surgery and then postoperatively twice daily until the first bowel movement, discharge from the hospital, or a maximum of 7 days (Taguchi et al, 2001).

- c. Interim results from an additional clinical trial of postoperative ileus in hysterectomy patients (n=124) demonstrated that 12 milligrams (mg) of oral alvimopan administered 2 hours before surgery and then postoperatively twice daily until the first bowel movement resulted in a faster return to normal gastrointestinal (GI) function than placebo, 3 mg, or 6 mg alvimopan. The drug effect was more dramatic in patients who had longer surgical procedures (greater than 1.8 hours). Patients who did not receive the preoperative dose of alvimopan at least 90 minutes before surgery did not experience a faster return to GI function (Schmidt, 2004).

- 1.4 PEDIATRIC DOSAGE
  - 1.4.1 NORMAL DOSE
    - A. Safety and effectiveness have not been established in pediatric populations.

2.0 PHARMACOKINETICS
- 2.1 ONSET AND DURATION
  - 2.1.1 ONSET
    - A. INITIAL RESPONSE:
      - 1. Postoperative Ileus, oral
        - a. In clinical trials, alvimopan administration at least 90 minutes before the initiation of surgery was required in order to achieve clinical benefit (Schmidt, 2004).
    - B. PEAK RESPONSE:
      - 1. Opioid bowel dysfunction, oral: 4 to 7 hours (Schmidt, 2001).
        - a. In a single dose study of patients treated with chronic opioids for nonmalignant cancer pain or methadone for opioid withdrawal, maximum response (time to first bowel movement) was within 4 hours with a 3 milligram alvimopan dose and within 7 hours of a 0.5 milligram alvimopan dose (Schmidt, 2001).

- 2.3 ADME
  - 2.3.1 ABSORPTION
    - A. BIOAVAILABILITY (F):
      - 1. Oral: 0.03% (animal data) (Schmidt, 2001).
        - a. Human data lacking. In animal studies, alvimopan was poorly absorbed following oral administration; oral bioavailability reported as 0.03% in dogs (Schmidt, 2001).
  - 2.3.2 DISTRIBUTION
    - 2.3.2.1 DISTRIBUTION SITES
      - A. OTHER DISTRIBUTION SITES:
          - a. In animal studies, alvimopan administered either orally or intravenously had a limited ability to cross the blood-brain barrier (Schmidt, 2001; Zimmerman, 1994).
  - 2.3.4 EXCRETION
    - 2.3.4.1 BREAST MILK
      - A. BREASTFEEDING: Unknown
        - 1. No human lactation data are available.

3.0 CAUTIONS
- 3.1 CONTRAINDICATIONS
  - A. Hypersensitivity to alvimopan
3.2 PRECAUTIONS

- A. Crohn's disease or other bowel disorders associated with diarrhea
- B. Electrolyte imbalance
- C. Obstructive bowel disease

3.3 ADVERSE REACTIONS

3.3.3 CENTRAL NERVOUS SYSTEM

- A. CENTRAL NERVOUS SYSTEM EFFECTS
  - 1. NERVOUSNESS has been reported in healthy volunteers following the administration of alvimopan (Schmidt, 2001).

3.3.5 GASTROINTESTINAL

- A. GASTROINTESTINAL EFFECTS
  - 1. In some patients with opioid bowel dysfunction, single alvimopan doses of 3 milligrams or more have resulted in severe ABDOMINAL CRAMPS, LOOSE STOOL and/or DIARRHEA, NAUSEA, and VOMITING (Schmidt, 2001).
  - 2. The most common adverse events reported in healthy volunteers were dose related and included ABDOMINAL PAIN (31%), FLATULENCE (31%), and DIARRHEA (21%). NAUSEA was also reported (Schmidt, 2001).

3.3.6 KIDNEY / GENITOURINARY

- A. GENITOURINARY EFFECTS
  - 1. POLYURIA has been reported in healthy volunteers after the administration of alvimopan (Schmidt, 2001).

3.3.7 LIVER

- A. HEPATIC EFFECTS
  - 1. Clinically significant ELEVATED LIVER FUNCTION TESTS were reported in 2 patients after the administration of alvimopan during a Phase 1 ascending dose study (Schmidt, 2001).

3.4 TERATOGENICITY / EFFECTS IN PREGNANCY

3.4.A TERATOGENICITY

- 1. No human teratogenicity data are available.
- 2. In preliminary in vitro and in vivo animal studies, no reproductive or developmental safety issues were identified (Schmidt, 2001).

4.0 CLINICAL APPLICATIONS

4.3 PLACE IN THERAPY

- A. In human trials, alvimopan appears to be a safe and effective inhibitor of opioid-mediated changes in gastrointestinal (GI) function without affecting opioid-mediated central effects such as analgesia. Alvimopan shows potential clinical usefulness in the management of postoperative ileus and the management of opioid bowel dysfunction in patients receiving chronic opioid therapy. For the treatment of opioid-mediated GI dysfunction, the peripherally restricted activity of alvimopan is a distinct advantage over existing opioid antagonists such as naloxone and naltrexone. In addition, the limited systemic absorption and penetration of the blood-brain barrier minimizes the incidence of adverse effects (Schmidt, 2004; Kurz & Sessler, 2003).

4.4 MECHANISM OF ACTION/PHARMACOLOGY

4.4.A MECHANISM OF ACTION

- 1. Alvimopan is a potent antagonist of peripheral mu opioid receptors. In animal studies, alvimopan was 200 times more potent at antagonizing peripheral mu opioid receptors than central mu opioid receptors following intravenous administration. In mouse models, alvimopan precipitated diarrhea in morphine-dependent mice without antagonizing morphine-induced analgesia. In dog studies, oral
administration of alvimopan resulted in poor systemic absorption and oral bioavailability of approximately 0.03%. Whole body radiography studies in rats demonstrated that even after intravenous administration, alvimopan does not penetrate the blood-brain barrier. With oral administration to rats, alvimopan is distributed throughout the gastrointestinal tract, mostly in the gut wall, with minimal distribution to the blood or other tissues (Schmidt, 2001).

- Two randomized, placebo-controlled, human studies demonstrated that alvimopan inhibits morphine-induced increases in gastrointestinal (GI) transit time, but has no effect on postoperative morphine analgesia. No significant adverse events were reported (Liu et al, 2000).

**B. REVIEW ARTICLES**

- 1. The pathophysiology and potential new therapies of opioid bowel dysfunction is reviewed (Kurz & Sessler, 2003).
- 2. A review of alvimopan is provided (Schmidt, 2001).
- 3. A review of alvimopan for the prevention of postoperative ileus is presented (Akca et al, 2002).

**4.5 THERAPEUTIC USES**

**A. OPIOID BOWEL DYSFUNCTION**

- **OVERVIEW:**

  - **FDA APPROVAL:** Adult, no; pediatric, no
  - **EFFICACY:** Adult, possibly effective
  - **DOCUMENTATION:** Adult, fair

- **SUMMARY:**

  - In an unpublished study, alvimopan improved bowel function in patients treated with opioids for chronic pain and patients treated with methadone for opioid withdrawal
  - Alvimopan did not affect opioid analgesia or management of opioid withdrawal

- **ADULT:**

  - In an unpublished study, alvimopan improved bowel function in patients with opioid bowel dysfunction due to long-term treatment with opioids for nonmalignant chronic pain (n=67) or methadone for opioid withdrawal (n=34). Patients participated in 1 of 2 studies, a single dose study (n=75) or a progressive dosing forced titration study (n=26). In the single dose study, patients received placebo or a single dose of oral alvimopan (0.5 milligrams (mg), 1.5 mg, or 3 mg). Within 12 hours of alvimopan administration, significant increases in the incidence of effective bowel movements and stool weight were reported for all alvimopan groups. The percentage of patients with a bowel movement within 12 hours of alvimopan administration were 30%, 68%, 77%, and 100% for the placebo, 0.5 mg, 1.5 mg, and 3 mg groups, respectively (p less than 0.001 for overall treatment with alvimopan). Mean stool weights for these groups were 51 grams (g), 161 g, 290 g, and 388 g, respectively (p=0.006 for overall treatment with alvimopan). There were also dose-related decreases in the incidence of hard dry stool (p less than 0.001 for overall treatment with alvimopan) and moderate to severe straining (p less than 0.001 for overall treatment with alvimopan) and moderate to severe straining (p less than 0.001 for overall treatment with alvimopan) and moderate to severe straining (p less than 0.001 for overall treatment with alvimopan). Maximum response was within 4 hours of the highest alvimopan dose and within 7 hours of the lowest dose. Patients in the highest dose group reported some gastrointestinal adverse effects, including loose stools, cramps, and/or diarrhea. In the forced titration study, for 4 successive days patients received either placebo (n=9) or increasing doses of alvimopan (0.5 mg, 1.5 mg, 3 mg, and 4.5 mg; n=17) once daily. Daily bowel movements were reported in 81% of the alvimopan patients compared to 39% of those in the placebo group. In the alvimopan group, mean stool weights on days 1 to 4 were 107 g, 181 g, 355 g, and 262 g while mean stool weights in the placebo group on days 1 to 4 were 51 g, 95 g, 81 g, and 85 g, respectively. The difference in
stool weight between patients in the alvimopan and placebo groups were significant at alvimopan doses of 1.5 mg (day 2) or higher (p=0.002 for overall alvimopan treatment). The plateau effect was thought to be due to the elimination of retained constipation-related feces on previous days and a return to normal stool volume on the fourth day. For both studies, alvimopan had no effect on opioid analgesia or management of opioid withdrawal (Peck, 2004; Schmidt, 2001).

B. POSTOPERATIVE ILEUS

1. OVERVIEW:

FDA APPROVAL: Adult, no; pediatric, no
EFFICACY: Adult, effective
DOCUMENTATION: Adult, good

2. SUMMARY:

- Effectively reduced postoperative ileus in patients undergoing partial colectomy or total abdominal hysterectomy
- Shortened time to recovery of gastrointestinal function and duration of hospitalization
- Did not antagonize opioid-mediated analgesia

3. ADULT:

a. Interim results from a clinical trial of alvimopan for the prevention of postoperative ileus in hysterectomy patients (n=124) demonstrated that 12 milligrams (mg) of oral alvimopan administered 2 hours before surgery then postoperatively twice daily until the first bowel movement resulted in a faster return to normal gastrointestinal (GI) function than placebo, 3 mg, or 6 mg alvimopan. Return to normal GI function was an average of 0.5 days faster in the 12 mg alvimopan group compared to placebo (p=0.06). The drug effect was more dramatic in patients who had longer surgical procedures (greater than 1.8 hours), with a return to normal GI function an average of 0.9 days faster in the 12 mg group compared to placebo (p=0.01). Patients who did not receive the preoperative dose of alvimopan at least 90 minutes before surgery did not experience a faster return to GI function (Schmidt, 2004).

b. In a randomized clinical trial, pre-and postoperative administration of alvimopan shortened the time to recovery of gastrointestinal (GI) function and duration of hospitalization in patients undergoing partial colectomy (n=15) or total abdominal hysterectomy (n=63). Patients were randomly assigned to receive placebo (n=26), 1 milligram (mg) alvimopan (n=26), or 6 mg alvimopan (n=26). Study medication was administered 2 hours before surgery and then postoperatively twice daily until the first bowel movement, discharge from the hospital, or a maximum of 7 days. All patients received general anesthesia and postoperative intravenous patient-controlled analgesia with either morphine sulfate or meperidine hydrochloride. Efficacy was assessed by evaluating time to first passage of flatus, time to first bowel movement, and time until patient was ready for discharge. Compared to placebo, patients in the 6 mg alvimopan group had significantly shorter median times to first passage of flatus (70 hours versus 49 hours, p=0.03), first bowel movement (111 hours versus 70 hours, p=0.01), and time until patient was ready for discharge (91 hours versus 68 hours, p=0.03). Efficacy measures in the 1 mg alvimopan group were not significantly different from placebo. In addition, there was significantly less nausea (p=0.003) and vomiting (p=0.03) in the 6 mg alvimopan group compared to the 1 mg alvimopan and placebo groups. No significant differences in visual analog scale pain scores or cumulative morphine doses were observed, suggesting that alvimopan did not antagonize opioid-mediated analgesia. No alvimopan-associated adverse events were reported (Taguchi et al, 2001).
6.0 REFERENCES


7.0 AUTHOR INFORMATION

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