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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-566**

**Medical Review(s)**

04/30/04

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

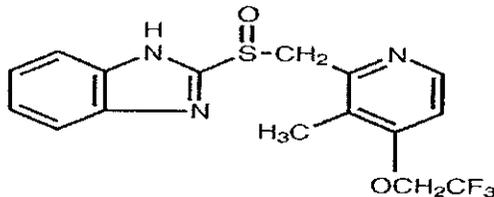
Division of Gastrointestinal & Coagulation Drug Products  
Medical Officer's Review of a NDA Re-Submission

**FROM:** Eric Brodsky, MD, Medical Officer

**NDA#:** 21-566

**REGULATORY DATES:** Sponsor's Original Submission Date: 12/20/02  
Sponsor's Resubmission Date: 1/10/04  
Medical Officer Completion Date: 4/26/04  
Prescription Drug User Fee Act Due Date: 7/12/04

**DRUG NAME:** **PREVACID I.V. (lansoprazole) for Injection**



**EMPIRIC FORMULA:** C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S

**CHEMICAL NAME:** 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl] benzimidazole

**DRUG TYPE:** Proton Pump Inhibitor

**SPONSOR:** TAP Pharmaceutical Products Inc., 675 North Field Drive,  
Lake Forest, IL 60015

**ROUTE:** Intravenous

**PROPOSED INDICATION:** Short-term treatment (up to 7 days) of all grades of **erosive esophagitis** (EE) when patients are unable to take the oral prevacid formulations. Once the patient is able to take medications orally, therapy can be switched to a prevacid oral formulation.

**DOSE/FORMULATION/ ADMINISTRATION:** Each pack contains one single dose vial of lyophilized powder (which contains 30 mg of lansoprazole — the active ingredient) and one required in-line filter. The powder is first reconstituted with 5 mL of sterile water, and then further diluted with either 50 mL of 0.9% Sodium Chloride, Lactated Ringer's, or 5% Dextrose solution. The final reconstituted solution is administered intravenously over 30 minutes with the supplied in-line filter.

## **I. BACKGROUND:**

The sponsor initially submitted NDA 21-566 [PREVACID I.V. for Injection (prevacid I.V.)] on December 20, 2002 for the short-term treatment (up to 7 days) of all grades of erosive esophagitis (EE) when patients are unable to take the oral prevacid formulations. Prevacid I.V. is an intravenous formulation of prevacid (lansoprazole), a proton pump inhibitor. Oral prevacid (capsules) was initially approved for the treatment of all grades of EE and several other acid-related disorders on May 10, 1995.

In the initial prevacid I.V. NDA submission, the sponsor completed one U.S. clinical trial in the treatment of EE patients (Study M01-308) and three U.S. clinical trials in healthy subjects (Studies M01-307, M95-306, and M96-486.) The study reports were reviewed by Dr. Narayan Nair, a medical officer in the Division of GI and Coagulation Drug Products (The Division). Dr. Nair found that prevacid I.V. was bioequivalent to oral prevacid in Study M01-308 using pharmacodynamic parameters [they were bioequivalent for the maximal acid output (MAO) and they approached bioequivalence for the basal acid output (BAO)]. Dr. Nair recommended approval of NDA 21-566, pending the labeling review. Please see Dr. Nair's review of NDA 21-566 dated September 8, 2003 for details.

On October 23, 2003, The Division took an approvable action on NDA 21-566 due to deficiencies in the chemistry compatibility of prevacid I.V. and required the sponsor to:

- 1) Conduct studies to identify the etiology of the instability of the drug product in several admixture solutions.
- 2) Reformulate the drug product so that it is compatible with admixture solutions.
- 3) Co-package the drug product with an in-line filter for removal of the particulates from the admixture and demonstrate that there is no loss of potency when the admixture is filtered as an interim solution.

The sponsor re-submitted NDA 21-566 for prevacid I.V. on January 12, 2004. This re-submission contained a complete response to all of the chemistry deficiencies identified in the first cycle of review. The sponsor conducted chemistry studies to support the use of prevacid I.V. with a required in-line filter. The results of these studies indicate a Pall Supor® 1.2 µm filter is effective in removing sub-visual particulate matter that forms when prevacid I.V. is admixed with solution. Furthermore, the use of the in-line filter had no impact on the potency of prevacid I.V. After evaluating these studies, Dr. Al-Hakim, Ph.D., the chemistry reviewer for The Division, concluded that these studies resolve all of the chemistry deficiencies. Therefore, Dr. Al-Hakim recommended approval of NDA 21-566, pending the labeling review. Please see his review dated 3/26/04 for details.

This second NDA submission contains no new clinical studies or information. Thus, my medical officer's review of this submission is focused on the labeling evaluation.

## II. LABELING REVIEW:

The following are my recommendations for labeling changes:

- 1) In the “**INDICATIONS AND USAGE**” section of the label, add the statement, “for a total of 6 to 8 weeks.”

The successful treatment of EE with oral prevacid occurs after 6 to 8 weeks of consecutive daily treatment. In Study M87-092 (a randomized, double-blinded, multi-center, parallel group, placebo-control, dose-ranging, 8-week phase 3 trial), the EE healing rates with 30 mg of oral prevacid at 4 weeks, 6 weeks, and 8 weeks were 73%, 87%, and 87% respectively. Treatment of EE with oral prevacid for less than 6 to 8 weeks lowers the efficacy of prevacid in the healing of EE.

Many physicians may *incorrectly* assume that the intravenous prevacid formulation is “stronger” than the oral prevacid formulation and these physicians may *mistakenly* believe that EE can be completely treated over the short term (in 7 days.) Therefore, the “**INDICATIONS AND USAGE**” section of the label should emphasize that the total recommended duration of EE treatment with prevacid is 6 to 8 weeks which includes up to 7 days of prevacid I.V. administration.

- 2) In the “**INDICATIONS AND USAGE**” section of the label, add the statement, “The safety and efficacy of PREVACID I.V. for Injection as an initial treatment of EE have not been demonstrated.”

The sponsor conducted only one prevacid I.V. trial (Study M01-308) in EE patients. In this study, EE patients were all initially treated with oral prevacid, and then they were randomized to intravenous placebo or prevacid I.V. Since, prevacid I.V. has not been administered to EE patients as an initial treatment, the safety and efficacy of prevacid I.V. in the initial treatment of EE have not been demonstrated.

The current “**INDICATIONS AND USAGE**” section of the label of PROTONIX I.V. for Injection (protonix I.V.) states that the “safety and efficacy of PROTONIX I.V. for Injection as an initial treatment of patients having GERD with a history of EE have not been demonstrated.” To create *a level playing field* with the only approved intravenous proton pump inhibitor, protonix I.V., the prevacid I.V. label should have a similar statement.

- 3) In the “**ADVERSE REACTIONS**” section of the label, change the following statement, <sup>C</sup>

1 The sentence should be the following: “In four U.S. trials involving 161 subjects exposed to PREVACID I.V. for Injection, the following treatment-related adverse events were reported in  $\geq 1\%$  of subjects.”

My statement gives a more accurate exposure of subjects and patients to prevacid I.V.

- 4) In the “**ADVERSE REACTIONS**” section of the label, add the word “Oral” after the word “PREVACID” in the table entitled, “Incidence of Possibly or Probably Treatment-Related Adverse Events in Short Term, Placebo-Controlled Studies.” This additional word will add

clarity to the table by highlighting that these adverse drug events occurred with the use of oral prevacid (not prevacid I.V.)

- 5) In the “**DOSAGE AND ADMINISTRATION**” section of the label substitute the phrase, “**J**” for the following phrase, “*when patients are unable to take the oral therapy.*”

According to the Webster’s New World Dictionary the word “alternative” means: providing a choice between things. Thus, the sponsor’s proposed statement implies that patients can receive prevacid I.V. even if they can tolerate oral therapy. This statement is incongruent to the sponsor’s statement in the “**INDICATIONS AND USAGE**” section of the label: “when patients are unable to take the oral formulations, PREVACID I.V. for Injection is indicated as an alternative for ...”

The oral prevacid formulations have endoscopic evidence of successful EE healing in clinical trials, have been used in the United States since 1995, and have had an exposure to millions of U.S. patients. In contrast, prevacid I.V. has indirect evidence of efficacy (through pharmacodynamic data) and has a lower exposure to subjects (only 161 U.S. subjects have received a dose of prevacid I.V.) Therefore, physicians should be encouraged to switch patients to an oral formulation as soon as patients can tolerate oral therapy.

- 6) In the “**DOSAGE AND ADMINISTRATION**” section of the label, add the phrase, “Once the patient is able to take medications orally, therapy can be switched to an oral prevacid formulation for a total of 6 to 8 weeks.” Please see my comments in 1).

### **III. RECOMMENDATIONS FOR REGULATORY ACTION:**

This medical officer recommends that NDA 21-566 is approvable pending the required labeling changes. If the sponsor accepts the labeling changes, then this medical officer recommends approval of PREVACID I.V. for injection for the short-term treatment (up to 7 days) of all grades of EE in patients who are unable to take the oral formulations.

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/s/  
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Eric Brodsky  
4/30/04 10:12:36 AM  
MEDICAL OFFICER

Ruyi He  
4/30/04 11:41:37 AM  
MEDICAL OFFICER  
I concur Dr. Brodsky's comments and recommendations.

10/09/03

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
September 30, 2003

**DATE:**

**TO:**

Joyce Korvick, MD  
Deputy Director  
Division of Gastrointestinal/Coagulation Drug Products  
HFD-180

**FROM:**

Hugo E. Gallo-Torres, MD, PhD, PNS  
Medical Team Leader, Gastrointestinal Drugs  
Division of Gastrointestinal/Coagulation Drug Products  
HFD-180

**SUBJECT:**

NDA 21-566, **Prevacid** (lansoprazole I. V. for Injection  
**Submitted:** December 20, 2002  
TAP Pharmaceutical Products Inc.  
Lake Forest, IL 60015  
**Indication:** short-term treatment (up to 7 days)  
of all grades of **erosive esophagitis**, in patients  
**unable to take the oral formulations.**  
• **Re: Recommendation for regulatory action.**

*Table of Contents*

I. Executive Summary.....2

II. Background Information/Scientific Rationale.....3

III. Summary Review/Conclusion by Discipline.....6

    A. CHEMISTRY.....6

    B. ANIMAL PHARMACOLOGY/TOXICOLOGY.....8

    C. CLINICAL PHARMACOLOGY/BIOPHARM.....10

    D. CLINICAL.....13

IV. Overall Comments/Conclusions on Efficacy and Safety.....17

V. Recommendations for Regulatory Action/Labeling.....19

## I. Executive Summary

TAP Pharmaceutical Products Inc. has submitted **NDA 21-566** and requested approval of **PREVACID® I.V.**, a sterile formulation of the proton pump inhibitor lansoprazole sodium for the short-term (up to 7 days) of all grades of erosive esophagitis as an alternative when patients are unable to take oral formulations. Once the patient is able to take medication orally, therapy can be switched back to the oral route. In support of their application, the sponsor submitted results of two well-designed and apparently well-executed pivotal [**M01-308**, in erosive esophagitis patients and **-307** in healthy volunteers] and two supportive [**M95-306**, single dose] and **M96-486** [once-a-day for 5 days] studies. Using **pentagastrin** as the gastric acid stimulant, pharmacodynamic parameters, including **maximal acid out, basal acid output and intragastric pH** were determined in a standardized approach.

From the available evidence, assessed through multidisciplinary reviews, the MTL concludes that LANSO, at the intravenously administered dose of 30 mg once-a-day: 1. Is effective; 2. Can maintain an adequate anti-secretory activity [as the oral form]; 3. Can be used as an alternate to 30mg oral LANSO in those EE patients that are unable to take the oral medication and 4. Is safe. It is further concluded that, taken in conjunction, the data submitted by the sponsor demonstrate a favorable benefit/risk profile for LANSO I.V. for short-term use in patients with EE who cannot take oral medication.

**Approval of I.V. LANSO 30 mg once-a-day is recommended.**

Approval during this first cycle is preferred. The I.V. form of LANSO is to be used as an alternate to all the oral formulations of 30-mg LANSO per day in those erosive esophagitis patients who are unable to take oral medication. Before the approval action is taken, **all types of plastic bags**

**and solutions must be tested** for compatibility/incompatibility and they **all** must be shown to be compatible.

Furthermore, before the approval action is taken, the compatibility data must be incorporated in the labeling. But in the medical team leader's opinion, the current available information about the compatibility issue is inadequate for approval. **If the compatibility data are not**

satisfactory, I.V. LANSO 30 mg could still be approved, if it were to be **co-packaged with compatible [ ] bags, stickers, and specific instructions**. If the co-packaging approach is not acceptable the recommendation is **approvable**. With the **approvable** regulatory action, the applicant should be asked to commit to initiate studies to address compatibility issues with *all* available plastic bags and solutions.

## II. Background Information/Scientific Rationale

Lansoprazole (LANSO) (Prevacid®) was the second<sup>1</sup> of by now five oral forms of Proton Pump Inhibitors (PPIs) available in the United States and abroad. PPIs are gastric acid anti-secretory agents that suppress gastric acid secretion by inhibiting the enzyme  $H^+/K^+$ -ATPase. This enzyme is the proton pump that exchanges luminal hydrogen ions. This proton pump constitutes **the final common pathway** of gastric acid secretion, and is abundant in the gastric mucosa where it is involved with the **acid-producing parietal cell**. After binding to this enzyme irreversibly, LANSO [like other PPIs] inactivates it and thereby **abolishes response to all types of acid secretion stimulation**. Because of these pharmacological properties, LANSO [and other PPIs] are useful in conditions where profound inhibition of acid secretion is needed.

**Three oral dosage forms** of LANSO (TAP Pharmaceuticals) are currently approved: delayed release 15 and 30 mg capsules (NDA 20-406)<sup>2</sup>, delayed release 15 and 30 mg/packet for suspension (NDA 21-281), and orally disintegrating 15 and 30 mg tablets (NDA 21-428).

The approved indications for the orally available products are: short-term treatment of active duodenal ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, maintenance of healed duodenal ulcers, short-term treatment of active benign gastric ulcer, healing of non-steroid anti-inflammatory drugs (NSAID)-associated gastric ulcer, risk reduction of NSAID-associated gastric ulcer, gastroesophageal reflux disease (GERD), short-term treatment of symptomatic GERD, short-term treatment of erosive esophagitis (EE), maintenance of healing of EE, and pathological hypersecretory conditions including Zollinger-Ellison syndrome.

With regard to the GERD (gastro-esophageal reflux disease) indications, the inactivation of the  $H^+/K^+$ -ATPase enzyme results in a profound and long lasting

<sup>1</sup> The first was omeprazole (Prilosec®) now available OTC

<sup>2</sup> The FDA approved this initial oral formulation on May 10, 1995

(>24h) pharmacodynamic effect. This effect in turn causes a reduction of the potency of the material refluxed from the stomach into the esophagus to produce erosive esophagitis, one of the two existing forms of GERD [the other is symptomatic GERD (s-GERD)]. The propensity for reflux is likewise reduced by a significant decrease in gastric volume; acid refluxed into the esophagus would otherwise be injurious to the esophageal mucosa. In addition, an increase in pH (to >4) favors the inactivation of pepsin, a proteolytic enzyme produced by the oxyntic cells of the stomach. Pepsin, somehow, contributes to esophageal mucosal damage. Finally, normal salivary flow may facilitate the neutralization of the reduced total output and acid concentration and esophageal motility may hasten the removal of the refluxed gastric contents.<sup>3</sup>

Through NDA 21-566, the applicant is seeking approval of a parenteral (intravenous = I.V.) form of LANSO. According to the sponsor, *Prevacid I.V. for injection is specifically indicated for the short-term treatment (up to 7 days) of all grades of erosive esophagitis as an alternative when patients are unable to take oral formulations. Once the patient is able to take medication orally, therapy can be switched back to the oral route.*

The **Dosage and Administration** Section of the labeling would read: 30 mg lansoprazole per day administered by I.V. infusion 30 minutes for up to 7 days.

The specific scientific rationale behind the use of I.V. LANSO in the treatment of EE (erosive esophagitis) is, in principle, the same as that delineated above for the use of oral LANSO for the same indication, with the following additional clarifications/requirements for when it is appropriate for the I.V. formulation to substitute for the oral form.

- The I.V. formulation is expected to act through the same mechanism of action than that proposed for the orally administered material.
- Specifically, the scientific rationale behind the use of I.V. LANSO in the treatment of EE is the ability of this PPI to inhibit both **BASAL** and **STIMULATED gastric acid secretion** irrespective of the stimulus. These important parameters are measured as **BAO** (Basal Acid Output) and **MAO** (Maximal Acid Output). A demonstration of this pronounced PD effect is important because, although association does not necessarily establish cause-to-effect relationship, EE is nearly always associated with **reflux of acid gastric contents into the esophagus** and the consensus is that acid causes

<sup>3</sup> Based on the available evidence, orally administered LANSO does not seem to have an influence on other pathophysiological factors (decreased LES pressure, inefficiency of esophageal clearance, motility-antimotility effects, decreased resistance of the esophageal tissue to injury, ability of the esophageal tissue to repair, etc ) known to play a role in determining whether a patient with GER (gastro-esophageal reflux) will have esophagitis

esophagitis, although other causes, such as reflux of biliary secretions, need to be considered under certain clinical conditions.

- It follows that the major rationale for the use of I.V. administered LANSO in the treatment of EE (when used as a substitute for oral LANSO) will have to be its well-documented anti-secretory effect, which, in this particular situation, needs to be no different from that obtained with orally administered LANSO.
- The Division requested studies in both erosive esophagitis patients and healthy subjects. The sponsor submitted results of two pivotal (**M01-308**, in patients with erosive esophagitis and **M01-307**, in healthy subjects) and two supportive trials (**M95-306** and **M96-486**) carried out in healthy subjects. An explanation of why M01-307 -in spite of being carried out in a study population of healthy subjects- qualifies as one of the two pivotal trials, follows.
- The issue is how applicable to the GERD situation are results of **pharmacodynamic studies in healthy subjects**. The evidence at hand suggests that there is no reason to suspect that GERD patients may respond differently from the acid secretion viewpoint than healthy volunteers. Most patients with GERD are neither potential nor real hypersecretors. This issue was addressed by B. Hirschowitz<sup>4</sup>, one of the top investigators in this field. He studied fasting gastric contents (volume, pH, H<sup>+</sup>, pepsin, and bile) and basal and pentagastrin-stimulated H<sup>+</sup> and pepsin secretion in 696 patients, 169 with endoscopically defined (and graded 1 to 4) EE and 527 controls without esophagitis. It was shown that esophagitis (and its complication -stricture) were not related to high acid and pepsin secretion. Dr. Hirschowitz's results further demonstrated that, unless they have a concomitant duodenal ulcer (DU), GERD patients do not secrete acid to the same extent as DU patients (this indication is not the subject of NDA 21-566). It is worth noting that when properly classified and matched for background (gender and the presence of DU), even patients with Barrett's esophagus did not seem to have greater outputs of gastric acid or pepsin than esophageal patients without Barrett's<sup>5</sup>.  
From the above-noted considerations, the sponsor's submission [in NDA 21-566] of two pivotal studies, one (M01-308) in EE patients, the other (M01-307) in healthy subjects, is appropriate and acceptable.
- The other issue that needs to be addressed is the use in pivotal trials, of pharmacodynamic endpoints, BAO (basal acid output) and MAO (maximal acid output) rather than clinical outcomes (healing of endoscopically demonstrable esophageal lesions). The secretagogue used was Pentagastrin (PG), a commonly

<sup>4</sup> "A Critical Analysis, with Appropriate Controls, of Acid and Pepsin Secretion in Esophagitis. *Gastroenterology* 98: A60 (1990)

<sup>5</sup> Collen MJ et al [*Gastroenterology* 98: 654-661 (1990)] described a subgroup of patients with long-standing symptomatic GERD who were hypersecretors and required increased acid-suppressive therapy. Many of these individuals also had underlying Barrett's epithelium

employed gastric secretion stimulant that allows testing under standardized conditions. Studies in healthy subjects have shown that 80% maximal gastric secretory response is reached in ca. 80% of individuals with a dose of 0.6  $\mu$ /kg/h. Maximal gastric acid secretion in nearly all experimental subjects in whom the gastric acid secretion machinery is normal, is observed at PG doses of 6  $\mu$ /kg/h (a 10-fold higher dose of the stimulant, used in some of the experiments submitted by the sponsor). But at these higher doses of PG, the incidence of side effects due to the gastric acid stimulant is high. In summary, for consistency and parity, the approach used in the evaluation of I.V. LANSO is the same used during the evaluation and eventual approval of I.V. pantoprazole (the only intravenously available PPI in the US). Finally, even with PPIs, no significant healing rates are expected after 7 days of treatment.

### III. Summary Review/Conclusion by Discipline

#### A. CHEMISTRY

Dr. Ali Al-Hakim's recommendation is that the application is **approvable**, pending addressing and resolution of the chemistry issues enumerated at the end of this sub-section. Listed below are excerpts from Dr. Al-Hakim's Chemistry review for NDA 21-566, dated September 25, 2003.

- Lansoprazole (Prevacid® I.V.) for injection, 30 mg, is a lyophilized drug product packaged in 5 mL single dose vials. The vial is sealed with stopper. In addition to the 30 mg LANSO active ingredient, the drug product contains inactive ingredients<sup>6</sup>. The drug product contains an emulsifier, which is added to each vial during filling because complete withdrawal of the reconstituted solution from the vial is not possible.
- For patient use, 30 mg of LANSO, 30 mg LANSO is reconstituted with 5 mL of sterile water for injection (pH 11) and further diluted in 50 mL of 0.9% sodium chloride for injection (pH 10.2). The reconstituted solution can be held for 1h when stored at 25° C prior to further dilution. The diluted solution stored at 25° C should be administered within 24h. The diluted solution should be administered to the patient over 30 min.

<sup>6</sup> These include mannitol, (60 mg); meglumine, (10 mg); and sodium hydroxide, for pH adjustment.

<sup>7</sup>

- LANSO drug substance is a white to brownish-white powder. [

LANSO is a stable [

] LANSO also [

- The drug substance is [ becoming slightly soluble at pH 11 and sparingly soluble [

- Main issues related to the drug product, listed in Dr. Al-Hakim's review are:

[

-

-

-

-

- The following is a summary description of how the product is intended to be used:

Inject 5 mL of sterile water for injection, USP, into a 30 mg vial of Prevacid® I.V. for injection (6 mg/mL). Mix gently until the powder is dissolved. The pH of this solution is about 11.2. This reconstituted solution can be held for 1h when stored at 25° C prior to further dilution. Dilute with 50 mL of 0.9% sodium hydroxide. The diluted solution is stored at 25° C and has a pH of ca. 10.2. This solution should be administered within 24h. The solution should be administered to the patient over 30 min. Prevacid® I.V. for injection should not be mixed with other drugs or diluents as this may cause incompatibilities. [

Compatibility studies were performed between the drug product reconstituted solution and infusion set and infusion bag. No compatibility issues were reported.

- According to the Chemistry review the application under NDA 21-566 is **approvable**. The major issue that remains unresolved and prevents approval, is the compatibility of the drug product solution with other I.V. bags (non-

<sup>8</sup> LANSO drug substance manufactured for the commercial [

]

In a September 29, 2003 addendum to his Chemistry review of NDA 21-566, Dr. Al-Hakim recommended that the following issues be conveyed in the Disciplinary Review Letter to the applicant.

1. Compatibility studies which should be conducted using commonly used diluents even if they are not identified in the proposed drug product labeling (e.g. Lactate Ringer's Injection, 5% Dextrose Injection, etc). The studies should include:

A- I.V. bags of all commercial compositions, supplied by different manufacturers, that contain various solutions.

**These studies should be performed** because there is a high probability that I.V. bags and solutions **not identified in the package insert** may be used in the clinical setting.

**The studies are required** because the possibility of **particulate formation** will result in potential potency loss and safety concerns.

2. Three copies of methods validation should be provided. These copies should be prepared as per FDA guideline "GUIDELINE FOR SUBMITTING SAMPLES ANSD ANALYTICAL DATA FOR METHODS VALIDATION". Refer to 21 CFR 314.50.

**NOTE:** Chemistry recommendations for labeling are given in Dr. Al-Hakim's review.

## **B. PRECLINICAL PHARMACOLOGY/TOXICOLOGY**

After reviewing the evidence (September 15, 2003), Dr. Ke Zhang, the Pharmacology/Toxicology reviewer recommends **approval** of the application. Highlights of Dr. Zhang's review are given below.

- I.V. administered LANSO inhibited basal gastric acid secretion at  $ID_{50}$  of 0.28 mg/kg in rats and 0.14 mg/kg in dogs<sup>10</sup>. This effect was as or more effective than that obtained after oral administration of the drug.
- Following I.V. administration of LANSO, the plasma levels of the unchanged drug declined quickly with  $t_{1/2}$  of 0.3h in rats, and  $t_{1/2\alpha}$  of 0.6h and  $t_{1/2\beta}$  of 0.6 to 11h in dogs<sup>11</sup>.
- The metabolic patterns of LANSO were similar following oral and I.V. administration in rats and dogs.

<sup>9</sup> As noted by Dr. Al-Hakim, there is a tendency for this type of drug product to form **particulate** when it comes in contact with some I.V. bags

<sup>10</sup> Inhibition of gastric acid secretion was also demonstrated following I.V. administration of LANSO at 30 mg/day in humans

<sup>11</sup> In humans, the plasma level of LANSO decreased rapidly with a terminal  $t_{1/2}$  of 1h following both oral and I.V. administration.

- Irrespective of the route of administration (oral or I.V.) ca. 26 to 32 % and 64 to 69 % of the administered radioactivity were excreted in the urine and feces, respectively, over 72h in both rats and dogs.
- I.V. administration of LANSO produces higher systemic exposure as compared to the oral route administration in animals [these findings are reproduced in humans].
- In acute toxicity studies, the minimal lethal dose of LANSO [in saline] was 218 mg/kg in male mice and 167 mg/kg in female rats. In both species of animals, the following signs of toxicity were noted: decrease in locomotion activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, and ataxic gait.
- Not unexpectedly, in 13-week I.V. toxicity studies, the stomach was the target organ of toxicity in both rats and dogs. Histopathological examination revealed eosinophilic, hypertrophic and hyperplastic chief cells and microaggregation of the ECL cells in the stomach of rats, and atrophy, vacuolation and necrosis of the parietal cells, and hyperplasia of the foveolar and neck region of the stomach. In addition, thymus [atrophy], and liver [hypertrophy of the centrilobular hepatocytes] were also identified as target organs of toxicity in rats. [NOTE: All of these are expected findings, based on previous toxicity data with oral LANSO].
- Treatment with I. V. administered LANSO:
  - a) did not affect fertility and mating performance of M and F rats at I.V. doses of up to 30 mg/kg/day in the Segment I Fertility and General Reproductive Performance studies in rats;
  - b) was not teratogenic at I.V. doses of up to 30 mg/kg/day in the Segment II Teratology study in rats and rabbits;
  - c) did not produce any adverse effects on perinatal and postnatal development at I.V. doses of up 30 mg/kg/day in the Segment III study in rats;
  - d) revealed no hemolytic potential in rabbit blood at LANSO concentration of 6 mg/mL (1:1 mixture) *in vitro* hemolytic studies; and
  - e) at 6 mg/mL, produced mild edema and inflammatory cell infiltration at the injection site in rabbits.

In conclusion, no additional non-clinical studies are recommended. Recommendations for labeling are given in Dr. Zhang's review.

### C. CLINICAL PHARMACOLOGY/BIOPHARM

All studies submitted in support of NDA 21-566 included **pharmacodynamic evaluations**. Summary review of the pivotal trials, **M01-308** (conducted in subjects with erosive esophagitis) and **M01-307** (conducted in healthy subjects) is given in Section D. of the current review. The current summary of the Biopharm review, centers around the supportive studies, **M95-306** and **M96-486**, both conducted in healthy volunteers and reviewed in detail by Dr. Tien-Mien Chen (September 17, 2003), the Biopharm reviewer. The emphasis is on PK data since PD information is addressed in detail in the Clinical Section of the current review.

- Regarding PK results, I.V. administration of LANSO 30 mg QD resulted in higher systemic exposure (higher  $C_{max}$  and AUC values) compared to that of oral QD dosing of LANSO 30 mg. For gastric acid output suppression on Day 7, I.V. 30-min infusion of LANSO 30 mg QD showed an improvement over oral route with respect to BAO. However, in these EE patients, MAO, assessed after the two routes of administration, did not differ significantly. In healthy adults, I.V. LANSO was not significantly different from the oral LANSO with respect to either MAO or BAO.
- Studies **M95-306** and **M96-486**, reviewed in detail by Dr. Chen, were designed to evaluate PK and PD, i.e., **24-h intragastric pH**, in healthy volunteers following single and multiple doses of LANSO, respectively.
- The question of how does the I.V. PK [and PD] of LANSO compare to that of oral LANSO is answered by results in **Study M95-306, one of the two supportive studies submitted in NDA 21-566**. This was a 38-subject, randomized, open-label, crossover, single-center [R.A. Blum, Buffalo, NY] study, set to evaluate the safety, PKs, and PDs of **single doses** of I.V. LANSO in healthy subjects. These results were compared to those obtained with a 30 mg oral dose of LANSO<sup>12</sup>.

As seen in Table 1, after equivalent doses of 30 mg, I.V. administration over 30- min. resulted in higher systemic exposure (higher  $C_{max}$  [155% ↑] and AUC [35% ↑] values) compared to that of oral dosing. The I.V. and oral terminal half-lives, however, were similar. As with oral or I.V. dosing, little accumulation (<10%) of plasma LANSO levels was observed in healthy subjects after once-a-day multiple dosing to steady state. Thirty (30) mg and 60 mg of LANSO given by I.V. 30-min. infusion exhibited dose-proportionality. Relative to oral dosing, after LANSO 30 mg I.V. was administered over 30, 60, or 120 min.,  $C_{max}$  decreased as the infusion time increased with similar AUC (**Table 1**) and intragastric pH values (**Table 2**). The

<sup>12</sup> 33 subjects [31M and 2F] completed the trial. Subjects were dosed in 3 groups of 12. Venous plasma samples were analyzed using a validated HPLC method. Gastric pH was measured using a C

mean absolute bioavailability of Prevacid oral 30 mg capsule was determined to be about 70%.

**Table 1**  
**Study M95-306**  
**Mean LANSO Single-Dose PK Parameters After Oral or I.V. Administration**

Regimen Parameter	Dose Administration				
	Oral 30 mg	30 mg over 30 min	30 mg over 60 min	30 mg over 120 min	60 min over 30 min
$C_{max}$ (ng/mL)	682	1736	1346	934	3589
$T_{max}$ (h)	2.0	0.5	1.0	2.0	0.5
$AUC_{0-\infty}$ (ng-h/mL)	2300	3103	3163	3017	7130.
$T_{1/2}$ (h) <sup>#</sup>	1.2	1.1	1.1	1.1	1.2
CL (L/h)	19.5*	12.8	12.7	13.4	10.5
$Vd_{ss}$ (L)	-----	17.7	17.5	20.6	16.3

This Table corresponds to Table 1 in Dr. Chen's Biopharm review, with significant modifications. The  $\pm$  SEMs have been omitted for simplification of presentation. # Harmonic mean \* Calculated as CL/F

**Table 2**  
**Study M95-306**  
**Mean Intra-gastric pH Values and Mean % of Time that the intra-gastric pH Values were above 3 and 4 during the 24-h Monitoring Period**

Summary of pH Assessments (Single-Dose)				
Regimen				
	Oral 30 mg	I.V. 30 mg over 30 min	I.V. 30 mg over 60 min	I.V. 30 mg over 120 min
Mean 0-23 h pH	3.16	3.39	3.59	3.44
% of time pH >				
3	43.5	50.3	54.6 <sup>a</sup>	51.8
4	32.9	36.8	41.3	39.4

This Table corresponds to Table 2 in Dr. Chen's Biopharm review, with some modifications

a) Statistically significant difference compared to oral 30 mg (p<0.05).

- The question of comparison of PKs and PDs following multiple dosing administration of the I.V. vs the oral formulation of LANSO is answered by results in **Study M96-486, the other supportive study submitted in NDA 21-566**. M96-486 was a 36-subject, randomized, open-label, crossover, single-center  $\square$  trial. The study was set to evaluate the tolerability, PKs, and PDs of multiple doses of I.V. LANSO [30 mg/day], [administered for 5 consecutive days] in comparison to those of LANSO 30 mg/day administered orally [also for 5 consecutive days].

As summarized in Table 3, after multiple dosing, I.V. LANSO 30 mg QD (Treatments C and D) also showed no significant difference (at p=0.05 level) from oral QD dosing (Treatment A) on Day 5. These data demonstrate that PKs were not altered when LANSO was administered in either of the two vehicles, PEG-400 or 0.9% Sodium Chloride.

**Table 3**  
**Study M96-486**  
**Mean Intra-gastric pH Values and Mean % of Time that the Intra-gastric pH Values were Above 3 and 4 During the 24-h Monitoring Period on Day 5**

Summary of pH Assessments (Day 5)					
Regimen					
	<u>Baseline</u>	<u>A:</u> Oral 30 mg	<u>B:</u> Vehicle Only (PEG)	<u>C:</u> I.V. 30 mg (in PEG) over 30 min	<u>D:</u> I.V. 30 mg (in 0.9% NaCl) over 30 min
Mean 0-24 pH	3.33	5.25*	3.28	5.27*. <sup>#</sup>	5.36*. <sup>#</sup>
% of time pH > 3	45.3	83.9*	44.1	85.6*. <sup>#</sup>	85.5*. <sup>#</sup>
4	31.1	77.6*	31.0	79.4*. <sup>#</sup>	79.6*. <sup>#</sup>

This Table corresponds to Table 3 in Dr. Chen's Biopharm review, with minor modifications

\* Statistically significant difference (p<0.05) found between active treatments and baseline.

<sup>#</sup> No significant difference between I.V. (Treatments C and D) and oral (Treatment A).

- In his Biopharm review, Dr. Chen also provided an answer to the question "was the gastric acid output suppression similar between oral and I.V dosing of Prevacid® 30 mg QD in patients and in healthy subjects"[details of these findings are given in section D. of the current review].

Dr. Chen noted that overall; the I.V. administration of 30 mg Prevacid QD results in similar effects obtained with orally administered drug when the parameter maintenance of gastric acid output suppression is considered. This finding supports the proposed indication. He further commented that in patients, LANSO 30 mg QD given by I.V. 30-min. infusion for 7 days showed an improvement over the oral dosing in terms of the BAO parameter, but this improvement of the I.V. over the oral form, was not replicated in analyses of MAO. Moreover, I.V. (Day 7) showed an improvement when compared to I.V. (Day 1) in terms of BAO data. But again, this finding was not replicated in analyses of MAO data. Finally, data in healthy subjects indicated that, for MAO and BAO, equivalency was established.

- In the **Executive Summary** of his Biopharm review, Dr. Chen noted that the PK and PD data submitted in support of this NDA originated from four Clinical

Pharmacology studies. I.V. administration of LANSO 30 mg QD resulted in higher systemic exposure [higher peak plasma concentration ( $C_{max}$ ) and the area under the plasma concentration-time curve (AUC) values] compared to that of orally administered LANSO 30 mg QD. Although I.V. 30-min. infusion of LANSO 30 mg QD was associated with an improvement over the oral route in gastric acid output suppression with respect to BAO, no significant differences with respect to MAO were seen in patients on Day 7. Dr. Chen concluded that, in the final analysis, an equivalent dose of 30 mg LANSO administered by I.V. 30-min. infusion every day for 7 days produces **similar gastric acid output suppression** compared to orally administered drug. The MTL agrees with this conclusion. The Biopharm reviewer stated that from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) perspective, NDA 21-566 for Prevacid® I.V. for Injection submitted on 12/20/02 is **acceptable** provided that the sponsor and Agency can come to a satisfactory agreement with respect to the language in the package insert. The Agency's CPB related labeling changes are included in Appendix 1 (p. 9) of Dr. Chen's review.

#### **D. CLINICAL**

A summary description of the four U.S. efficacy and PD studies of LANSO for injection, is found in Table 1 of Dr. Narayan Nair's clinical review of this application (NDA 21-566). His review is dated September 30, 2003. Also given in Dr. Nair's clinical review are details of clinical review methods, and an integrated review of efficacy. The current review addresses primarily results and conclusions from the two pivotal trials, one [M01-308] conducted in patients with erosive esophagitis, the other [M01-307] in healthy volunteers. Results and conclusions from the two supportive studies, M95-306 [single dose] and M96-486 [multiple dose consisting of once-a-day dosing for 5 consecutive days], both in healthy volunteers, were addressed in Section C. of the current review.

##### **Study M01-308 (Pivotal)**

- Based on Dr. Nair's review and conclusions, this was a well-designed and apparently well-executed trial. The design was that of a Phase 2, randomized, two period (open-label in Period 1 and double-blind in Period 2), placebo-controlled, multi-center study carried out in patients with erosive esophagitis (EE).
- The study consisted of 3 time periods: 1) Pretreatment (screening procedures described in detail in Dr. Nair's review; diary to be completed daily); 2) Period 1 (open-label 30 mg oral LANSO, to be self-administered each morning 30 min before the first meal or snack, for 7

days); and 3) Period 2 (double-blind randomization into I.V. administration of either 30 mg LANSO or placebo, also for 7 days).

- The study population (inclusion/exclusion criteria) was adequate for the proposed study.
- The schedule of study procedures for efficacy and safety are described in detail in Table 3 of Dr. Nair's review. The critical determinations were those of MAO (maximal acid output) and BAO (basal acid output) on the following days: Last Day (Day 7) of Treatment Period 1 (Oral LANSO) and Last Day (Day 7) of Treatment Period 2 (I.V. LANSO). MAO and BAO were also determined on the First Day (Day 1) of Treatment Period 2 (I.V. LANSO).
- The **primary endpoint** was a comparison of the **MAO/BAO** after the Last Dose (Day 7) of I.V. LANSO to that after the Last Dose (Day 7) of oral LANSO. The null hypothesis was defined as the population average MAO/BAO of I.V. LANSO being greater than or equal to 120% times that of oral LANSO. The two dosage forms were considered to be **pharmacodynamically equivalent** if the ratio of the average for I.V. LANSO to that of oral LANSO was less than 120%. A significance level of 0.05 was required to reject the null hypothesis and conclude equivalence. For each subject administered I.V. LANSO in Treatment Period 2, the difference between MAO/BAO while on the oral LANSO and the MAO/BAO on the I.V. LANSO was calculated as subtracting 1.2 times the Last Day Oral LANSO from the Last Day I.V. LANSO value. A one-sided t test was performed on these differences to assess the equivalence on the basis of MAO and BAO. Although clinical/statistical evaluations of I.V. LANSO vs Placebo were included, the MTL does not comment on these analyses because this study's objective was to determine if I.V. LANSO can be used instead of the orally administered form. We already know that, compared to placebo, LANSO is active.

## Results

- The treatment groups were balanced with regard to demographic parameters. Observed differences were small and not expected to influence outcome.
- Details on the disposition of patients are given in Dr. Nair's review. It is noted that all 87 patients that enrolled in the trial completed treatment with oral LANSO 30 mg during Treatment Period 1. Of these 87, 20 were randomized to receive oral LANSO 30 mg on Study Days 1 to 7 and I.V. Placebo on Study Days 8 to 14. The other 67 patients were randomized to receive oral LANSO 30 mg on Study Days 1 to 7 and I.V. LANSO 30 mg on Study Days 8 to 14.

- The patient summary of premature terminations and the reasons for excluding patients from evaluable analyses are displayed in Tables 5 and 9, respectively, of Dr. Nair's review.
- The protocol-stipulated criteria for equivalence were met for MAO but not for BAO (Table 4). But these results for BAO are acceptable. The median BAO was less with the I.V. LANSO than with the oral form [**0.51 vs 0.89 mEq/h**, respectively] signifying that, for this parameter and under the experimental conditions of M01-308<sup>13</sup>, **the I.V. LANSO was more effective gastric acid anti-secretory than the oral form.**

**Table 4**  
**Study M01-308**  
**Summary of MAO and BAO Data on Treatment Day 7 Obtained from Oral and I.V. Dosing with Lansoprazole 30 mg once-a-day**

Median	mEq/h		p-value <sup>a</sup>
	Oral (Day 7)	I.V. (Day 7)	
MAO	7.31	7.64	<b>0.002</b>
BAO	0.89	0.51	<b>0.059</b>

a) p-value of <0.05 establishes equivalency [the null hypothesis that Oral (Day 7) and I.V. (Day 7) LANSO 30 mg differed by more than 20% is rejected]

- Results of MAO and BAO data obtained after the Last Day of Treatment Period 2 (Day 7 of LANSO I.V.) in comparison to those on the First Day of Treatment Period 2 (Day 1 of LANSO I.V.) are displayed in Table 5. As with the primary endpoint, the equivalence of the last I.V. administration and the first I.V. administration was established because the null hypothesis that they differed by more than 20% was rejected. The BAO results are of special interest because they show that the intravenously administered formulation **is more effective on Day 7 (0.51 mEq/h) than on Day 1 (0.64 mEq/h)**. Due to this **finding, strictly speaking**, the criteria for BAO after the Last Day of I.V. administration and the First Day of I.V. administration were not established with statistical significance. One interpretation of these findings is that on Day 1, steady state levels of the intravenously administered drug have not yet been achieved and that one needs several days of I.V. administration to achieve the best results.

<sup>13</sup> The sponsor stated that these BAO differences were due to a larger than expected variability generated at one site that had several outliers.

**Table 5**  
**M01-308**

**Summary of MAO and BAO Data on Days 1 and 7 [Treatment Period 2] Obtained with once-a-day Intravenously Administered Lansoprazole, 30 mg**

Median	mEq/h following I.V. administration		p-value <sup>a</sup>
	Day 1	Day 7	
MAO	8.19	7.64	<0.001
BAO	0.64	0.51	N.S.

a) p-value <0.05 establishes equivalency since the null hypothesis that I.V. (Day 1) and I.V.(Day 7) LANSO 30 mg differed by more than 20% is rejected.

### Study M01-307

This two-period (7 days each), open-label, single center, parallel design trial was set to compare the effects of I.V. LANSO to those of oral LANSO in healthy volunteers. At various time intervals, samples of gastric contents were collected for 1h to determine BAO and then collected for 2h to determine MAO. Gastric acid production was stimulated by subcutaneous injection of pentagastrin (6 µg/kg). The null hypothesis was that the MAO and BAO for I.V. LANSO would differ from oral LANSO by greater than 20%. If this hypothesis were rejected, then the two modes of administration would be judged to be equivalent. As shown in Table 6, in this study, that **null hypothesis** that the MAO and BAO of I.V. LANSO differed by greater than 20% from that of oral LANSO **was rejected**. Therefore, the study demonstrated that, **in healthy volunteers, I.V. LANSO met the criteria for equivalence.**

**Table 6**  
**Study M01-307**

**Summary of MAO and BAO Data Obtained from Oral and I.V. Dosing with Lansoprazole 30 mg on Day 7**

Median	mEq/h		p-value <sup>a</sup>
	Oral (Day 7)	IV (Day 7)	
MAO	4.76	5.13	0.027
BAO	0.42	0.27	0.034

a) p-value <0.05 establishes equivalency since null hypothesis that Oral (Day 7) and I.V. (Day 7) LANSO 30 mg differed by more than 20% is rejected.

- In Study M01-307, the equivalence of the last I.V. administration (Day 7) and the First I.V. administration (Day 1) was established since the null hypothesis that, in those days, MAO and BAO differed by more than 20% was rejected (Table 7).

**Table 7**  
**Study M01-307**  
**Summary of MAO and BAO Data on Days 1 and 7, Obtained with once-a-day**  
**Intravenously Administered Lansoprazole, 30 mg**

Median	mEq/h, following I.V. administration		p-value <sup>a</sup>
	Day 1	Day 7	
MAO	6.86	5.13	<0.001
BAO	0.58	0.27	0.009

a) p-value <0.05 establishes equivalency since the null hypothesis that I.V. (Day 1) and I.V. (Day 7) LANSO 30 mg differed by more than 20% is rejected.

#### **IV. Overall Comments/Conclusions on Efficacy and Safety**

##### **EFFICACY**

The sponsor of NDA 21-566 is seeking approval of I.V. lansoprazole 30 mg for use in adults for the indication short-term treatment (up to 7 days) of all grades of erosive esophagitis (EE) in patients who are unable to take the oral medication. The indication is restricted to those EE patients that have already started on or are being treated with 30 mg of the oral formulation of the drug. In support of their application, the sponsor submitted results of two well-designed and apparently well-executed pivotal [M01-308, in erosive esophagitis patients and M01-307 in healthy volunteers] and two supportive [M95-306, single dose and M96-486, once-a-day dose for 5 days] studies. The most important scientific rationale to recommend approval of the I.V. form is that this dose of 30 mg LANSO should demonstrate the same [equipotent/equivalent] anti-secretory effects as the already approved, safe and effective, orally administered LANSO formulation.

From his review of the evidence, assessed in detail in separate reviews by the Biopharm and the Medical reviewers, the MTL concludes that the 30 mg I.V. once-a-day dose of the drug can maintain the same degree of anti-secretory activity already obtained after a 7-day regimen of 30 mg given orally. This conclusion is further supported by PK results (Dr. Chen's Biopharm review) and by pharmacological studies in animals (Dr. Zhang's Animal Pharmacology/Toxicology review). In the material that follows, the MTL provides answers to four important questions on Efficacy.

## Questions on Efficacy

### 1. Is 30 mg I.V. once-a-day effective?

This question is settled by results of pivotal studies **M01-308** [in EE patients] and **-307** [in healthy volunteers] and further supported by data from studies **M95-306** [single dose in healthy volunteers] and **M96-486** [once-a-day dose for 5 days, also in healthy volunteers]. Data from the pivotal (as well as supportive) trials using MAO, BAO as the primary endpoints and measurements of intragastric pH, demonstrated that I.V. LANSO **met protocol stipulated criteria for equivalence**. The null hypothesis that the MAO or BAO on I.V. LANSO differed by more than 20% from that seen with oral LANSO was rejected in both pivotal trials, except in Study M01-308 where BAO after I.V. LANSO was less due to the fact that, under these experimental conditions in EE patients as well as variability in BAO determinations, **the I.V. formulation seemed to be more effective than the oral one.**

### 2. Can an "adequate" anti-secretory activity be maintained?

Based on the results displayed in Tables 4 through 7 of the current review, the answer to this question is yes, since, in most instances, the anti-secretory activity demonstrated with the I.V. formulation was similar to that seen with the oral form. Moreover, these data also showed that, anti-secretory effects on Day 7 with the I.V. formulation are maintained in comparison to those on Day 1.

### 3. Can 30 mg I.V. LANSO once-a-day be used as an alternate to 30 mg oral LANSO per day in those EE patients that are unable to take the oral medication?

The answer to this question is also YES. Studies in NDA 21-566 but specially results of Study M01-308 (in EE patients) demonstrated that 30 mg I.V. LANSO once-a-day can be used as an alternate to 30 mg in those patients who are unable to take oral medication. From the detailed review of the data in critical Study M01-308, the MTL concludes that  $MAO_{I.V.} = MAO_{P.O.}$  and that  $BAO_{I.V.} = BAO_{P.O.}$  It is worth reiterating that the use of 30 mg LANSO I.V. as an alternate to 30 mg oral form of the drug is further supported by pivotal study M01-307 and supportive data from studies M95-306 and M96-486, in all of which, adequate parameters of gastric acid secretion were evaluated.

4. L

] There are presently no data

on injection site AEs in pediatric populations and no information as to whether the high pH of the administered I.V. solution may have untoward effects.

In the material that follows, the MTL answers questions related to safety.

### **Questions on Safety**

#### **1. Is the information on patient exposure adequate?**

The available information on patient exposure is adequate. The clinical review reveals that the ISS consisted of two pivotal and two supportive trials. These trials enrolled 161 individuals who received at least one dose of I.V. LANSO. Of these, 62 were patients with EE while the other 99 were healthy subjects. The cumulative duration of exposure is displayed in Table 16 of Dr. Nair's review. Exposure was short-term [no more than 7 days]<sup>14</sup>.

#### **2. Is once-a-day 30 mg LANSO safe?**

From his detailed review of the evidence, Dr. Nair concluded that the applicant has demonstrated the safety of the proposed I.V. formulation of lansoprazole. It is noted that LANSO is already approved [and marketed] as safe and efficacious. At the randomized clinical trial level, the safety review of the pivotal as well as the supportive studies in NDA 21-566 did not uncover findings of concern. The clinical reviewer conducted an additional review of the adverse events reported in 17 non-US trials<sup>15</sup> that were not included in the ISS. Analysis of these data demonstrated a safety profile that appeared comparable to that of the oral form regarding short-term use. The Medical Reviewer concluded, and the MTL agrees that, taken in conjunction, the data in the ISS, those from the non-US trials, and the post-marketing information from the oral formulation, clearly establish the safety of I.V. LANSO.

## **V. Recommendations for Regulatory Action**

**The MTL recommendation is that of NDA 21-566, for Intravenous lansoprazole, 30 mg once-a-day, should be approved. Approval during this first cycle is preferred, but this needs to be carefully done.** This I.V. form of the drug is to be used as an alternate to 30 mg lansoprazole per day in those patients with erosive esophagitis that are unable to take the oral medication.

- Before the approval action is taken, all types of plastic bags [ ]<sup>1</sup> and all types of solutions must be tested for compatibility/incompatibility.

<sup>14</sup> If a single subject received I.V. LANSO on more than one occasion with an intervening washout period, each administration of the I.V. LANSO was counted separately.

<sup>15</sup> The number of patients enrolled in these 17 studies and the duration of exposure in all of the completed supportive non-US trials, are given in Table 16 (page 32) of the Medical Officer's Review. The duration varied from 1 day to 8 weeks but it was mostly 7 days or less.

- If the above-proposed approach is not satisfactory, the product should be approved if it were to be co-packaged with dedicated [ ] bags and stickers with instructions to be placed on the dispensing labels of the I.V. bags, instructing that **only the provided [ ] bags must be used**. This approach is needed in order to decrease the possibility of administration of the drug product in [ ] bags or in bags that have not been tested. **The ideal package would contain one vial and one [ ] bag per carton, with no need to separate the two on storage**. But with the proper the use of instructional stickers on the I.V. containers, the risk of administration in [ ] bags may not be significant.
- If the co-packaging approach is not acceptable the recommendation for NDA 21-566 is **approvable**. With this regulatory action, the applicant must be asked to commit to initiate studies designed to address compatibility/incompatibility issues will all available classes of plastic bags and all possible solutions to be used with the I.V. formulation.
- **It needs to be noted that wording regarding what is so far known about the compatibility issue should be incorporated in the labeling**. But, in the MTL's opinion, this approach would not be sufficient for approval.
- **The final recommendation is to approve the application only after the compatibility/incompatibility issues data on all available bags and solutions are satisfactorily addressed by the sponsor and assessed by the Agency.**

**LABELING:** The recommendations for changes in the proposed labeling are found at the end of each individual discipline review.

- The DESCRIPTION, DOSAGE AND ADMINISTRATION and other sections of the labeling would need to be modified depending on the available data and the regulatory action taken.
- If the co-packaging approach is accepted, this requirement to use the drug should be clearly spelled in the **PRECAUTIONS section of the labeling**.

Hugo E. Gallo-Torres, MD, PhD, PNS  
 Medical Team Leader, GI Drugs  
 HFD-180

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Hugo Gallo Torres  
10/9/03 06:37:40 PM  
MEDICAL OFFICER

This is the MTL (GI Drugs) secondary/multidisciplinary review of  
NDA 21-566, LANSO I.V. for the short-term (up  
to 7 days) treatment of all grades of  
EE in patients unable to take the oral  
medications. Included are recommendations form regulatory action.

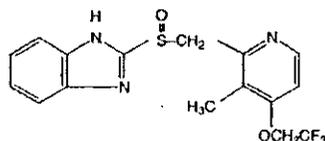
09/30/03

## Medical Officer Review of NDA 21-566: Prevacid<sup>®</sup> I.V. (Lansoprazole) for Injection, 30 mg

Date Submitted: 20 December 2002  
Date Received: 20 December 2002  
Date Assigned: 21 December 2002  
Date Completed: 8 September 2003

Applicant: TAP Pharmaceutical Products Inc.  
675 North Field Drive  
Lake Forest, IL 60015  
Contact person: Doug Donovan

Drug: Proprietary Name - Prevacid  
Generic Name - Lansoprazole  
Chemical Name - 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]  
methyl] sulfinyl] benzimidazole  
Molecular formula - C<sup>16</sup>H<sup>14</sup>F<sup>3</sup>N<sup>3</sup>O<sup>2</sup>S  
Molecular structure -



Drug Class: Substituted benzimidazole proton pump inhibitor

Formulation: intravenous solution

Route of Administration: Infusion; 30 mg over 30 minutes

Reviewer: Narayan Nair, M.D.

## *Table of Contents*

<b>Table of Contents .....</b>	<b>2</b>
<b>Executive Summary .....</b>	<b>5</b>
<b>I.    Recommendations .....</b>	<b>5</b>
A.    Recommendation on Approvability .....	5
B.    Recommendation on Phase 4 Studies and/or Risk Management Steps .....	5
<b>II.   Summary of Clinical Findings .....</b>	<b>5</b>
A.    Brief Overview of Clinical Program .....	5
B.    Efficacy .....	6
C.    Safety .....	7
D.    Dosing .....	8
E.    Special Populations .....	9
<b>Clinical Review .....</b>	<b>10</b>
<b>I.    Introduction and Background .....</b>	<b>10</b>
A.    Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups .....	10
B.    State of Armamentarium for Indication(s) .....	10
C.    Important Milestones in Product Development .....	10
D.    Other Relevant Information .....	11
E.    Important Issues with Pharmacologically Related Agents .....	11
<b>II.   Clinically Relevant Findings From Chemistry, Animal Pharmacology and           Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other           Consultant Reviews .....</b>	<b>11</b>

<b>III.</b>	<b>Human Pharmacokinetics and Pharmacodynamics.....</b>	<b>12</b>
	A. Pharmacokinetics .....	12
	B. Pharmacodynamics .....	12
<b>I.V..</b>	<b>Description of Clinical Data and Sources .....</b>	<b>12</b>
	A. Overall Data .....	12
	B. Tables Listing the Clinical Trials.....	12
	C. Postmarketing Experience .....	14
	D. Literature Review.....	14
<b>V.</b>	<b>Clinical Review Methods.....</b>	<b>14</b>
	A. How the Review was Conducted .....	14
	B. Overview of Materials Consulted in Review.....	14
	C. Overview of Methods Used to Evaluate Data Quality and Integrity .....	14
	D. Were Trials Conducted in Accordance with Accepted Ethical Standards.	14
	E. Evaluation of Financial Disclosure.....	15
<b>VI.</b>	<b>Integrated Review of Efficacy.....</b>	<b>15</b>
	A. Brief Statement of Conclusions .....	15
	B. General Approach to Review of the Efficacy of the Drug.....	15
	C. Detailed Review of Trials by Indication.....	15
	D. Efficacy Conclusions .....	30
<b>VII.</b>	<b>Integrated Review of Safety .....</b>	<b>30</b>
	A. Brief Statement of Conclusions .....	30
	B. Description of Patient Exposure .....	30
	C. Methods and Specific Findings of Safety Review.....	36
	D. Adequacy of Safety Testing.....	52
	E. Summary of Critical Safety Findings and Limitations of Data .....	52

<b>VIII.</b>	<b>Dosing, Regimen, and Administration Issues.....</b>	<b>53</b>
<b>IX.</b>	<b>Use in Special Populations.....</b>	<b>53</b>
	A. Evaluation of Sponsor’s Gender Effects Analyses and Adequacy of Investigation.....	53
	B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy .....	54
	C. Evaluation of Pediatric Program.....	57
	D. Comments on Data Available or Needed in Other Populations .....	57
<b>X.</b>	<b>Conclusions and Recommendations .....</b>	<b>57</b>
	A. Conclusions.....	57
	B. Recommendations.....	58
<b>XI.</b>	<b>Appendix.....</b>	<b>58</b>
	A. Other Relevant Materials .....	39

Appears This Way  
On Original

## CLINICAL REVIEW

### Executive Summary Section

# Clinical Review for NDA 21-566

## Executive Summary

### I. Recommendations

#### A. Recommendation on Approvability

This medical officer recommends approval for intravenous (I.V.) lansoprazole for use in adults for the indication of short-term treatment (up to 7 days) of all grades of erosive esophagitis when patients are unable to take the oral formulation. ¶

The applicant has demonstrated a favorable risk benefit profile for this drug and indication. Oral lansoprazole is currently approved for short term treatment of erosive esophagitis. However, for patients who cannot take oral medications the options are limited for this condition. TAP Pharmaceutical Products Inc. (TAP) has submitted a New Drug Application (NDA) in regards to lansoprazole for injection. This submission consists of two pivotal and two supportive trials that utilize pharmacodynamic parameters to establish that I.V. lansoprazole is equivalent to oral lansoprazole. The safety database demonstrates that the type, and incidence of adverse events for subjects who receive I.V. lansoprazole is similar to those who receive the oral formulation. I.V. lansoprazole is well tolerated with most of the adverse events being mild in severity and self-limiting.

#### B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The applicant has requested approval for use in adults ¶

¶ However, the data submitted consist solely of use in subjects over the age of 18 years. Oral lansoprazole is approved for pediatric use based on data demonstrating its safety and efficacy in this age range. Without supporting data in pediatric patients specific to the I.V. formulation approval is not recommended for its use in this population.

Visual disturbances have been seen in patients who have taken intravenous omeprazole (a drug in the same class as lansoprazole). It is unclear if these adverse events were due to intravenous omeprazole or concomitant illness in the patient population. The safety database with this submission did not demonstrate a pattern of visual toxicity with I.V. lansoprazole. However, it would be prudent to require TAP submit to the agency any post-marketing reports it receives pertaining to ophthalmologic adverse events. This would allow discovery of a signal of toxicity that may not have been present in the pre-approval data.

### II. Summary of Clinical Findings

#### A. Brief Overview of Clinical Program

The applicant's submission is based on two pivotal and two supportive trials. The pivotal trials were designated as M01-307, and M01-308. Study M01-307 was a Phase I, open-label

## CLINICAL REVIEW

### Executive Summary Section

study conducted in healthy subjects. Study M01-308 was a Phase 2, double-blind, randomized, placebo-controlled study that was conducted in subjects with erosive esophagitis. The supportive trials were designated as M95-306 and M96-486. These were Phase 1, randomized, open-label, single-center studies conducted in healthy subjects.

The safety database consisted of 161 individuals who received at least one dose of I.V. lansoprazole. Of these, 99 were healthy subjects, and 62 were patients with erosive esophagitis. In addition, the applicant submitted safety data on 17 trials conducted outside the U.S. The supportive studies that were conducted outside the U.S. consisted of 1921 subjects. Most of these were healthy volunteers who received I.V. lansoprazole. The longest duration of these trials was 7 days.

#### B. Efficacy

The applicant has submitted sufficient data to demonstrate efficacy of I.V. lansoprazole. Lansoprazole is previously approved in an oral formulation. The data submitted in this NDA are primarily based on pharmacodynamic endpoints to establish equivalency between the I.V. and oral formulation. These endpoints (basal acid output [BAO], maximal acid output [MAO] and intragastric pH monitoring) are standard measurements utilized to study proton pump inhibitors, H<sub>2</sub> antagonists and other anti-secretory drugs. In both patients and healthy volunteers, the applicant was able to demonstrate that I.V. lansoprazole met pre-specified criteria for equivalence.

TAP conducted two pivotal and two supportive studies in support of this NDA. The pivotal trials were designated as M01-307, and M01-308. Study M01-307 was a Phase 1, open-label study conducted in healthy subjects. Study M01-308 was a Phase 2, double-blind, randomized, placebo-controlled study that was conducted in subjects with erosive esophagitis. The supportive trials were designated as M95-306 and M96-486. These were Phase 1, randomized, open-label, single-center studies conducted in healthy subjects.

For the pivotal trials, the protocol specified that I.V. lansoprazole could be considered equivalent to oral lansoprazole if the population average of BAO and MAO after 7 days of I.V. lansoprazole was less than or equal to 120% the population average of BAO and MAO after 7 days of oral lansoprazole. The null hypothesis that the BAO or MAO on I.V. lansoprazole differed by more than 20% from oral lansoprazole was rejected in both the pivotal trials with one exception. In the pivotal trial M01-308 (the trial conducted in patients) the null hypothesis of I.V. being inferior to oral lansoprazole was not rejected at a 0.05 significance level. Although the median BAO in this trial was less with I.V. lansoprazole compared to oral lansoprazole, the p-value was greater than 0.05. The applicant states that this is due to a larger than expected variability generated at one site that had several outliers. This reviewer concurs with the applicant's explanation. It should be noted that the p-value approached significance at 0.059. Another important fact is that the median BAO for I.V. lansoprazole was significantly less than placebo ( $p < 0.005$ ).

Pivotal trial M01-308 also addressed the question of efficacy in addition to that of equivalency. Data was collected comparing I.V. lansoprazole to I.V. placebo in regards to BAO and MAO. The median BAO after 7 days of I.V. administration by I.V. lansoprazole was 0.51 mEq/hour compared to 3.19 mEq/hour, after 7 days of I.V. administration of I.V. placebo. The data revealed that I.V. lansoprazole suppressed BAO to a greater extent compared to placebo. There was a statistically significant difference for the median BAO measured in patients on the

## CLINICAL REVIEW

### Executive Summary Section

last day of I.V. lansoprazole (Study Day 15) when compared to the last day of I.V. placebo ( $p < 0.005$ ). There was a statistically significant difference for the change in MAO measurements from the last day of oral lansoprazole (Study Day 8) to the last day of I.V. lansoprazole (Study Day 15) ( $p < 0.001$ ) compared to I.V. lansoprazole 30 mg subjects. The median MAO of I.V. lansoprazole and I.V. placebo was 7.64 mEq/hour and 26.90 mEq/hour, respectively. The data revealed that I.V. lansoprazole is effective in suppression of MAO when compared to I.V. placebo.

Subjects recorded their antacid use in a diary during the course of this study. These data were used to assess symptom relief. Subjects who received I.V. lansoprazole had statistically significant less use of the antacid Gelusil as measured by the median and the percent of days that Gelusil was used ( $p = 0.012$ ) and for the average number of Gelusil tablets taken per day ( $p < 0.001$ ). The median of the average number of antacid tablets consumed per day was 0.6 and 3.6 for the I.V. lansoprazole and I.V. placebo subjects, respectively. Subjects who received I.V. placebo used antacid an average of 91.1% of days (approximately 6 to 7 days out of 7) versus an average of 51.5% of days (approximately 3 to 4 days out of 7) for those who received the I.V. lansoprazole.

The supportive studies utilized the pharmacodynamic parameter of intragastric pH to assess equivalence. Equivalence was defined as -0.5 to 1 pH units for the difference of treatment means between the oral and I.V. formulations. In both the supportive studies, these criteria were met albeit at a 90% confidence interval rather than 95%.

#### C. Safety

The safety database consisted of two pivotal and two supportive trials containing 161 individuals who received at least one dose of I.V. lansoprazole. Of these, 99 were healthy subjects and 62 were patients with erosive esophagitis. No subjects died during the pivotal or supportive studies. No subject withdrew from the trial due to serious adverse events from the study drug. The only event likely related to I.V. lansoprazole that led to withdrawal was a rash that was mild in severity. Overall, the frequency, severity and type of adverse events were similar between I.V. and oral lansoprazole with the exception of events related to the injection site.

When data from all subjects who received I.V. lansoprazole in the combined pivotal and supportive studies were analyzed, greater proportions of subjects in the I.V. lansoprazole regimen were noted to have adverse events of injection site pain, injection site inflammation, injection site reaction, and injection site edema (6%, 6%, 3%, and 3%, respectively) compared to the I.V. placebo regimen (1%, 0%, 3%, and 0%, respectively) and to the oral lansoprazole regimen (1%, <1%, 0%, and <1%, respectively). However, the applicant reported only three of nineteen subjects as having injection site events that were considered possibly, probably, or definitely related to study drug. The alternate etiologies proposed by the investigators were due to the I.V. catheter, infiltration of I.V. site, occluded vein, phlebotomy, or I.V. tubing as a result of the I.V. catheter remaining in place for up to 72 hours. The applicant does not justify why so few of the injection site adverse events were recorded as related to the study drug. This may have led to an underestimation of the adverse events related to injection site problems.

An I.V. formulation of omeprazole had a questionable association with optic problems. Because of this, special attention was paid to evaluate for this adverse event. For each of the pivotal U.S. studies, ophthalmologic examinations were performed on all subjects at the Pretreatment, Study Day 15 Visit and if a subject prematurely terminated from the study. For the

## CLINICAL REVIEW

### Executive Summary Section

supportive U.S. study M95-306, these assessments were performed on all subjects at the screening visit, the evening prior to study drug administration in each crossover period, on the day of discharge for each crossover period, and at the post treatment visit. These ophthalmologic examinations consisted of visual acuity testing using the Snellen letter eye chart and fundoscopic examination of the retina. Two subjects (2/87; 2%), both of whom completed the study, reported two vision-related adverse events during pivotal study M01-308. Subject #839 was a 78 year old female who reported blurred vision on Study Days 10 and 13 during Period 2 (I.V. lansoprazole 30 mg). This was judged by the investigator as due to hypoglycemia. Subject #872 reported decreased visual acuity in his right eye on Study Day 15 (1 day following the last dose of I.V. lansoprazole 30 mg). The etiology of this event is unclear but visual acuity tests and fundoscopic exams were normal.

Another notable finding in the safety database was the incidence of abnormal liver function tests in several subjects. The significance of this finding is unclear. All these abnormalities were mild in severity and resolved without intervention. Oral lansoprazole has been reported to cause increase in liver function tests. This data would seem to indicate that I.V. lansoprazole also could cause an increase in liver enzymes. Although there was no statistical difference in the number of subjects with abnormal liver tests between oral lansoprazole and I.V. lansoprazole subjects, statistical analysis can be misleading regarding this finding. Hepatic reactions to medication are often idiosyncratic and may be missed when solely comparing absolute numbers. It is reassuring, however, in the vast use of oral lansoprazole there have been no clear cases of hepatic failure attributable to this drug. It is likely the I.V. formulation has the same properties as the oral.

The non-U.S. studies that were not submitted in support of the efficacy claim were not included in the integrated summary of safety by the applicant. The applicant did however provide safety data on these 17 studies consisting of 1921 subjects. Most of these were healthy volunteers who received I.V. lansoprazole. The longest duration of these trials was 7 days. The review of these additional data was problematic. Although, these studies contained a large number of subjects, the applicant chose not to integrate the safety data from these trials but rather present the safety results individually. In addition, the studies contained very heterogeneous populations ranging from healthy volunteers to critically ill patients requiring intensive care treatment. For these reasons, this medical officer focused on the serious adverse events and deaths that occurred in these trials and assessed them for causality. No subjects experienced serious adverse events related to ocular toxicity nor liver abnormalities. Upon review of the serious adverse events in these studies, none were judged to be related to the study drug.

#### **D. Dosing**

TAP chose to develop the 30 mg I.V. lansoprazole dose because this is the dose of the oral formulation that is currently approved for use in short-term treatment of erosive esophagitis. The pivotal and supportive studies demonstrated that acid suppression following administration of I.V. lansoprazole 30 mg as a bolus injection was as or more effective than the oral lansoprazole 30 mg dose. In the Supportive Study M95-306 different infusion times were evaluated. Data from this study demonstrated that acid suppression of the 30-minute bolus infusion was similar to that of the 60- and 120-minute bolus infusions and the safety profiles for 30-, 60-, and 120-minute bolus infusions of 30 mg lansoprazole were similar as well. Thus, with these data I.V. lansoprazole 30 mg over 30 minutes was selected. The data submitted by the

## CLINICAL REVIEW

### Executive Summary Section

applicant support a one week regimen as opposed to long term use. The proposed labeling states that I.V. lansoprazole can be used for up to 7 days

For administration, I.V. Lansoprazole is to be reconstituted in 5 mL Sterile Water for Injection, USP in preparation of use. Reconstitution yields a solution with a concentration of 6 mg/mL with a pH of approximately 11 that is stable for [redacted] when stored at 25°C (77°F). Before administration to the patient, further dilution in 50 mL of 0.9% Sodium Chloride is required. This solution has a pH of approximately 10.2. Because of the small volume (55 mL) and the length of the infusion (30 minutes) this high pH is unlikely to cause acid-base disturbances in adults. TAP states the solution should be administered within [redacted] of reconstitution and stored at 25°C (77°F). I.V. lansoprazole should not be mixed with other drugs or diluents due to incompatibilities. The intravenous line should be flushed before and after administration.

#### E. Special Populations

The pivotal and supportive studies were not powered to establish equivalence between the oral and I.V. lansoprazole formulations in subsets based on gender, age or race. The applicant did carry out subgroup analyses were for race (Caucasian and Non-Caucasian), and age (less than 65 years and at least 65 years) for combined data from Studies M01-308 and M01-307. Due to small sample sizes in the Non-Caucasian (n=5) and geriatric (>65 years of age, n=9) groups, these analyses consisted of descriptive statistics (including minimum, median, maximum, and mean) rather than formal statistical tests. In the subgroup analyses of pharmacodynamic parameters, no clinically significant differences were observed between male and female subjects and between Caucasian subjects and subjects of other races.

There was a relative paucity of subjects over 65 years of age. Only three subjects had BAO values and only four subjects had MAO values who were 65 years or older. These small numbers did not permit statistical analysis to demonstrate the equivalence of I.V. lansoprazole to oral lansoprazole in the elderly. The pattern of adverse events experienced by older subjects (at least 65 years) compared to younger (less than 65 years) subjects was similar in the combined pivotal and supportive studies. Slightly higher percentages of older subjects reported treatment-emergent adverse events than younger subjects in those who received I.V. lansoprazole. However, no older I.V. lansoprazole-treated subject had a treatment-related adverse event. Due to the small numbers, no significant conclusion can be made.

In regards to gender, the safety profile for I.V. lansoprazole was similar for females and males.

As with the other subset analyses, these studies were not powered to allow formal statistical testing based on racial group. In regards to adverse events, safety profile between races was similar. Caucasians experienced a higher frequency of adverse events than other racial groups in these trials, but no conclusions can be drawn due to the small numbers for all groups. The current oral lansoprazole label states that Asians have an increase in the AUC when compared to patients in the U.S. However, since the approval of oral lansoprazole no safety or efficacy differences in various ethnic subgroups have come to light. TAP did not submit data pertaining to patients with hepatic and renal impairment and use of I.V. lansoprazole.

# CLINICAL REVIEW

## Clinical Review Section

### Clinical Review

#### I. Introduction and Background

##### A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

TAP Pharmaceutical Products Inc. (TAP) has submitted a New Drug Application (NDA) in regards to lansoprazole for injection. The proposed trade name is "PREVACID® I.V." Lansoprazole belongs to the proton-pump inhibitor class of medications. Lansoprazole for injection has the same active ingredient as PREVACID® (lansoprazole) Delayed-Release Capsules, PREVACID® (lansoprazole) For Delayed-Release Oral Suspension and PREVACID® SoluTab™ (lansoprazole) Delayed-Release Orally Disintegrating Tablets (NDA 20-406, NDA 21-281 and NDA 21-428 for respectively). The applicant's proposed indication is for the short-term treatment (up to 7 days) of all grades of erosive esophagitis, when patients are unable to take the oral formulations. The proposed dose is 30 mg lansoprazole per day administered by intravenous infusion over 30 minutes for up to 7 days. This formulation of lansoprazole is intended for adults [ ]

##### B. State of Armamentarium for Indication(s)

There are four other proton pump inhibitors approved for oral use in the United States. The only proton pump inhibitor available in an injectable formulation in the U.S. is pantoprazole which was approved March 22, 2001.

##### C. Important Milestones in Product Development

Lansoprazole is a proton pump inhibitor and was initially approved in an oral formulation by the FDA on May 10, 1995. It reduces the pH of the stomach by inhibition of the (H<sup>+</sup>K<sup>+</sup>)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Lansoprazole is supplied as enteric-coated capsules as well as an oral suspension and orally disintegrating tablets. It is approved for the following indications:

- Short-term treatment of active duodenal ulcer
- *H. pylori* eradication
- Maintenance of healed duodenal ulcers
- Short-term treatment of active benign gastric ulcer
- Healing of NSAID-associated gastric ulcer
- Risk reduction of NSAID-associated gastric ulcer
- Gastroesophageal reflux disease (GERD)
- Maintenance of healing of erosive esophagitis
- Pathological hypersecretory conditions including Zollinger-Ellison Syndrome

To evaluate an intravenous formulation of lansoprazole TAP conducted a Phase I, single dose study designated as study M95-306. This protocol was designed to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of oral and I.V. lansoprazole and placebo in healthy volunteers. On February 20, 1997, a pre-NDA meeting was held to discuss the results of study M95-306 and additional requirements necessary to support an NDA filing. At this meeting, the Division recommended a PK/PD study be conducted in patients. The Agency also suggested that additional analyses of the PK/PD data be conducted to address the safety and efficacy of the formulation and the high pH after reconstitution.

# CLINICAL REVIEW

## Clinical Review Section

On December 22, 2000, TAP submitted NDA [ ] for intravenous lansoprazole. Despite the request that TAP conduct studies in patients, this NDA consisted of data derived from two PK/PD studies performed solely in healthy volunteers. Another teleconference was held on February 15, 2001, between the Agency and TAP to discuss the deficiencies in the submission. At this discussion, it was communicated to TAP that since no data regarding patients were provided, NDA [ ] could not be filed. On February 20, 2001, TAP voluntarily withdrew NDA [ ]. Another teleconference was held on March 26, 2001 to discuss designs for protocols that should be performed prior to a re-submission. At this conference, the agency proposed protocol designs that had the following features:

- A randomized, double-blind, placebo-controlled PD study
- The study have two periods each lasting 7 days
- Days 1-7 patients would take oral lansoprazole and day 8-15 they would take intravenous lansoprazole.
- The endpoint would be a comparison of gastric acid secretion response such as basal acid output (BAO) and maximum acid output (MAO) in patients with erosive esophagitis (EE).

Based on this design TAP submitted a proposed protocol. Their proposal differed from the Agency's recommendation in the following areas:

- no testing of a 15 mg dose of intravenous lansoprazole
- no placebo arm in the PK study in normals

On June 13, the agency responded that the proposed protocols were acceptable.

TAP submitted the NDA on December 20, 2002. A 60-day filing meeting was held at the Agency and it was decided that the application was filable.

### **D. Other Relevant Information**

Lansoprazole is approved for use to treat adults with GERD in 105 countries in North and South America, Africa, Asia, and Europe. It has been marketed in the U.S. since 1995.

### **E. Important Issues with Pharmacologically Related Agents**

Two other drugs in the proton pump inhibitor class have released intravenous formulations. Omeprazole was released in intravenous formulation in Germany but was withdrawn from the market due to ocular changes. Pantoprazole is available in the U.S. There have been some issues related to chemistry in regards to pantoprazole. The current formulation has a tendency to precipitate and the manufacturer of this drug is conducting post-marketing studies to resolve this issue.

## **II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews**

The chemistry review was conducted by Dr. Ali Al-Hakim. He noted that TAP had tested lansoprazole in one type of I.V. bag [ ]. He raised the concern about the lack of testing in other I.V. bags and the potential for formation of particulate matter in different I.V. bag types. A request was made of TAP to perform such testing but they have yet to provide the results. If the applicant does not perform such testing, it may be necessary to either make this NDA approvable or make significant revisions to the label.

The biopharmaceutic review was conducted by Dr. Tien-Mien Chen. He reported no pharmacology issues that would prevent approval.

## CLINICAL REVIEW

### Clinical Review Section

### III. Human Pharmacokinetics and Pharmacodynamics

#### A. Pharmacokinetics

In healthy subjects who received 30 mg of lansoprazole by intravenous infusion over 30 minutes, the mean peak plasma concentration of lansoprazole ( $C_{max}$ ) was 1705 ( $\pm$  292) ng/mL. The mean area under the plasma concentration versus time curve (AUC) was 3192 ( $\pm$  1745) ng-h/mL. With 7-day once daily repeated intravenous administration of 30 mg lansoprazole, the pharmacokinetics of lansoprazole did not change with time. Lansoprazole distributes mainly in extracellular fluid with a volume of distribution of lansoprazole of approximately 15.7 ( $\pm$  1.9) L, and it is 97% protein bound in plasma.

Lansoprazole is metabolized in the liver into two major metabolites: 5-hydroxylansoprazole and lansoprazole sulfone. The 5-hydroxylation of lansoprazole is primarily catalyzed by CYP2C19, and the sulfoxidation of lansoprazole is primarily catalyzed by CYP3A4/5. The plasma half-life of lansoprazole is 1.5 hours; however the inhibition of the proton pump lasts much longer due to the covalent binding of the proton pump at the gastric parietal cell.

#### B. Pharmacodynamics

Lansoprazole inhibits gastric acid secretion by inhibiting the parietal cell membrane enzyme ( $H^+$ ,  $K^+$ ) -ATPase also known as the proton pump. Lansoprazole suppresses gastric acid secretion by specific inhibition of the proton pump at the secretory surface of the gastric parietal cell. Apparently, lansoprazole is transformed into two active species that inhibit acid secretion within the parietal cell canaliculus, but are not present in the systemic circulation. This leads to inhibition of both basal and stimulated gastric acid secretion.

### IV. Description of Clinical Data and Sources

#### A. Overall Data

The applicant's submission is based on two pivotal and two supportive trials. The pivotal trials were designated as M01-307, and M01-308. Study M01-307 was a Phase 1, open-label study conducted in healthy subjects. Study M01-308 was a Phase 2, double-blind, randomized, placebo-controlled study that was conducted in subjects with erosive esophagitis. The supportive trials were designated as M95-306 and M96-486. These were Phase 1, randomized, open-label, single-center studies conducted in healthy subjects.

#### B. Tables Listing the Clinical Trials

Table 1 displays pertinent details related to the pivotal and supportive trials.

# CLINICAL REVIEW

## Clinical Review Section

**TABLE 1 Description of All U.S. Efficacy and Pharmacodynamic Studies of Lansoprazole for Injection**

Study Number (Sponsoring Country)	Study Design	Treatment Doses Studied (Randomization)	Duration of Treatment (Dosing)	Applicants Summary of Primary Effectiveness Outcome
<b>Pivotal U.S. Studies</b>				
M01-308 (U.S.)	Randomized, two-period (open-label in Period 1 and double-blind in Period 2), placebo-controlled, multicenter in erosive esophagitis subjects	<u>Period 1</u> Open-label oral lansoprazole 30 mg QD <u>Period 2</u> (2 groups, 3:1) I.V. lansoprazole 30 mg with sterile water OR I.V. placebo in a double-blind fashion	<u>Periods 1 - 2</u> 7 consecutive days each with no washout period	Seven days of treatment with I.V. lansoprazole was equivalent to oral lansoprazole in the ability to suppress gastric acid output. As expected, replacing oral lansoprazole with placebo led to a loss of gastric acid suppression. The 30 mg oral and 30 mg I.V. formulations of lansoprazole were equivalent in suppressing pentagastrin-stimulated (MAO) gastric acid output after 7 days of treatment in subjects with erosive esophagitis. The median BAO value showed greater acid suppression with I.V. lansoprazole compared to oral lansoprazole. However, the dissimilarity between the groups was such that equivalency could not be claimed as the hypothesis of I.V. being inferior to oral was not rejected; the p-value was nearly significant (p=0.059).
M01-307 (U.S.)	Open-label, two-period, single-center in healthy subjects	<u>Period 1</u> Oral lansoprazole 30 mg QD <u>Period 2</u> I.V. lansoprazole 30 mg QD with sterile water	<u>Periods 1 - 2</u> 7 consecutive days each with no washout period	Seven days of oral lansoprazole 30 mg dosing followed by 7 days of I.V. lansoprazole 30 mg dosing significantly suppressed gastric acid output as compared to baseline. This study also demonstrated that 7 days of treatment with I.V. lansoprazole 30 mg was equivalent to oral lansoprazole 30 mg in the ability to suppress gastric acid output.
<b>Supportive U.S. Studies</b>				
M95-306 (U.S.)	Randomized, open-label, single-dose, six-way crossover, single-center, assessed 24-hour intragastric pH	Oral lansoprazole 30 mg I.V. vehicle only with PEG (30-minute infusion) I.V. lansoprazole 30 mg with PEG (120-minute infusion) I.V. lansoprazole 30 mg with PEG (60-minute infusion) I.V. lansoprazole 30 mg with PEG (30-minute infusion) I.V. lansoprazole 60 mg with PEG (30-minute infusion)	<u>Periods 1 - 6</u> Single dose with a minimum 7-day washout period between successive crossover periods	Acid suppression following administration of I.V. lansoprazole 30 mg was as or more effective than the oral lansoprazole 30 mg. Intravenous lansoprazole 60 mg provided significantly greater acid suppression than oral lansoprazole 30 mg and I.V. lansoprazole 30 mg administered over 30 minutes. Acid suppression of the 30-minute infusion was similar to that of the 60-minute and 120-minute infusions.
M96-486 (U.S.)	Randomized, open-label, multiple-dose, four-way crossover, single-center, assessed 24-hour intragastric pH	Oral lansoprazole 30 mg I.V. vehicle only with PEG (30-minute infusion) I.V. lansoprazole 30 mg with PEG (30-minute infusion) I.V. lansoprazole 30 mg with NaCl (30-minute infusion)	<u>Periods 1 - 4</u> 5 consecutive days each with a minimum 7-day washout period between successive crossover periods	Intravenous lansoprazole 30 mg (with or without PEG diluent) was pharmacologically equivalent to oral lansoprazole 30 mg on both Study Days 1 and 5. After 5-day QD repeated oral or I.V. administration of lansoprazole 30 mg, the pharmacodynamics of lansoprazole were enhanced compared to Study Day 1. Acid suppression following I.V. lansoprazole 30 mg was as or more effective than the oral lansoprazole 30 mg, suggesting that I.V. administration is an effective and safe alternative to oral administration in a clinical setting.

U.S. = United States; QD = once daily; I.V. = intravenous; PEG = polyethylene glycol; NaCl = 0.9% saline  
(Reference: Table 2.0b, page 11, Overview of Efficacy, Electronic submission)

# CLINICAL REVIEW

## Clinical Review Section

### C. Postmarketing Experience

Orally administered lansoprazole was approved in 1995. The Adverse Event Reporting System (AERS) has collected data on all adverse events reports associated with lansoprazole that have been received by the Agency. This consists of 10,115 events as shown below.

**TABLE 2- Most Frequent (>1% Of Reported Events) Postmarketing Adverse Events**

MedDRA PT Term	Lansoprazole Events=10,115
Diarrhea Nos	2.6%
Condition Aggravated	2.1%
Nausea	1.6%
Pyrexia	1.5%
Abdominal Pain Nos	1.3%
Drug Interaction Nos	1.3%
Dizziness (Excl Vertigo)	1.2%
Headache Nos	1.1%
Vomiting Nos	1.1%
Dyspnea Nos	0.9%

(Reference: Table 6.0a, Page 26, NDA 21-507 )

### D. Literature Review

The applicant submitted multiple references in support of this NDA. This consists of 11 articles from peer-reviewed journals and other sources. Please see the appendix for a full listing.

## V. Clinical Review Methods

### A. How the Review was Conducted

The applicant's submission is based on two pivotal, and two supportive trials. The focus of this review is on the pivotal trials specifically the trial M01-308 that was performed in patients. Further information about the supportive trials can be found in the pharmaceuticals review.

### B. Overview of Materials Consulted in Review

The review materials consisted of a full electronic submission that contained the safety and efficacy data as well as all the support documents.

### C. Overview of Methods Used to Evaluate Data Quality and Integrity

All case report forms and supplemental narratives were reviewed in detail for all subjects with serious adverse events. No discrepancy was found between the case report forms and the applicant's data. No DSI audit of the study sites was performed.

### D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trial was performed within accepted ethical standards. It was conducted under the auspices of an Internal Review Board. Each patient signed a detailed informed consent, which explained the possible complications, benefits and risks from participation in detail.

# CLINICAL REVIEW

## Clinical Review Section

### **E. Evaluation of Financial Disclosure**

Upon review of the financial disclosure by the investigators, there were no financial improprieties that would cast doubt on the findings of this study. None of the investigators listed by the applicant was on the FDA debarred list.

## **VI. Integrated Review of Efficacy**

### **A. Brief Statement of Conclusions**

The applicant has submitted sufficient data to demonstrate efficacy of I.V. lansoprazole. Lansoprazole is previously approved in an oral formulation. The data submitted in this NDA are primarily based on pharmacodynamic endpoints to establish equivalency between the I.V. and oral formulation. These endpoints (basal acid output (BAO), maximal acid output (MAO) and intragastric pH monitoring) are standard measurements utilized to study proton pump inhibitors and other anti-secretory drugs. In both patients and healthy volunteers, the applicant was able to demonstrate that I.V. lansoprazole met pre-specified criteria for equivalence.

### **B. General Approach to Review of the Efficacy of the Drug**

TAP conducted two pivotal and two supportive studies in support of this NDA. The pivotal trials were designated as M01-307, and M01-308. Study M01-307 was a Phase I, open-label study conducted in healthy subjects. Study M01-308 was a Phase 2, double-blind, randomized, placebo-controlled study that was conducted in subjects with erosive esophagitis. The supportive trials were designated as M95-306 and M96-486. These were Phase 1, randomized, open-label, single-center studies conducted in healthy subjects. For the purposes of the medical review, Study M01-308 was thoroughly evaluated. The data from the other studies performed in healthy volunteers was reviewed but further detail can be found in the pharmacokinetic review.

### **C. Detailed Review of Trials by Indication**

#### **1. Study Objectives and Endpoints**

The objective of the study was to compare the pharmacodynamics of I.V. lansoprazole 30 mg to oral lansoprazole 30 mg (capsules) in subjects with erosive esophagitis. The primary endpoint was a comparison of the steady state pharmacodynamic response using basal acid output (BAO) and pentagastrin-stimulated maximal acid output (MAO) 21 hours after the last dose of I.V. lansoprazole (Study Day 15) as compared to 21 hours after the last dose of oral dosing (Study Day 8). There were two secondary endpoints as listed below:

- the BAO and MAO results obtained 21 hours after the first dose of I.V. lansoprazole (Study Day 9) versus those obtained 21 hours after the last dose of oral lansoprazole (Study Day 8)
- the BAO and MAO results obtained after the last dose of I.V. lansoprazole (Study Day 15) versus those obtained 21 hours after the first dose of I.V. lansoprazole (Study Day 9).

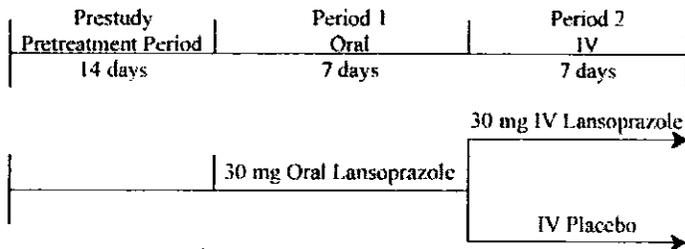
#### **2. Study Design and Methodology**

Study M01-308 was a Phase 2, double-blind, randomized, placebo-controlled study that was conducted in subjects with erosive esophagitis. The following figure displays the study design:

# CLINICAL REVIEW

## Clinical Review Section

**Figure 1 : Pivotal U.S. Study M01-308 Study Design**



(Reference: Page 102, Overview of Efficacy, Electronic submission)

The study was divided into three time periods (Pretreatment Period, Period 1, and Period 2). All screening procedures were completed in the 2 weeks prior to beginning study drug. The screening procedures consisted of a complete medical history, physical examination, including 12-lead electrocardiogram (ECG), routine ophthalmic examination (visual acuity and fundoscopic examination), laboratory evaluations, and endoscopy. Each subject received a diary that was to be completed daily. After successful completion of the screening procedures, subjects were eligible to enter the study. During the Period 1, subjects received open-label lansoprazole 30 mg orally once daily for one week. Oral lansoprazole was self-administered each morning approximately 30 minutes prior to the first meal or snack. On Study Day 7, subjects took study drug in the clinic prior to the first meal or snack at approximately 1100. Twenty one hours after the last dose oral lansoprazole, BAO and MAO were measured in the following manner. A nasogastric tube was placed and low continuous/intermittent suction of approximately 20-50 mm Hg was applied to tube. The volume of the stomach secretions was collected for 1 hour to determine BAO. MAO was stimulated by subcutaneous injection of pentagastrin (6 µg/kg) and gastric secretions were collected for 2 hours.

After the completion of Period 1, patients were randomized to receive intravenous lansoprazole 30 mg versus intravenous placebo in a three to one ratio. These were administered in a double blind manner without a washout period. BAO and MAO were measured on two other occasions in Period 2, prior to dosing on Study Day 9 (evaluating the first dose of I.V. and on the morning of Study Day 15 (evaluating the last dose of IV administration). Subjects were given the antacid Gelusil to use for symptom relief during the study. Subjects were to complete a daily diary to document the time of self-administration of oral lansoprazole and to record the frequency of Gelusil use. The following table displays the schedule of study procedures.

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On Original

## CLINICAL REVIEW

### Clinical Review Section

**TABLE 3- Schedule of Study Procedures in Lansoprazole Study M01- 308**

Procedure	Pretreatment Period		Treatment Period 1		Treatment Period 2			Post-Treatment Final Visit
	Pretreatment Visit	Day -1	Days 1-6	Day 7	Day 8	Day 9	Days 10-14	Day 15
Informed Consent Signed <sup>a</sup>	X							
Complete Medical History	X							
Concurrent Medication Review	X	X			X	X	X	X
Interim Medical History		X						
Complete Physical Examination	X							X
12-Lead Electrocardiogram	X							X
Ophthalmic Examination	X							X
Brief Physical Examination		X			X			
Endoscopy with Rapid Urease Test	X							
Vital Signs <sup>b</sup>	X	X			X	X	X	X
Routine Fasting Laboratory Evaluations	X				X <sup>c</sup>			X
Serum Pregnancy Test (All Females)	X							X
Adverse Event Assessment				X	X	X	X	X
BAO and MAO Assessment <sup>d</sup>					X	X		X
Dispense Period 1 Oral Lansoprazole		X						
Oral Study Medication Dosing <sup>e</sup>			X	X <sup>f</sup>				
I.V. Study Medication <sup>g</sup>					X	X	X	
I.V. Infusion Site Assessments					X	X	X	
Dispense Pretreatment Diary	X							
Dispense Period 1 Diary		X						
Dispense Period 2 Diary					X			
Dispense Gelusil <sup>®</sup>	X	X <sup>h</sup>			X <sup>h</sup>	X <sup>h</sup>	X <sup>h</sup>	
Return Pill Count for Period 1 Drug				X				
Return and Review Pretreatment Diary		X						
Return and Review Period 1 Diary				X				
Return and Review Period 2 Diary								X

a Before any study-specific procedures were performed.

b To be performed at a consistent time each day prior to and after BAO/MAO procedures and/or dosing with study medication.

c Prior to study drug administration.

d Subjects were not to take any food or drink (except small sips of water) or Gelusil<sup>®</sup> beginning at 2200 hours of the evening prior to this procedure.

e Subjects self-administered study drug each morning approximately 30 minutes prior to the first meal or snack.

f Study drug to be administered in the clinic.

g Infusion was to be between 1100 and 1130 daily.

## CLINICAL REVIEW

### Clinical Review Section

(Reference: Table 9.5a, page 49, Electronic submission)

#### 3. Eligibility Criteria

The study population was adequate for the proposed study. All subjects were to meet the following inclusion/exclusion criteria to take part in the study:

- Subject signed and understood the informed consent prior to beginning the Pretreatment Period. The subject must have been able to understand and cooperate with study requirements.
- Subject had grade 2, 3 or 4 esophageal findings according to the TAP grading scale during the Pretreatment endoscopy.
- Subject did not have a gastric or duodenal ulcer (a lesion with appreciable depth >3 mm) or a hiatal hernia >5 cm.
- Subjects currently using prescription or non-prescription doses of histamine H<sub>2</sub>-receptor antagonists (including ranitidine [Zantac®], cimetidine [Tagamet®], famotidine [Pepcid®], and nizatidine [Axid®]) or proton pump inhibitors (including lansoprazole [Prevacid®], omeprazole [Prilosec®], rabeprazole [Aciphex®], pantoprazole [Protonix®], and esomeprazole [Nexium®]) were to discontinue their use prior to beginning the first dose of study drug and throughout the study.
- Subjects taking antacids (except for the Gelusil® provided) were to discontinue their use prior to the Pretreatment Period and throughout the study.
- Subject did not have a diagnosis of Barrett's esophagus (with or without dysplastic changes).
- Subject did not have a co-existing systemic disease affecting the esophagus, (i.e., scleroderma, viral or fungal infection), or radiation therapy to the region of the esophagus, or caustic or physiochemical trauma to the esophagus.
- Subject was at least 18 (or legal age of consent) years of age.
- Subject was able to tolerate an endoscopy, nasogastric (NG) tube placement, and I.V. infusions on multiple occasions.
- Subject did not have current esophageal stricture requiring dilatation (the endoscope must have passed freely into the stomach during endoscopy). Any strictures must not have been dilated within 12 weeks prior to beginning the Pretreatment Period.
- Subject did not have a positive test for *H. pylori* by rapid urease test (CLO<sub>2</sub> test).
- Subject did not have evidence of uncontrolled, clinically significant cardiovascular, pulmonary, renal, hepatic, metabolic, gastrointestinal, neurological or endocrine disease or other abnormality (other than the erosive esophagitis disease being studied).
- Subject did not have evidence of Zollinger-Ellison syndrome, esophageal varices, symptomatic pancreatobiliary tract disease, cholecystitis, rheumatoid arthritis, lupus, or malignancy (except basal cell carcinoma). Subjects with Gilbert's disease were eligible for the study.
- Subject had laboratory, biochemical and hematological parameters within normal laboratory limits as listed in the [ ] manual or if abnormal, must have been judged clinically acceptable by the investigator. Alanine aminotransferase (ALT) [serum glutamic pyruvic transaminase (SGPT)], and aspartate aminotransferase

## CLINICAL REVIEW

### Clinical Review Section

(AST) [serum glutamic oxaloacetic transaminase (SGOT)] must have been lower than two times the upper limit of normal. Subjects with elevated 2 X ULN) ALT/SGPT and/or AST/SGOT values at the initial Screening Visit were not to be re-screened. Creatinine must have been less than or equal to 2 mg/dL. Subject was at least 18 (or legal age of consent) years of age.

- Subject did not have evidence of current alcohol abuse, illegal drug use or drug abuse in the past 12 months.
- Subject did not use bisphosphonates such as Fosamax and Actonel® within 30 days of beginning the Pretreatment Period and throughout the study.
- Subject did not chronically (defined as  $\geq$  12 doses/month) use aspirin, or aspirin-containing products which contained  $>$ 325 mg of aspirin within 30 days of beginning the Pretreatment Period or while on study. Non-prescription compounds containing aspirin included Ecotrin®, all Alka-Seltzer® compounds, and Ascriptin®. (aspirin  $\leq$  325 mg/day was allowed).
- Subject did not chronically (defined as  $\geq$  12 doses/month) use NSAIDs, including COX II NSAIDs, within 30 days of beginning the Pretreatment Period and throughout the study.
  - Examples of NSAIDs include fenoprofen, ibuprofen, naproxen, ketoprofen, piroxicam, tolmetin, sulindac, phenylbutazone, and indomethacin. Over-the-counter compounds which contain ibuprofen include Nuprin®, Advil®, Medipren®, Midol 200®, and Trendar®. Aleve® is an over-the-counter compound which contains naproxen. Orudis KT® and Actron® are over-the-counter compounds which contain ketoprofen.
  - Examples of COX II NSAIDs include celecoxib (Celebrex®) and rofecoxib (Vioxx®).
- Subject did not use oral corticosteroids greater than or the equivalent of 10 mg/day of prednisone within 30 days of beginning the Pretreatment Period and throughout the study. Subject discontinued Carafate® (sucralfate) prior to the first dose of study drug and throughout the study.
- Subject discontinued the use of any prokinetic agents prior to the first dose of study drug and throughout the study. Examples of prokinetic agents include Propulsid®, Reglan®, and Urecholine®.
- Subject did not have known allergies to any proton pump inhibitor (including lansoprazole [Prevacid®], omeprazole [Prilosec®], rabeprazole [Aciphex®], pantoprazole [Protonix®], or esomeprazole [Nexium®]) or to pentagastrin.
- Female subjects of child-bearing potential were non-lactating and agreed to continue to use an effective means of birth control. Female subjects of child-bearing potential were required to have a negative pregnancy test.
- Subject had not donated or lost 550 mL or more of blood volume (including plasmapheresis) or had a transfusion of any blood product within 12 weeks of beginning the Pretreatment Period.
- Subject did not have a history of gastric, duodenal or esophageal surgery except the simple oversew of an ulcer.
- Subject had not taken any investigational drug(s) within the 12 weeks (84 days) prior to beginning the Pretreatment Period.

## CLINICAL REVIEW

### Clinical Review Section

(Reference: Investigational Plan, pages 37-39, Electronic Submission)

• *Medical Officer Comment: The inclusion and exclusion criteria were appropriate for this study.*

#### 4. Statistical analysis

The primary endpoint was a comparison of the BAO/MAO 21 hours after the last dose of I.V. lansoprazole (Study Day 15) to 21 hours after the last dose of oral dosing (Study Day 8). The null hypothesis was defined as the population average BAO/MAO of I.V. lansoprazole being greater than or equal to 120% times that of oral lansoprazole. The two dosage forms were considered to be therapeutically equivalent if the ratio of the population average for I.V. lansoprazole to that of oral lansoprazole was less than 120%. A significance level of 0.05 was required to reject the null hypothesis and conclude equivalency. For each subject administered I.V. lansoprazole in Period 2, the difference between the BAO/MAO while on the oral lansoprazole and the BAO/MAO on the intravenous lansoprazole. This is calculated by subtracting 1.2 times the Study Day 8 lansoprazole value from the Study Day 15 I.V. lansoprazole value. A one-sided t test was performed on these differences to assess the equivalence on the basis of BAO and MAO. If the probability distribution for the difference exhibited substantial deviation from normality, a non-parametric test was implemented. An analysis of covariance was used to assess differences between I.V. lansoprazole and I.V. placebo on Study Day 15. The BAO or MAO results after the last dose of oral lansoprazole (Study Day 8) served as the covariate.

Secondary endpoints were the BAO and MAO results obtained 21 hours after the first dose of I.V. lansoprazole (Study Day 9) compared to those obtained 21 hours after the last dose of oral lansoprazole (Study Day 8) and the BAO and MAO results obtained after the last dose of I.V. lansoprazole (Study Day 15) compared to those obtained 21 hours after the first dose of I.V. lansoprazole (Study Day 9). For these comparisons a t-test or a corresponding non-parametric test was utilized as well. When the study was concluded it was shown the data exhibited substantial deviation from normality. Thus, as per protocol plan, a nonparametric one-sided Wilcoxon signed rank test was performed.

#### 5. Results

##### Demographics

Total enrollment in the study consisted of 87 subjects by 13 investigators. The majority of subjects were male (68%) and Caucasian (79%). The mean age was 46.8 years with a range from 18 to 78 years. A summary of the demographic and baseline characteristics of the study population is presented in the following table.

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## CLINICAL REVIEW

### Clinical Review Section

**TABLE 4 -- Demographic and Baseline Characteristics in Lansoprazole Study M01-308**

Variable	Oral Lansoprazole 30 mg (N=37)	IV Placebo (N=20)	IV Lansoprazole 30 mg (N=67)
<b>Gender</b>			
Male	59 (68%)	12 (60%)	47 (70%)
Female	28 (32%)	8 (40%)	20 (30%)
<b>Race</b>			
Caucasian/Non-Hispanic	69 (79%)	17 (85%)	52 (78%)
Caucasian/Hispanic	14 (16%)	3 (15%)	11 (16%)
Black/Non-Hispanic	3 (3%)	0	3 (4%)
Other/Non-Hispanic	1 (1%)	0	1 (1%)
<b>Age (years)<sup>a</sup></b>			
Mean (SD)	46.8 (13.0)	48.3 (14.2)	46.3 (12.7)
Minimum-Maximum	18-78	18-66	25-78
<b>Weight (kg)<sup>a</sup></b>			
Males	(N=59)	(N=12)	(N=47)
Mean (SD)	92.2 (15.9)	94.8 (16.7)	91.6 (15.8)
Minimum-Maximum	52-131	75-131	52-130
Females	(N=28)	(N=8)	(N=20)
Mean (SD)	79.6 (19.1)	76.1 (25.5)	81.1 (16.4)
Minimum-Maximum	41-116	41-116	54-110
<b>Height (cm)</b>			
Males	(N=59)	(N=12)	(N=47)
Mean (SD)	177.2 (8.7)	177.4 (6.9)	177.1 (9.2)
Minimum-Maximum	135-191	165-185	135-191
Females	(N=28)	(N=8)	(N=20)
Mean (SD)	162.1 (6.8)	163.7 (9.9)	161.4 (5.3)
Minimum-Maximum	150-183	150-183	150-173

(Reference: Table 11.2a, Study M01-308 Study Report, page 74, Electronic Submission)

There were no relevant differences between treatment arms in pre-existing conditions. Most of the subjects (67%; 58/87) reported the use of concurrent medications during the study. The most frequently reported concurrent medications were acetaminophen (for relief of aches, pains, and headaches), topical anesthetic spray (for NG tube placement), and hormone replacement therapies.

*Medical Officer Comments: The treatment groups were balanced with regard to most parameters. There were more male than female subjects for each treatment arm. There were fewer non-caffeine users in the placebo group. More subjects in the placebo arm had previous use of lansoprazole. These differences should not have affected outcome.*

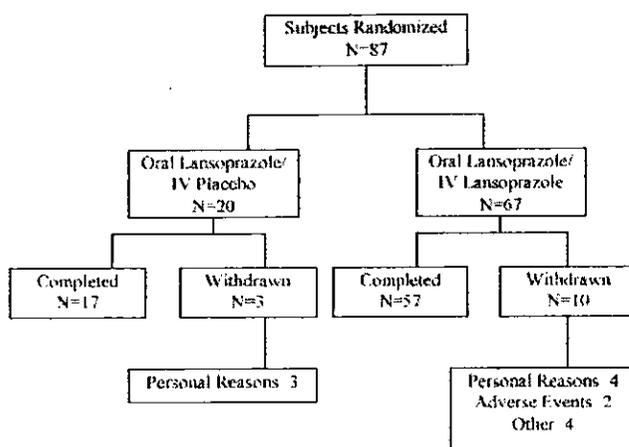
# CLINICAL REVIEW

## Clinical Review Section

### Disposition of Subjects

Of the 87 subjects who enrolled in the study, all 87 completed treatment with oral lansoprazole 30 mg during Period 1. Twenty were randomized to receive oral lansoprazole 30 mg on Study Days 1-7 and I.V. placebo on Study Days 8-14 and 67 were randomized to receive oral lansoprazole 30 mg on Study Days 1-7 and I.V. lansoprazole 30 mg on Study Days 8-14. The following figure displays the patient disposition.

**Figure 2 - Disposition of Randomized Subjects**



(Reference: Figure 10.1, Study M01-308 Study Report, page 68, Electronic Submission)

The following table displays a summary of subjects who withdrew from the trial.

**TABLE 5 - Subject Summary of Premature Terminations from Study M01-308**

Investigator Name/Subject #	Reason	Premature Termination Study Day
<b>I.V. Placebo</b>		
/874	Personal- withdrew consent	Day 7
'885	Personal- withdrew consent	Day 8
'820	Personal- withdrew consent	Day 13
<b>I.V. lansoprazole 30 mg</b>		
/841	Personal	Day 8
s/915	Personal	Day 8
'813	Personal	Day 7
'868	Personal	Day 7
/836	Adverse event- rash	Day 11
'837	Adverse event- increased cough, pharyngitis	Day 14
'935	Other- unable to pass NG tube	Day 8
'806	Other- unable to pass NG tube	Day 8
'865	Other- withdrew consent	Day 7
'879	Other- missed 3 consecutive study doses	Day 13

a All subjects completed Period 1 (7 days of oral lansoprazole 30 mg).

(Reference: Table 11.1d, page 74, Study M01-308 Study Report, Electronic Submission)

## CLINICAL REVIEW

### Clinical Review Section

The pharmacodynamic analyses included all subjects with available BAO and MAO data. The following tables display a summary of the number of subjects analyzed for each data set for BAO and MAO.

**TABLE 6 - Primary Endpoints: Last I.V. vs. Last PO  
Number of Lansoprazole Subjects with Available Data <sup>a</sup>**

	Study Day 8	Study Day 15	Study Days 8 & 15
BAO <sup>b</sup>	62	55	54
MAO <sup>c</sup>	61	56	55

a Does not include placebo subjects.

b N=81 subjects with data on Study Day 8 (Last PO) in both arms.

c N=80 subjects with data on Study Day 8 (Last PO) in both arms.

(Reference: Table 11.1a, page 72, Study M01-308 Study Report, Electronic Submission)

**TABLE 7 - Secondary Endpoint: First I.V. vs. Last PO  
Number of Lansoprazole Subjects with Available Data <sup>a</sup>**

	Study Day 8	Study Day 9	Study Days 8 & 9
BAO	62	55	54
MAO	61	55	54

a Does not include placebo subjects.

(Reference: Table 11.1b, page 72, Study M01-308 Study Report, Electronic Submission)

**TABLE 8 - Secondary Endpoint: Last I.V. vs. First I.V.  
Number of Lansoprazole Subjects with Available Data <sup>a</sup>**

	Study Day 9	Study Day 15	Study Days 9 & 15
BAO	55	55	51
MAO	55	56	52

a Does not include placebo subjects.

(Reference: Table 11.1c, page 72, Study M01-308 Study Report, Electronic Submission)

A decision regarding whether to exclude subjects from analysis was made prior to unblinding of treatment allocation. The following table displays the reasons subjects were excluded from the evaluable analysis.

# CLINICAL REVIEW

## Clinical Review Section

**TABLE 9 – Reason for Excluding Subjects from Evaluable Analysis**

Reason for Exclusion	Investigator/ Subject No.		
	Study Day 8	Study Day 9	Study Day 15
Missing 3 or more BAO volumes	'885 '888	'852	/893 /875,903
Missing 5 or more MAO volumes			/861
Missing 3 or more consecutive MAO volumes		/862	/861
Missing 3 or more consecutive study drug doses on any study days in Period 1 or in Period 2	/841 /835 '885 '874, 915 '813, 865, '879 '806	r/841 /835 n/885 '874, 915 '813, 865, 868 r/879 806	r/841 /835 '885 '874, 915 '813, 865, 868 r/879 '806 /836
Missing 2 or more consecutive study drug doses on any Study Days 5, 6, or 7 of Period 1 or in Period 2.	r/841 /835 '885 '874, 915 '813, 865, '868 r/879 '806	841 /835 '885 '874, 915 '813, 865, 868 '879 '806	r/841 /835 '885 '874, 915 '813, 865, 868 '879 '806
BAO/MAO procedures initiated before 21 hours or after 22 hours after the study drug dose on Study Days 8, 9, or 15.	r/841 '822 '840		

(Reference: Table 11.1d, page 73, Study M01-308 Study Report, Electronic Submission)

### Efficacy Results

The following table displays the primary efficacy endpoint - a comparison of the BAO/MAO 21 hours after the last dose of I.V. lansoprazole (Study Day 15) to 21 hours after the last dose of oral dosing (Study Day 8).

# CLINICAL REVIEW

## Clinical Review Section

**TABLE 10 - Summary of BAO/MAO Results Following the Last I.V. Lansoprazole Dose and the Last Oral Lansoprazole Dose in Lansoprazole Study M01-308**

	Lansoprazole 30 mg		p-Value†
	Last Day Oral (Study Day 8)	Last Day I.V. (Study Day 15)	
Median BAO	0.89 mEq/hr	0.51 mEq/hr	0.059
Median MAO	7.31 mEq/hr	7.64 mEq/hr	0.002

† Wilcoxon signed-rank test.

(Reference: Table 11.4a, page 78, Study M01-308 Study Report, Electronic Submission)

**Medical Officer Comments:** This protocol specified that I.V. lansoprazole could be considered equivalent to oral lansoprazole if the population average of BAO and MAO after 7 days of I.V. lansoprazole was less than or equal to 120% the population average of BAO and MAO after 7 days of oral lansoprazole. As can be seen in this table this criteria for equivalence was met for MAO but not for the BAO parameter.

In regards to BAO, the null hypothesis of I.V. being inferior to oral lansoprazole (i.e.,  $I.V. BAO - 1.2 \times PO BAO \geq 0$ ) was not rejected at a 0.05 significance level. There were 54 subjects with data on both days. Although the median BAO was less with the I.V. lansoprazole the p-value was greater than 0.05. The applicant states that this is due to a larger than expected variability generated at one site that had several outliers. It should be noted that the p-value approached significance at 0.059.

In regards to MAO, the null hypothesis that the MAO on I.V. lansoprazole differed by more than 20% from oral lansoprazole was rejected. There were 55 subjects with data on both days. The difference between I.V. and 120% of oral MAO values was statistically significantly less than zero. Thus, the null hypothesis of I.V. being inferior to oral lansoprazole was rejected at a 0.05 significance level ( $p=0.002$ ).

In order to assess the question of efficacy in addition to that of equivalency, data were collected comparing I.V. lansoprazole to I.V. placebo in regards to BAO, and MAO. The median BAO after 7 days of I.V. administration by I.V. lansoprazole was 0.51 mEq/hour compared to 3.19 mEq/hour ( $p=0.005$ ), after 7 days of I.V. administration of I.V. placebo. The data revealed that I.V. lansoprazole suppressed BAO to a greater extent compared to placebo. There was a statistically significant difference for the BAO measured in patients on the last day of I.V. lansoprazole (Study Day 15) when compared to the last day of I.V. placebo. There was a statistically significant difference for the change in MAO measurements from the last day of oral lansoprazole (Study Day 8) to the last day of I.V. lansoprazole (Study Day 15). ( $p<0.001$ ) compared to I.V. lansoprazole 30 mg subjects. The median MAO of I.V. lansoprazole and I.V. placebo was 7.64 mEq/hour and 26.90 mEq/hour, respectively. The data revealed that I.V. lansoprazole is effective in suppression of MAO when compared to I.V. placebo.

Subjects recorded their antacid use in a diary during the course of this study. These data were used to assess symptom relief. Subjects who received I.V. lansoprazole had statistically significant less use of the antacid Gelusil as measured by the median and the percent of days that

## CLINICAL REVIEW

### Clinical Review Section

Gelusil was used ( $p=0.012$ ) and for the average number of Gelusil tablets taken per day ( $p<0.001$ ). The median of the average number of antacid tablets consumed per day was 0.6 and 3.6 for the I.V. lansoprazole and I.V. placebo subjects, respectively. Subjects who received I.V. placebo used antacid an average of 91.1% of days (approximately 6 to 7 days out of 7) versus an average of 51.5% of days (approximately 3 to 4 days out of 7) for those who received the I.V. lansoprazole.

The following table displays the results pertaining to the secondary endpoint of the BAO and MAO results obtained 21 hours after the first dose of I.V. lansoprazole (Study Day 9) versus those obtained 21 hours after the last dose of oral lansoprazole (Study Day 8).

**TABLE 11 - Summary of BAO/MAO Results Following the First I.V. Lansoprazole Dose and the Last Oral Lansoprazole Dose in Lansoprazole Study M01-308**

	Lansoprazole 30 mg		p-Value†
	Last Day Oral (Study Day 8)	First Day I.V. (Study Day 9)	
Median BAO	0.89 mEq/hr	0.64 mEq/hr	<0.001
Median MAO	7.31 mEq/hr	8.19 mEq/hr	0.037

† Wilcoxon signed-rank test.

(Reference: Table 11.4b, Study M01-308 Study Report, Page 79, Electronic Submission)

*Medical Officer Comment: The criteria for equivalence of the first I.V. administration and the last oral administration for BAO and MAO were met since the null hypothesis that they differed by more than 20% was rejected ( $p<0.05$ ).*

The following table displays the results for the other secondary endpoint the BAO and MAO results obtained after the last dose of I.V. lansoprazole (Study Day 15) versus those obtained 21 hours after the first dose of I.V. lansoprazole (Study Day 9).

**TABLE 12- Summary of BAO/MAO Results Following the First I.V. Lansoprazole Dose and the Last I.V. Lansoprazole Dose in Lansoprazole Study M01-308**

	Lansoprazole 30 mg		p-Value†
	First Day I.V. (Study Day 9)	Last Day I.V. (Study Day 15)	
Median BAO	0.64 mEq/hr	0.51 mEq/hr	0.314
Median MAO	8.19 mEq/hr	7.64 mEq/hr	<0.001

† Wilcoxon signed-rank test.

(Reference: Table 11.4c, Study M01-308 Study Report, Page 79, Electronic Submission)

*Medical Officer Comments : The criteria for equivalence for BAO after the last I.V. administration and the first I.V. administration were not established with statistical significance. Because of marked variability, BAO data are less reliable than MAO data. As with the primary endpoint, the equivalence of the last I.V. administration and the first I.V. administration for MAO was established since the null hypothesis that they differed by more than 20% was rejected.*

# CLINICAL REVIEW

## Clinical Review Section

### 6. Other studies

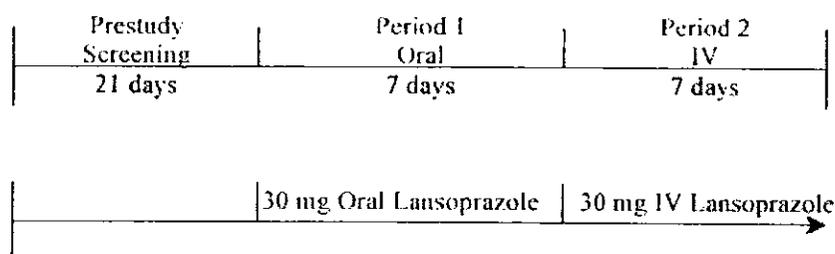
The other studies that were submitted with this NDA are summarized below. Since these studies did not involve patients, only healthy volunteers, a detailed review was not generated. What follows is a brief summary of the pertinent details of each trial.

#### Pivotal Study M01-307

Pivotal U.S. Study M01-307 was a two-period, open-label, single center study that used a parallel-group design. The study utilized healthy volunteers.

The following figure displays the study design.

**Figure 2 – Study Design M01-307**



At various intervals, gastric samples were collected for 1 hour to determine BAO and then collected for 2 hours to determine MAO via a nasogastric (NG) tube. MAO was stimulated by a subcutaneous injection of pentagastrin (6 µg/kg). BAO and MAO measurements were conducted on Study Day -1 and 21 hours after the last dose of study drug on Study Days 8 (evaluating the final 3 hours of oral lansoprazole, 9 (evaluating after the first dose of I.V. lansoprazole), and 15 (evaluating the dose of I.V. lansoprazole). The null hypothesis was that the BAO and MAO for I.V. lansoprazole would differ from oral lansoprazole by greater than 20%. The following table shows the results from this study.

**TABLE 13- Summary of BAO/MAO Results Following the Last Oral Lansoprazole Dose and the Last I.V. Lansoprazole Dose in Lansoprazole Study M01-307**

	Lansoprazole 30 mg		p-Value <sup>a</sup>
	Last Day Oral (Study Day 8)	Last Day IV (Study Day 15)	
Median BAO	0.42 mEq/hour	0.27 mEq/hour	0.034
Median MAO	4.76 mEq/hour	5.13 mEq/hour	0.027

<sup>a</sup>Wilcoxon signed-rank test.

*Medical Officer Comments: This study demonstrated that in healthy volunteers I.V. lansoprazole met the criteria for equivalence. The null hypothesis that the BAO and MAO of I.V. lansoprazole differed by greater than 20% from oral lansoprazole was rejected.*

## CLINICAL REVIEW

### Clinical Review Section

#### Supportive U.S. Study M95-306

Study M95-306 was a supportive study in support of this NDA. It was a Phase 1, randomized, open-label, six-way crossover, single-center study comparing single doses of I.V. lansoprazole to a 30 mg oral dose of lansoprazole. A vehicle only arm was included as one of the treatment arms. A total of 38 healthy subjects enrolled, 33 of whom completed dosing in all six crossover periods of the study. The dosing groups were as follows:

- Regimen A: Lansoprazole 30 mg capsule; oral administration
- Regimen B: Vehicle only (PEG); intravenous 10 mL administration in 50 mL 0.9% normal saline diluent (30-minute infusion)
- Regimen C: Lansoprazole 30 mg with PEG; intravenous 5 mL administration in 50 mL 0.9% normal saline diluent (120-minute infusion)
- Regimen D: Lansoprazole 30 mg with PEG; intravenous 5 mL administration in 50 mL 0.9% normal saline diluent (60-minute infusion)
- Regimen E: Lansoprazole 30 mg with PEG; intravenous 5 mL administration in 50 mL 0.9% normal saline diluent (30-minute infusion)
- Regimen F: Lansoprazole 60 mg with PEG; intravenous 10 mL administration in 50 mL 0.9% normal saline diluent (30-minute infusion)

Subjects were confined for approximately 36 hours (12 hours prior to infusion and 24 hours following infusion) during each crossover period. On Study Day 1 of each crossover period, twenty-four hour gastric pH monitoring occurred. A washout period of 7 days separated successive crossover periods. The following table displays the primary endpoint of the study the mean intragastric pH for the oral and I.V. lansoprazole doses.

**TABLE 14 - Intragastric pH Variable Means<sup>a</sup> for the Oral Lansoprazole 30 mg and I.V. Lansoprazole 30 mg Doses (Entire 23-Hour Post-Dose Period) and 90% Confidence Interval for Test on Equivalence (Supportive U.S. Study M95-306)**

	Oral Lansoprazole Dose	I.V. Lansoprazole Dose (Infusion Duration)		
	30 mg	30 mg (120 min)	30 mg (60 min)	30 mg (30 min)
Mean pH (0-23 hours)	3.16	3.44	3.59	3.39
90% CI <sup>b</sup>		-0.1178, 0.6922	0.0331, 0.8345	-0.1610, 0.6318
Percent of time pH >				
3	43.46	51.75	54.64 <sup>c</sup>	50.34
4	32.85	39.39	41.29	36.77
5	18.34	23.43	25.84	19.51
6	10.58	12.67	13.02	11.34

a The least squares mean accounted for the possibility of period effects.

b 90% confidence interval for difference of means between the oral dose and the intravenous doses.

c Statistically significant difference compared to oral lansoprazole (p<0.05).

(Reference: Table 6.2b, ISE, Page 55, Electronic Submission)

# CLINICAL REVIEW

## Clinical Review Section

**Medical Officer Comments:** For this protocol the range of equivalence was defined as -0.5 to 1 pH units for the difference of treatment means. All three 30 mg infusion rates were found to be equivalent to the oral 30 mg dose regimen with these criteria by using the two one-sided tests procedures via 90% confidence intervals. All three confidence intervals were contained in the range of equivalence.

### **Supportive U.S. Study M96-486**

Study M96-486 was another supportive study submitted with this NDA. It was a Phase I, randomized, open-label, multiple-dose, four-way crossover study to compare I.V. lansoprazole 30 mg doses with and without PEG diluent to an I.V. infusion of the vehicle with PEG and to oral lansoprazole 30 mg doses where each regimen lasted for 5 consecutive days. A total of 36 healthy subjects were enrolled. Subjects were randomly assigned in equal numbers to one of four sequences of regimens. The regimens were as follows:

- Regimen A: Lansoprazole 30 mg capsule; oral administration
- Regimen B: Vehicle only (PEG); intravenous 5 mL administration in 50 mL 0.9% normal saline diluent (30-minute infusion)
- Regimen C: Lansoprazole 30 mg with PEG; intravenous 5 mL administration in 50 mL 0.9% normal saline diluent (30-minute infusion)
- Regimen D: Lansoprazole 30 mg with 0.9% saline; intravenous 5 mL administration in 50 mL 0.9% normal saline diluent (30-minute infusion)

Twenty-four hour intragastric pH monitoring occurred on Study Day -1 and on Study Days 1 and 5 of each crossover period. There was a washout period of at least 7 days separating successive crossover periods.

The following table displays the primary pharmacodynamic endpoint the 24 hour mean intragastric pH on Study Day 1.

**TABLE 15 - Analysis of 24-Hour Mean Intragastric pH on Study Day 1: Point Estimates of Regimen Means and 90% Confidence Intervals for Tests of Equivalence of I.V. and Oral Regimens (Supportive U.S. Study M96-486)**

Regimen <sup>a</sup>	Estimate of Mean <sup>b</sup>		Difference in Mean pH	
	I.V.	Oral	Point Estimate	90% Confidence Interval
C vs A	4.95	4.75	0.2007	-0.0639-0.4654
D vs A	4.86	4.75	0.1130	-0.1534-0.3794

- a Regimen A: Lansoprazole 30 mg oral capsule; oral administration  
 Regimen C: Lansoprazole 30 mg with PEG; intravenous administration (30-minute infusion)  
 Regimen D: Lansoprazole 30 mg with 0.9% saline; intravenous administration (30-minute infusion)

b Least squares mean.

c The difference (I.V. minus oral) of the least squares means.

(Reference: Table 6.2g, page 62, ISE, Electronic Submission)

**Medical Officer Comments:** For this protocol the range of equivalence was defined as -0.5 to 1 pH units for the difference of treatment means. Each of the infusion regimens met this criterion for equivalence.

## CLINICAL REVIEW

### Clinical Review Section

#### **D. Efficacy Conclusions**

The applicant has submitted sufficient data to demonstrate efficacy of I.V. lansoprazole. Lansoprazole is previously approved in an oral formulation. Thus, the primary endpoints of the two pivotal studies and two supportive studies submitted in support of this NDA utilize pharmacodynamic endpoints to establish equivalency between the oral and I.V. formulation. The pivotal study M01-308 demonstrated that patients with erosive esophagitis who receive I.V. lansoprazole use fewer antacids than those who receive placebo. Both pivotal studies measured BAO, and MAO as parameters to assess equivalence between the oral and I.V. formulation. The pivotal protocols specified that I.V. lansoprazole could be considered equivalent to oral lansoprazole if the population average of BAO and MAO after 7 days of I.V. lansoprazole was less than or equal to 120% the population average of BAO and MAO after 7 days of oral lansoprazole. In the pivotal study that involved patients, these criteria for equivalence was met for MAO but was borderline for the BAO parameter. The applicant states that this is due to a larger than expected variability generated at one site that had several outliers. It should be noted that the p-value approached significance at 0.059. For the pivotal study in healthy volunteers, the criterion for equivalence was met for both BAO and MAO.

The supportive studies utilized another pharmacodynamic parameter to assess equivalence, intragastric pH. Equivalence was defined as -0.5 to 1 pH units for the difference of treatment means between the oral and I.V. formulations. In both the supportive studies these criteria were met albeit at a 90% confidence interval rather than 95%.

### **VII. Integrated Review of Safety**

#### **A. Brief Statement of Conclusions**

The applicant has demonstrated the safety of this I.V. formulation of lansoprazole. Oral lansoprazole is already approved as safe and efficacious. A safety review of the pivotal trial and the supportive trials in this NDA uncovered no safety concern. An additional review was conducted of the adverse events that occurred in non-U.S. trials that were not included in the Integrated Summary of Safety (ISS). Analysis of these data demonstrates that the safety profile appears comparable to the oral formulation regarding short term use (up to 7 days). In summary, the combination of data in the ISS, the non-U.S. trials and postmarketing data from the oral formulation, all combine when assessed in conjunction to establish safety for I.V. lansoprazole.

#### **B. Description of Patient Exposure**

The ISS consisted of two pivotal and two supportive trials containing 161 individuals who received at least one dose of I.V. lansoprazole. Of these 99 were healthy subjects and 62 were patients with erosive esophagitis. The following table shows the cumulative duration of exposure. If a single subject received I.V. lansoprazole on more than one occasion with an intervening washout period, each administration of the I.V. lansoprazole was counted separately.

## CLINICAL REVIEW

### Clinical Review Section

**TABLE 16 - Cumulative Duration of Exposure for I.V. Lansoprazole (Combined Pivotal and Supportive U.S. Studies)**

Study	Total Daily Dose (duration)	Number of Days							
		≥0 <sup>a</sup>	≥1	≥2	≥3	≥4	≥5	≥6	7
All	Any Dose	320	299	159	159	158	157	86	82
M01-308 <sup>b</sup>	30 mg I.V. with NaCl (30 min)	67	62	60	60	59	58	58	54
M01-307 <sup>b</sup>	30 mg I.V. with NaCl (30 min)	29	28	28	28	28	28	28	28
M95-306 <sup>c</sup>	30 mg I.V. with PEG (120 min)	38	35						
	30 mg I.V. with PEG (60 min)	38	34						
	30 mg I.V. with PEG (30 min)	38	35						
	60 mg I.V. with PEG (30 min)	38	34						
M96-486 <sup>c</sup>	30 mg I.V. with PEG (30 min)	36	35	35	35	35	35		
	30 mg I.V. with NaCl (30 min)	36	36	36	36	36	36		

NaCl = Sodium chloride; PEG = polyethylene glycol

a Subjects randomized to receive lansoprazole I.V..

b Subjects received oral lansoprazole for 7 days prior to I.V. administration.

c Crossover studies; duration of exposure was calculated for each regimen.

(Reference: Table 5.3a, ISS, page 62, Electronic Submission)

In addition, the applicant submitted safety data on 17 trials conducted outside the U.S. These data were not included in the ISS. The following table lists the number of patients enrolled and duration in all of the completed supportive non-U.S. studies.

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## CLINICAL REVIEW

### Clinical Review Section

**TABLE 16 - Description of All of the Completed Supportive Non- U. S. Studies**

Study No. Country	Targeted Population	Doses/Treatments	Total Enrolled per Group	Duration
EC378 Germany	Healthy subjects	I.V. lansoprazole 30 mg QD (in glass bottle), I.V. lansoprazole 30 mg QD (in small vials), I.V. lansoprazole 30 mg BID (in glass bottle), and I.V. placebo BID (in glass bottle)	19 19 19 19	3 days × 4 (crossover)
EC053 Germany	Healthy subjects	I.V. lansoprazole 15 mg QD, oral lansoprazole 15 mg QD, and oral lansoprazole 30 mg QD	12 12 12	1 day × 3 (crossover)
EC179 France	Healthy subjects	I.V. lansoprazole 30 mg QD and I.V. lansoprazole 60 mg QD, versus I.V. placebo	12 12 3	7 days × 2
EC180 France	Healthy subjects	I.V. lansoprazole 30 mg QD, I.V. lansoprazole 60 mg QD, oral lansoprazole 30 mg, oral placebo, and I.V. placebo	12 12 12 3 3	7 days × 3 (crossover)
EC081 France	Healthy subjects	I.V. lansoprazole 15 mg QD, I.V. lansoprazole 30 mg QD, I.V. lansoprazole 60 mg QD, I.V. lansoprazole 90 mg QD, and I.V. placebo	12 12 12 9 12	1 day × 5 (crossover)
EC239 Italy	Patients with upper gastrointestinal hemorrhage due to peptic ulcers and erosions	I.V. lansoprazole 30 mg QD, I.V. lansoprazole 30 mg BID, I.V. lansoprazole 60 mg QD, versus ranitidine 200 mg QD	16 16 16 16	7 days

## CLINICAL REVIEW

### Clinical Review Section

**TABLE 16 - Description of All of the Completed Supportive Non- U. S. Studies (Cont.)**

Study No. Country	Targeted Population	Doses/Treatments	Total Enrolled per Group	Duration
CPH-301 Japan	Healthy subjects	Oral lansoprazole 30 mg QD; I.V. lansoprazole 30 mg QD with physiologicsaline and I.V. lansoprazole 30 mg QD with special vehicle	35 20 20	1 day 1 day × 2 (crossover)
CPH-302 Japan	Healthy subjects	Oral lansoprazole 30 mg QD, I.V. drip infusion of lansoprazole 30 mg QD, and I.V. bolus of lansoprazole 30 mg QD	18 18 18	5 days × 3 (crossover)
CPH-303 Japan	Healthy subjects	I.V. infusions of lansoprazole 30 mg QD, I.V. lansoprazole 15 mg BID, and I.V. drip infusion of lansoprazole 15 mg QD	18 17 16	5 days × 3 (crossover)
CPH-001 Japan	Healthy subjects	<u>Single Dose</u> I.V. bolus injections of lansoprazole 15 mg and 30 mg QD; <u>Multiple Dose</u> I.V. bolus injections of lansoprazole 30 mg QD; or I.V. bolus injections of lansoprazole 30 mg BID and 30 mg QD	27	1 day 1 day 3 days 2 days 1 day
CPH-010B Japan	Healthy subjects	I.V. lansoprazole 15 mg BID, I.V. lansoprazole 30 mg BID, and I.V. famotidine 20 mg BID	12 12 12	1 day × 3 (crossover)
CPH-010C Japan	Healthy subjects	I.V. lansoprazole 30 mg QD and I.V. lansoprazole 30 mg BID	8 8	1 day × 2 (crossover)

## CLINICAL REVIEW

### Clinical Review Section

**TABLE 16 - Description of All of the Completed Supportive Non- U. S. Studies (Cont.)**

Study No. Country	Targeted Population	Doses/Treatments	Total Enrolled per Group	Duration
CPH-011 Japan	Healthy subjects	I.V. bolus injections of lansoprazole 30 mg Q12H and I.V. lansoprazole 60 mg QD	11 11	1 day × 2 (crossover)
CPH-012 Japan	Healthy subjects	I.V. bolus injections of lansoprazole 7.5 mg Q12H, I.V. lansoprazole 15 mg Q12H, and I.V. lansoprazole 30 mg QD	12 12 12	1 day × 3 (crossover)
CPH-020 Japan	Healthy subjects	I.V. bolus (2-minutes) lansoprazole 30 mg BID and I.V. drip infusion (120-minutes) lansoprazole 30 mg BID	10 10	1 day × 2 (crossover)
CPH-030 Japan	Healthy subjects	I.V. lansoprazole 7.5 mg QD, I.V. lansoprazole 15 mg QD, and I.V. lansoprazole 30 mg QD	6 6 7	1 day × 3 (crossover)
CPH-042 Japan	Healthy subjects	Oral lansoprazole 30 mg QD; I.V. injection of lansoprazole 30 mg QD and oral omeprazole 20 mg QD	41 16 16	1 day 1 day × 2 (crossover)
CPH-043 Japan	Healthy subjects	Oral lansoprazole 30 mg QD; I.V. injection of lansoprazole 30 mg QD and I.V. injection of diazepam 5 mg QD	44 16 16	1 day 1 day × 2 (crossover)
CPH-044 Japan	Healthy subjects	Oral lansoprazole 30 mg QD and I.V. injection of lansoprazole 15 mg BID	30 10	1 day 3 days
CPH-050 Japan	Elderly (≥65 years of age), healthy subjects	I.V. injection of lansoprazole 15 mg QD	10	1 day

## CLINICAL REVIEW

### Clinical Review Section

**Table 10.1a Description of All of the Completed Supportive Non- U. S. Studies (Cont.)**

Study ID Country	Target Population	Dose/Regimen	Total Enrolled per Group	Duration
CCT-001 <sup>b</sup> Japan	Patients with upper gastrointestinal hemorrhage due to peptic ulcers and erosions	I.V. bolus injections of lansoprazole 15 mg Q12H or I.V. lansoprazole 30 mg Q12H	26 21	7 days
CCT-002 <sup>b</sup> Japan	Patients with upper gastrointestinal hemorrhage due to peptic ulcers and erosions	I.V. bolus injections and infusions of lansoprazole 15 mg Q12H, I.V. lansoprazole 30 mg Q12H, or I.V. famotidine 20 mg Q12H	67 65 64	7 days
CCT-102 Japan	Patients with exaggerated invasive stress-induced excessive gastric acid secretion	I.V. lansoprazole 7.5 mg BID I.V. lansoprazole 15 mg BID I.V. lansoprazole 30 mg BID	80 79 79	5 days
CCT-003 <sup>b</sup> Japan	Patients with postoperative stress	I.V. lansoprazole 15 mg Q12H or I.V. lansoprazole 30 mg Q12H	41 41	3 days
CCT-010 Japan	Patients with upper gastrointestinal hemorrhage	I.V. bolus injections or infusion of lansoprazole 15 mg Q12H versus I.V. famotidine 20 mg Q12H	119 117	7 days
CCT-030 Japan	Patients with postoperative stress	I.V. bolus injections or infusion of lansoprazole 15 mg BID versus I.V. famotidine 20 mg BID	95 100	3 days

# CLINICAL REVIEW

## Clinical Review Section

**TABLE 16 - Description of All of the Completed Supportive Non- U. S. Studies (Cont.)**

Study No. Country	Targeted Population	Doses/Treatments	Total Enrolled per Group	Duration
OCT-010 Japan	Patients with upper gastrointestinal hemorrhage due to peptic ulcers, acute gastric mucosal lesion or acute stress ulcer	I.V. bolus injections of lansoprazole 15 mg Q12H or	18	7 days
		I.V. bolus injections of lansoprazole 30 mg QD followed by oral lansoprazole 30 mg QD	18 34	8 weeks

(Reference: Table 10.1, page 89, ISS, Electronic Submission)

The supportive studies that were conducted outside the U.S. consisted of 1921 subjects. Most of these were healthy volunteers who received I.V. lansoprazole. The longest duration of these trials was 7 days.

### C. Methods and Specific Findings of Safety Review

#### 1. Methods

The applicant's claim of safety for I.V. lansoprazole is based on data from two pivotal and two supportive trials. This medical officer also reviewed additional safety data in 17 supportive trials conducted outside the U.S. All subjects who received at least one dose of the study drug were included in the safety analysis. The following tables display the safety variables in the pivotal and supportive trials.

**TABLE 17- Safety Variables in the Pivotal U.S. Lansoprazole for Injection Studies**

Procedure	Details/Comments
Medical and Social Histories	• Including baseline demographics
Complete or Brief Physical Examination	
Vital Signs	
12-lead electrocardiogram (ECG)	
Ophthalmological Examination	• Visual acuity • Funduscopic examination of the retina
Routine Fasting Laboratory Evaluation	
Pregnancy Test	• Females
Adverse Event Assessment	• Adverse events, vision-related adverse events, deaths, other serious adverse events, and premature terminations due to adverse events
I.V. Infusion Site Assessment	• Examination for signs of discoloration, bruising, signs of infection, bleeding, phlebitis, pain, and extravasation

# CLINICAL REVIEW

## Clinical Review Section

**TABLE 18 - Safety Variables in the Supportive U.S. Lansoprazole for Injection Studies**

Procedure	Details/Comments
Medical and Social Histories	• Including baseline demographics
Complete or Brief Physical Examination	
Vital Signs	
12-lead ECG	
Ophthalmological Examination (Study M95-306 only)	• Visual acuity • Funduscopic examination of the retina
Routine Fasting Laboratory Evaluation	
Pregnancy Test	• Females
Adverse Event Assessment	• Adverse events, vision-related adverse events, deaths, other serious adverse events, and premature terminations due to adverse events
I.V. Infusion Site Assessment	• Examination for signs of discoloration, bruising, signs of infection, bleeding, phlebitis, pain, and extravasation

(Reference: Tables 4.1a and 4.1b, pg 16 , ISS, Electronic submission)

For these pivotal trials, the number and corresponding proportion of subjects reporting treatment-emergent adverse events were tabulated by body system and COSTART III term. They were listed by severity following the definitions below:

- Mild: The adverse event was transient and easily tolerated by the subject.
- Moderate: The adverse event caused the subject discomfort and interrupted the subject's normal activities.
- Severe: The adverse event caused considerable interference with the subject's normal activities and may have been incapacitating or life-threatening.

The following definitions were utilized to assess causality:

- Definite: The adverse event followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), and satisfied any of the following:
  - Reappearance of similar reaction by repeated exposure (rechallenge); and causality (possibly, probably or definitely treatment-related )
  - Positive results in drug sensitivity tests (lymphocyte blastoid transformation test, skin test, etc.); or
  - Toxic level of the drug in blood or other body fluids.
- Probable: The adverse event followed a reasonable temporal sequence from administration of the study drug (including the course after withdrawal of the drug), and the possibilities of factors other than the drug, such as underlying disease complications, concomitant drugs, or concurrent treatment could have been excluded.

## CLINICAL REVIEW

### Clinical Review Section

- **Possible:** The adverse event followed a reasonable temporal sequence from administration of the study drug (including the course after withdrawal of the drug), and the possibility of drug involvement could not be excluded (e.g., existence of similar reports attributable to the suspected drug, its analog, or its pharmacological effect). However, other factors, such as underlying disease complications, concomitant drugs, or concurrent treatment were presumable.
- **Unlikely:** The adverse event had an improbable temporal sequence from administration of the drug, or it could be reasonably explained by other factors, including underlying disease complications, concomitant drugs, or concurrent treatment.
- **Not Related:** The adverse event did not follow a reasonable temporal sequence from administration of the study drug, or could be reasonably explained by other factors, including underlying disease complications, concomitant drugs, or concurrent treatment.

Since other I.V. formulations of proton-pump inhibitors have been associated with visual toxicity, particular attention was paid to adverse events associated with optic changes. Descriptive statistics including mean, standard deviations and quartiles were used for laboratory and vital signs measurement.

#### **2. Withdrawals**

##### **Pivotal Study M01-308 Withdrawals**

Eighty-seven subjects were enrolled in this study. Of these 13 withdrew from the study prior to its completion. Six of these subjects (1 randomized to I.V. placebo and 5 randomized to I.V. lansoprazole) prematurely terminated prior to receiving their first dose of I.V. treatment. The following table displays a summary of the premature terminations.

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## CLINICAL REVIEW

### Clinical Review Section

**TABLE 19 - Subject Summary of Premature Terminations (Pivotal Study M01-308)**

Investigator Name/Subject #	Reason	Premature Termination Study Day
I.V. Placebo		
'874	Personal- withdrew consent	Day 7 <sup>b</sup>
'885	Personal- withdrew consent	Day 8
'820	Personal- withdrew consent	Day 13
I.V. lansoprazole 30 mg		
'841	Personal	Day 8
'915	Personal	Day 8
'813	Personal	Day 7 <sup>b</sup>
'868	Personal	Day 7 <sup>b</sup>
'836	Adverse event- rash	Day 11
'837	Adverse event- increased cough, pharyngitis	Day 14
'835	Other- unable to pass NG tube	Day 9 <sup>b,c</sup>
'806	Other- unable to pass NG tube	Day 8 <sup>b</sup>
'865	Other- withdrew consent	Day 7 <sup>b</sup>
879	Other- missed 3 consecutive study doses	Day 13

a All subjects completed Period 1 (7 days of oral lansoprazole 30 mg).

b Subject prematurely terminated prior to receiving their first dose of I.V. treatment.

c Subject received 8 days of oral lansoprazole 30 mg.

(Reference: Table 5.1b, page 25, ISS, Electronic Submission)

The narratives for the patients who withdrew because of adverse events were reviewed. The following lists pertinent details regarding patients who withdrew secondary to adverse events.

- #836 was a 43-year-old Caucasian female with a past medical history significant for asthma, chronic sinus drainage, seasonal allergies, fatty-liver, Type II diabetes, rotator cuff tear, L-4 herniated disc, and multiple keratoses in arms. She prematurely withdrew from the study due to a mild flushing rash (COSTART Term: rash) after receiving 11 days of lansoprazole therapy (oral lansoprazole 30 mg for 7 days and I.V. lansoprazole 30 mg for 4 days). This was classified as probably related to study drug.
- #837 was a 25-year-old Caucasian male with a history of hayfever and back trouble. He withdrew from the trial due to a moderate sore throat and cough (COSTART Term: pharyngitis, cough increased) after receiving 14 doses of lansoprazole therapy (oral lansoprazole 30 mg for 7 days and I.V. lansoprazole 30 mg for 7 days). The subject was treated with over the counter lozenges and the event resolved 7 days later. This event was not considered related to the study drug.

## CLINICAL REVIEW

### Clinical Review Section

*Medical Officer Comments: Both these adverse events appear to be correctly classified by the investigator.*

#### **Pivotal Study M01-307 Withdrawals**

Twenty-nine subjects were enrolled in this study by one investigator. One subject withdrew on Study Day 8 (after completing 7 days of oral lansoprazole and prior to I.V. lansoprazole dosing) due to his inability to tolerate insertion of the NG tube.

#### **Supportive Study M95-306 Withdrawals**

One subject discontinued the study due to an adverse event (dyspepsia). This subject received lansoprazole 30 mg intravenously over 30 minutes and developed moderate dyspepsia that resolved only after 22 days. This event was considered to have no relationship to study medication administration and thought to have been related to possible trauma from the pH probe.

#### **Supportive Study M96-486 Withdrawals**

Thirty-six subjects were enrolled in this study by one investigator. One subject withdrew prematurely due to adverse events (headache and epistaxis). The headache was thought to be unlikely related to the study drug and more likely a tension headache. The epistaxis was a result of insertion of the pH probe.

*Medical Officer Comments: None of the withdrawals were due to serious adverse events were causally related to the study drug in the pivotal and supportive trials conducted in the U.S. The only event likely related to I.V. lansoprazole that led to withdrawal was a rash that was mild in severity.*

### **3. Adverse events**

The following table displays the most frequent treatment-emergent adverse events that occurred in subjects who received at least one dose of the study drug in Studies M01-308, M01-307, M95-306, and M95-486.

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# CLINICAL REVIEW

## Clinical Review Section

**TABLE 20 - Most Frequent <sup>a</sup>Treatment-Emergent Adverse Events Observed During the Combined Pivotal and Supportive U.S. Studies**

COSTART Term	n (%)
	I.V. Lansoprazole (N=299) <sup>b</sup>
Any Event	83 (28%)
Headache	21 (7%)
Injection Site Pain	19 (6%)
Injection Site Inflammation	18 (6%)
Nausea	16 (5%)
Pharyngitis	15 (5%)
Injection Site Reaction	9 (3%)
Injection Site Edema	8 (3%)
Abdominal Pain	6 (2%)
Vasodilatation	6 (2%)

a Occurring in 2% of subjects.

b Denominator includes both healthy subjects and patients with erosive esophagitis. A subject who received more than one I.V. lansoprazole regimen was counted two or more times.  
(Reference: Table 6.1a, page 37, ISS, Electronic Submission)

*Medical Officer Comments; None of the adverse events listed above are unexpected with exception of pharyngitis, which occurred in 5% of the subjects. It is possible that this was due to the irritation of repeated invasive procedures such as NG tube placement and pH probe rather than due to I.V. lansoprazole.*

### Pivotal Study M01-308 Adverse Events

The following table displays the adverse events for Study M01-308.

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# CLINICAL REVIEW

## Clinical Review Section

**TABLE 21 - Most Frequent<sup>a</sup> Adverse Events Observed During the Treatment Periods (Pivotal Study M01-308)**

COSTART Term	Treatment Group n (%)		
	Oral Lansoprazole 30 mg (N=87)	I.V. Placebo (N=19)	I.V. Lansoprazole 30 mg (N=62)
<b>Treatment-Emergent Adverse Events</b>			
Any Event	4 (5%)	9 (47%)	25 (40%)
Pharyngitis	1 (1%)	1 (5%)	9 (15%)
Headache	0	3 (16%)	4 (6%)
Abdominal Pain	0	1 (5%)	2 (3%)
Diarrhea	0	1 (5%)	2 (3%)
Paresthesia	0	0	2 (3%)
Rash	1 (1%)	1 (5%)	2 (3%)
Abnormal Vision	0	0	2 (3%)
Pain	2 (2%)	1 (5%)	1 (2%)
<b>Possibly, Probably, or Definitely Treatment-Related Adverse Events</b>			
Any Event	0	2 (11%)	3 (5%)

a Occurring in  $\geq 2\%$  or 2 or more subjects in any treatment group.  
(Reference: Table 6.1b, page 38, ISS, Electronic Submission)

A summary of all adverse events considered possibly or probably related to study drug is presented in the following table.

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## CLINICAL REVIEW

### Clinical Review Section

**TABLE 21 - Possibly and Probably Treatment-Related Adverse Events (Pivotal Study M01-308)**

Subject #/ Age (years)/ Gender	Adverse Event Description	COSTART Term	Onset Day	Duration	Relationship to Study Drug	Severity	Alternative Etiology
<b>Oral Lansoprazole 30 mg/I.V. Placebo</b>							
810/58/Female	Intermittent worsening of heartburn	Dyspepsia	14 (I.V.)	2 days	Possible	Mild	GERD
904/66/Male	Abdominal pain	Abdominal pain	8 (I.V.)	5 days	Possible	Moderate	Gastroenteritis
	Intermittent diarrhea	Diarrhea	8 (I.V.)	4 days	Possible	Mild	Gastroenteritis
<b>Oral Lansoprazole 30 mg/I.V. Lansoprazole 30 mg</b>							
836/43/Female	I.V. site assessment very slightly pink above site Tender to touch Flushing rash	Injection site pain  Rash	9 (I.V.)  11 (I.V.)	2 hours  2 days	Possible  Probable	Mild  Mild	Irritation from medication  not applicable
852/35/Male	Diarrhea	Diarrhea	10 (I.V.)	4 days	Possible	Mild	Upset gastrointestinal tract from dietary source
853/47/Male	Abdominal cramps	Abdominal pain	8 (I.V.)	22 minutes	Possible	Mild	Secondary to the pentagastrin or NG tube placement

(Reference: Table 6.1c, page 42, ISS, Electronic Submission)

*Medical Officer Comments: All the adverse events in this study were of mild to moderate severity and resolved without treatment.*

# CLINICAL REVIEW

## Clinical Review Section

The following table displays the adverse events that occurred in the other pivotal study M01-307.

**TABLE 22 - Most Frequent Adverse Events Observed During the Dosing Periods (Pivotal Study M01-307)**

COSTART Term	Dosing Regimen (%)	
	Oral Lansoprazole 30 mg QD (N=29)	I.V. Lansoprazole 30 mg QD (N=28)
<b>Treatment-Emergent Adverse Events</b>		
Any Event	21 (72%)	28 (100%)
Injection Site Inflammation	1 (3%)	18 (64%)
Injection Site Pain	2 (7%)	16 (57%)
Nausea	10 (34%)	11 (39%)
Injection Site Edema	1 (3%)	7 (25%)
Vasodilatation	5 (17%)	6 (21%)
Injection Site Reaction	0	5 (18%)
Headache	4 (14%)	5 (18%)
Pharyngitis	6 (21%)	3 (11%)
Abdominal Pain	2 (7%)	3 (11%)
Insomnia	1 (3%)	3 (11%)
Ear Pain	0	3 (11%)
Skin Disorder	4 (14%)	2 (7%)
Vomiting	3 (10%)	2 (7%)
Dizziness	3 (10%)	2 (7%)
Asthenia	0	2 (7%)
Chest Pain	0	2 (7%)
Neck Pain	1 (3%)	2 (7%)
Anorexia	0	2 (7%)
Paresthesia	1 (3%)	2 (7%)
Rhinitis	3 (10%)	0
<b>Possibly, Probably, or Definitely Treatment-Related Adverse Events</b>		
Any Event	0	5 (18%)
Injection Site Reaction	0	3 (11%)

a Occurring in 2% or 2 or more subjects in either regimen.

(Reference: Table 6.1d, page 41, ISS, Electronic Submission)

*Medical Officer Comments: This study demonstrated a much higher rate of adverse events related to the injection site when compared to the other studies in this submission. In addition, there was a high rate of nausea seen in both the oral and the I.V. treatment arm. It is unclear the significance of these findings although all the adverse events in this study were of mild to moderate severity and resolved without treatment.*

# CLINICAL REVIEW

## Clinical Review Section

The following table presents a summary of all adverse events considered possibly or probably related to the study drug from M01-307.

**TABLE 23 - Possibly and Probably Treatment-Related Adverse Events (Pivotal Study M01-307)**

Subject #/ Age (years)/ Gender	Adverse Event Description	COSTART Term	Onset Date & Time	Duration	Relationship to Study Drug	Severity	Alternative Etiology
701/40/Male	Itching at right hand I.V. site	Injection site reaction	8/17/00	3 days	Possible	Mild	I.V. tubing
702/34/Female	Feels faint	Dizziness	12/09/06a	4 minutes	Possible	Mild	Phlebotomy
	Feels hot	Vasodilation	12/09/06a	4 minutes	Possible	Mild	Pentagastrin
703/20/Male	Itching at right hand I.V. site	Injection site reaction	9/05/00	2 days	Possible	Mild	I.V. tubing
706/23/Female	Bitter taste in mouth about one half way through time of normal saline I.V. infusion	Taste perversion	14/10/00a	11 minutes	Probable	Mild	not applicable
710/21/Male	Itching at left hand I.V. site	Injection site reaction	9/09/30	2 days	Possible	Mild	I.V. tubing

(Reference: Table 6.1e, page 42, ISS, Electronic Submission)

*Medical Officer Comments: The applicant does not justify why so few of the injection site adverse events were recorded as related to the study drug. The alternative etiologies assigned by the investigator to all of these events included "I.V., I.V. catheter, infiltration of I.V. site, occluded vein, phlebotomy, or I.V. tubing as a result of the I.V. catheter remaining in place for up to 72 hours". This approach may have led to an underestimation of the adverse events related to injection site problems.*

*The other adverse events considered are non-specific and of questionable clinical significance.*

The following table for the supportive trial M95-306 displays a similar adverse event profile compared to the other trials.

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# CLINICAL REVIEW

## Clinical Review Section

**TABLE 24 - Most Frequently Reported<sup>a</sup> Adverse Events and Possibly or Probably Related Adverse Events (Supportive U.S. Study M95-306)**

COSTART Term	Dosing Regimen (%)					
	O.P.I. E 10 mg (N=11)	V. Placebo (N=30)	I.V. Placebo (20 mg) (N=5)	I.V. Dose (Injection Duration)		
				I.V. 10 mg (30 min) (N=4)	I.V. 10 mg (30 min) (N=5)	I.V. 50 mg (30 min) (N=1)
<b>Treatment-Emergent</b>						
<b>Adverse Event</b>						
Any Event	3 (9%)	6 (17%)	5 (14%)	8 (24%)	5 (14%)	6 (18%)
Headache	2 (6%)	2 (6%)	3 (9%)	1 (3%)	3 (9%)	3 (9%)
Injection Site Reaction	0	2 (6%)	1 (3%)	0	0	1 (3%)
Nausea	0	0	1 (3%)	2 (6%)	0	1 (3%)
Vomiting	0	0	0	2 (6%)	0	0
<b>Possibly or Probably Related Adverse Event</b>						
Any Event	1 (3%)	0	1 (3%)	3 (9%)	1 (3%)	1 (3%)
Nausea	0	0	1 (3%)	2 (6%)	0	1 (3%)

<sup>a</sup> Reported by two or more subjects in any dosing regimen. Lan = lansoprazole  
(Reference: Table 6.1f, page 43, ISS, Electronic Submission)

In regards to the supportive study M96-486, the overall incidence of adverse events was generally similar to that among the other studies. Headache was the most commonly reported adverse event among all of the dosing regimens, reported by two subjects (6%) in the oral lansoprazole 30 mg regimen, four (11%) subjects in the I.V. PEG vehicle control regimen, and one (3%) subject in each of the I.V. lansoprazole regimens. The remaining adverse events were reported by no more than one subject in any dose regimen and all were mild in severity, with the exception of one event. This was an accidental injury considered to be moderate in severity. In terms of causality, all adverse events in the supportive study M96-486 were either not related or unlikely related to study drug.

#### 4. Injection site events

When data from all subjects who received I.V. lansoprazole in the combined pivotal and supportive U.S. studies were analyzed, greater proportions of subjects in the I.V. lansoprazole regimen were noted to have adverse events of injection site pain, injection site inflammation, injection site reaction, and injection site edema (6%, 6%, 3%, and 3%, respectively) compared to the I.V. placebo regimen (1%, 0%, 3%, and 0%, respectively) and to the oral lansoprazole regimen (1%, <1%, 0%, and <1%, respectively).

However, the applicant reported only three subjects in the I.V. lansoprazole regimen as having injection site events that were considered possibly, probably, or definitely related to study drug. The alternate etiologies proposed by the investigators were due to the I.V. catheter, infiltration of I.V. site, occluded vein, phlebotomy, or I.V. tubing as a result of the I.V. catheter remaining in place for up to 72 hours.

*Medical Officer Comments: The ascertainment of the etiology of injection site events has the appearance of seeming somewhat arbitrary and thus, may have led to a under-estimation of the actual incidence of this side effect.*

# CLINICAL REVIEW

## Clinical Review Section

### 5. Deaths

No subjects died during the pivotal or supportive studies.

### 6. Laboratory Findings

The following table displays the laboratory studies that were obtained during the pivotal and supportive studies.

**TABLE 25 - Laboratory Studies Evaluated during Pivotal and Supportive Studies**

Hematology Tests	Chemistry Tests	Urinalysis
Hemoglobin	Albumin	Specific Gravity
Hematocrit	Total Protein	pH
Red Blood Cell (RBC) Count	Glucose	Glucose
White Blood Cell (WBC) Count with Differential	Blood Urea Nitrogen (BUN)	Ketones
Platelet Count	Creatinine	Protein
	Aspartate Aminotransferase (AST)	Microscopic Examination
	Alanine Aminotransferase (ALT)	
	Gamma Glutamyl Transferase (GGT)	
	Alkaline Phosphatase	
	Total Bilirubin	
	Total Cholesterol	
	Calcium	
	Inorganic Phosphorus	
	Sodium	
	Potassium	
	Chloride	
	Uric Acid	

a To be collected after an 8-hour fast.

(Reference: Page 52, ISS, Electronic Submission)

All of the laboratory parameters were evaluated by statistical comparisons between treatment groups for the pivotal and supportive studies. No clinically meaningful statistical differences were seen when pairwise comparisons were made between treatment groups. There were clinically significant differences seen in individual subjects. A summary of the individual subjects with hematology values which met the predefined criteria for further clinical review during the study is displayed in the Table 26.

# CLINICAL REVIEW

## Clinical Review Section

**TABLE 26 - Subjects With Hematology Values Reaching Levels Requiring Further Clinical Review (Pivotal Study M01-308)**

Investigator Site/Subject No.	Study Period/Day	Treatment Group	Hematology Parameter (Units)	Screening Value	Clinical Review Value	Final Value	NL Range
856	POST/15	I.V. lansoprazole 30 mg	Hematocrit (%)	38	<b>35</b>	<b>35</b>	39-54%
/879	2/8	I.V. lansoprazole 30 mg	Eosinophils (%)	4.1	<b>11.9</b>	<b>10.0</b>	0.0-6.8%
	POST/22	I.V. lansoprazole 30 mg	Eosinophils (%)	4.1	<b>10.0</b>	<b>10.0</b>	0.0-6.8%
/890	POST/15	I.V. lansoprazole 30 mg	Eosinophils (%)	9.7	<b>12.3</b>	<b>12.3</b>	0.0-6.8%

NL = normal laboratory range; POST = posttreatment

Limit of concern: Eosinophils (%)  $\geq 10$ ; Hematocrit (%)  $\leq 35$  (Male)

NOTE: All subjects received open-label oral lansoprazole 30 mg during Period 1.

a Treatment subject received at the time of the further clinical review level, or the treatment from the preceding treatment period, if during the posttreatment period.

b Last value obtained.

Screening corresponds to value obtained prior to Period 1; Study Days correspond to values obtained during the specified treatment period.

Note: The bolded and underlined values are those meeting the predefined criteria requiring further clinical review. A laboratory value is included as a value requiring further clinical review if it meets the predefined limits **and** is more extreme than or equal to the subject's baseline value.

(Reference: Table 7.2a, page 57, ISS, Electronic Submission)

*Medical Officer Comments: The patient narratives were reviewed for each of these subjects and none of these changes were likely due to the study drug. Subject 856 had a slight decrease in hematocrit likely secondary to repeated phlebotomy. Subjects 879 and 890 had an increase in eosinophils due to bronchitis and anemia respectively.*

A summary of the individual subjects with chemistry values that met the predefined criteria for further clinical review during the study M01-308 is displayed in the following table.

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# CLINICAL REVIEW

## Clinical Review Section

**TABLE 27-Subjects With Chemistry Values Reaching Levels Requiring Further Clinical Review (Pivotal Study M01-308)**

Investigator Name/ Subject No.	Study Period/Day	Treatment Group <sup>a</sup>	Chemistry Parameter (units)	Screening	Clinical Review Value	Final Value <sup>b</sup>	NL
836 <sup>c</sup>	2/8	IV lansoprazole 30 mg	Glucose (mg/dL)	221	<b>252</b>	156	70-115
837	2/8	IV lansoprazole 30 mg	Uric Acid (mg/dL)	8.5	<b>9.1</b>	8.8	2.1-8.2
	POST/20	30 mg			<b>10.1</b>		
851	2/8	IV lansoprazole 30 mg	SGPT/ALT (U/L)	39	<b>115</b>	71	6-43
	2/8	IV lansoprazole 30 mg	GGT (U/L)	60	<b>194</b>	<b>215</b>	10-61
	2/12 POST/15	30 mg			<b>197</b> <b>215</b>		
852	2/8	IV lansoprazole 30 mg	Uric Acid (mg/dL)	13.4	<b>10.3</b>	8.2	2.1-8.2
				10.9			
856	2/8	IV lansoprazole 30 mg	GGT (U/L)	191	<b>199</b>	167	10-61
862	POST/15	IV lansoprazole 30 mg	SGPT/ALT (U/L)	40	<b>70</b>	<b>70</b>	6-34
	2/8	IV lansoprazole 30 mg	SGOT/AST (U/L)	17	<b>71</b>	<b>82</b>	9-34
	POST/15	30 mg			<b>89</b>		
880	POST/15	IV lansoprazole 30 mg	Uric Acid (mg/dL)	8.1	<b>9.4</b>	<b>9.4</b>	2.1-8.2

NL = normal laboratory range; POST = posttreatment Limit of concern; GGT (U/L) >2 x upper limit of normal; AST/SGOT (U/L) >2 x upper limit of normal; ALT/SGPT (U/L) >2 x upper limit of normal; Glucose (mg/dL) ≥250; Uric Acid (mg/dL) ≥9.0

NOTE: All subjects received open-label oral lansoprazole 30 mg during Period 1.

a Treatment subject received at the time of the further clinical review level, or the treatment from the preceding treatment period, if during the posttreatment period.

b Last value obtained.

c Subject had a history of type 2 diabetes.

Screening corresponds to value obtained prior to Period 1; Study Days correspond to values obtained during the specified treatment period.

Note: The bolded and underlined values are those meeting the predefined criteria requiring further clinical review. A laboratory value is included as a value requiring further clinical review if it meets the predefined limits and is more extreme than or equal to the subject's baseline value.

(Reference: Table 7.2b, Page 58, ISS, Electronic submission)

**Medical Officer Comments:** All the patient narratives were reviewed for these subjects. For all the subjects save one the lab abnormalities appeared to be due to an underlying conditions rather than the study drug. This exception was Subject #851. Subject #851 was a 41-year-old Caucasian male without significant medical history. He received lansoprazole for 14 days (oral lansoprazole 30 mg for 7 days and I.V. lansoprazole 30 mg for 7 days). The subject denied a history of ethanol use. At baseline, he had normal SGOT, SGPT, and GGT values (32 U/L, 39 U/L, and 60 U/L, respectively). On Study Day 8, the SGOT increased to 70 U/L and the SGPT and GGT both increased to levels requiring further clinical review (115 U/L and 194 U/L, respectively). On Study Days 12 and 15, the SGOT returned to within normal limits (33 U/L and 30 U/L, respectively), while the SGPT decreased to 78 U/L and 71 U/L respectively. The GGT remained elevated at 197 U/L and 215 U/L, respectively. It is unclear whether these changes were due to the study drug

# CLINICAL REVIEW

## Clinical Review Section

For the other pivotal study M01-307, the lab abnormalities were reviewed. All laboratory abnormalities were not clinically relevant or clearly attributable to the underlying disease states.

For supportive study M95-301 the lab abnormalities were reviewed. In regards to hematology values there were a few subjects who had changes in hematocrit and monocytes that were not clinically related. There were three subjects who had changes in the eosinophil count. However, upon review these appear to be due to underlying conditions (atopic dermatitis, allergies) and not related to administration of the study drug. Concerning chemistry values, two subjects had abnormalities in liver function tests that are displayed in the following table.

**TABLE 28 - Subjects With Hepatic Chemistry Values Reaching Levels Requiring Further Clinical Review (Supportive U.S. Study M95-306)**

Subject No.	Cross-Over Period	Regimen	Hepatic Chemistry Parameter (units)	Baseline	Study Day 1	Study Day 9	Study Day 25	NL
105	6	A	Total Bilirubin (mg/dL)	0.4	0.9	<b>2.1</b>	0.9	0.1-1.2
127	6	C	SGOT/AST (U/L)	23	21	<b>105</b>	N/A	0-50

Regimen A: Oral lansoprazole 30 mg; Regimen B: I.V. vehicle only (30-minute infusion); Regimen C: I.V. lansoprazole 30 mg (120-minute infusion); Regimen D: I.V. lansoprazole 30 mg (60-minute infusion); Regimen E: I.V. lansoprazole 30 mg (30-minute infusion); Regimen F: I.V. lansoprazole 60 mg (30-minute infusion)

Baseline corresponds to value obtained prior to Period 1; Study Days correspond to values obtained during the specified crossover period.

NL = normal laboratory range; N/A = Not available

Note: The bolded and underlined values are those meeting the predefined criteria requiring further clinical review. A laboratory value is included as a value requiring further clinical review if it meets the predefined limits **and** is more extreme than or equal to the subject's baseline value.

(Reference: Table 7.2f, page 62, ISS, Electronic submission)

Subject #105 was a 31-year-old Caucasian male who received the following dosing regimen: lansoprazole 30 mg I.V. (infused over 60 minutes), lansoprazole 30 mg I.V. (infused over 30 minutes), lansoprazole 30 mg I.V. (infused over 120 minutes), lansoprazole 60 mg I.V. (infused over 30 minutes), vehicle I.V. (infused over 30 minutes), lansoprazole 30 mg PO. The subject had a normal total bilirubin value for all six crossover periods that increased to a level requiring further clinical review (2.1 mg/dL; NL: 0.1-1.2 mg/dL) on Posttreatment Day 9. On Posttreatment Day 25, the total bilirubin was repeated and was within the normal range (0.9 mg/dL). Other liver function tests (AST, ALT, GGTP) were normal. The investigator did not consider any of these values to be clinically significant. The subject did not report any relevant adverse events and took no concurrent medications during the study. Given the rise was solitary in nature and occurred post-treatment it is not likely due to the study drug.

Subject #127 was a 24-year-old Caucasian male who received the following dosing regimen: lansoprazole 60 mg I.V. (infused over 30 minutes), lansoprazole 30 mg PO, lansoprazole 30 mg I.V. (infused over 30 minutes), vehicle I.V. (infused over 30 minutes), lansoprazole 30 mg I.V. (infused over 60 minutes), lansoprazole 30 mg I.V. (infused over 120 minutes). The subject had

## CLINICAL REVIEW

### Clinical Review Section

normal SGOT/AST and SGPT/ALT values at baseline and for all six crossover periods. On Posttreatment Day 9, the SGOT/AST value increased to a level requiring further clinical review (105 U/L; NL: 0-50 U/L) and the SGPT/ALT was also elevated at 66 U/L (NL: 0-50 U/L). The investigator considered these values to be clinically significant, of unknown etiology and ordered a repeat chemistry but the subject was lost to follow up. The fact that the lab values were normal during the treatment phase and abnormal only in post-treatment make it less likely these changes are due to the study drug. Although it is feasible this subject had a delayed increase in liver enzymes due to the study drug, it is difficult to draw firm conclusions without further follow-up.

The last study included in the integrated safety database was supportive study M96-486. Two subjects had lab findings of note in this study.

Subject #236 was a 23-year-old Hispanic male with no past medical history completed each of the four crossover periods. The subject had a baseline SGOT/AST of 17 IU/L (NL: 11-36 IU/L) and a SGPT/ALT of 18 IU/L (NL: 6-43 IU/L). On Study Day 19, Day 1 of Washout Period 2, the SGOT/AST increased to 46 IU/L and the SGPT/ALT to 99 IU/L. On Post Treatment Day 1, the SGOT/AST continued to increase to 100 IU/L and the SGPT/ALT to 179 IU/L. The SGOT/AST and SGPT/ALT were repeated on Post Treatment Day 31 to within normal limits with values of 27 IU/L and 39 IU/L, respectively. The subject also noted mild nasal congestion and mild abdominal discomfort and took no concurrent medications during the course of the study. The investigator attributed the abnormal liver tests to the study drug.

Subject #209 was a 38-year-old Hispanic male with an unremarkable medical history completed each of the four crossover periods. The subject's baseline values were an SGPT/ALT of 38 IU/L (NL: 6-43 IU/L), an SGOT/AST of 25 IU/L (NL: 11-36 IU/L), and a GGT of 49 IU/L (NL: 10-61 IU/L). On Study Day 29, Day 1 of Washout Period 2, the SGPT/ALT increased to 88 IU/L, the SGOT/AST to 48 IU/L and the GGT to 87 IU/L. Follow-up liver function tests were normal. The SGPT/ALT, SGOT/AST and GGT remained within normal limits at the completion of the study with values of 35 IU/L, 23 IU/L, and 46 IU/L, respectively. The subject reported no adverse events or took no concurrent medications during the course of the study.

***Medical Officer Comments:** Oral lansoprazole has been associated with an increase in liver function tests in rare instances. This data would seem to indicate that I.V. lansoprazole also could cause an increase in liver enzymes. Although there was no statistical difference in the number of subjects with abnormal liver tests between oral lansoprazole and I.V. lansoprazole subjects, statistical analysis can be misleading regarding this finding. Hepatic reactions to medication are often idiosyncratic and may be missed when solely comparing absolute numbers.*

#### 7. Vital Signs and Physical Examinations

No clinically relevant changes in vital signs or physical examinations were noted during the studies included in the ISS.

## CLINICAL REVIEW

### Clinical Review Section

#### 8. Visual Examinations

An I.V. formulation of omeprazole had a questionable association with optic problems. Because of this, special attention was paid to evaluate for this adverse event. For each of the pivotal U.S. studies, ophthalmologic examinations were performed on all subjects at the Pretreatment, Study Day 15 Visit and if a subject prematurely terminated from the study. For the supportive U.S. study M95-306, these assessments were performed on all subjects at the screening visit, the evening prior to study drug administration in each crossover period, on the day of discharge for each crossover period, and at the post treatment visit. These ophthalmologic examinations consisted of visual acuity testing using the Snellen letter eye chart and funduscopic examination of the retina. Two subjects (2/87; 2%), both of whom completed the study, reported two vision-related adverse events during pivotal study M01-308. Subject #839 was a 78 year old female who reported blurred vision on Study Days 10 and 13 during Period 2 (I.V. lansoprazole 30 mg). This was judged by the investigator as due to hypoglycemia. Subject #872 reported decreased visual acuity in his right eye on Study Day 15 (1 day following the last dose of I.V. lansoprazole 30 mg). The etiology of this event is unclear but visual acuity tests and funduscopic exams were normal.

#### 9. Additional Safety Data

The non-U.S. studies that were not submitted in support of the efficacy claim were not included in the ISS. The applicant did however provide safety data on these 17 studies. Upon review of the serious adverse events in these studies, none were judged to be related to the study drug.

*Medical Officer Comments: The review of these additional data was problematic. Although, these studies contained a large number of subjects, the applicant chose not to integrate the safety data from these trials but rather present the safety results individually. In addition, the studies contained very heterogeneous populations ranging from healthy volunteers to critically ill patients requiring intensive care treatment. For these reasons, this medical officer focused on the serious adverse events and deaths that occurred in these trials and assessed them for causality.*

#### D. Adequacy of Safety Testing

The safety data submitted by the sponsor are adequate. Oral lansoprazole has been a previously approved agent and is in widespread use. The applicant conducted adequate assessments of safety variables including for visual disturbances that purportedly occurred with I.V. omeprazole. The safety database submitted demonstrates that I.V. lansoprazole seems to have a similar safety profile to the oral formulation.

#### E. Summary of Critical Safety Findings and Limitations of Data

The applicant has demonstrated that I.V. lansoprazole has an acceptable safety profile. The adverse events in the pivotal and supportive studies were similar to what is seen with oral lansoprazole. The data are limited by the applicant's decision not to integrate data from non-U.S. studies in the safety database. This made review of this data problematic. Another limitation is the lack of exposure in critically ill patients in the supportive and pivotal trials. However, despite these limitations, sufficient data was submitted to establish that I.V. lansoprazole is safe.

## CLINICAL REVIEW

### Clinical Review Section

#### VIII. Dosing, Regimen, and Administration Issues

TAP chose to develop the 30 mg I.V. lansoprazole dose because this is the dose of the oral formulation that is currently approved for use in short-term treatment of erosive esophagitis. The pivotal and supportive studies demonstrated that acid suppression following administration of I.V. lansoprazole 30 mg given over 30 minutes was as or more effective than the oral lansoprazole 30 mg dose. In the Supportive Study M95-306 different infusion times were evaluated. Data from this study

demonstrated that acid suppression of the 30-minute infusion was similar to that of the 60- and 120-minute infusions and the safety profiles for 30-, 60-, and 120-minute infusions of 30 mg lansoprazole were similar as well. Thus, with this data I.V. lansoprazole 30 mg over 30 minutes was selected. The data submitted by the applicant supports a short term regimen as opposed to long term use. The proposed labeling states that I.V. lansoprazole can be used for up to 7 days

I.V. Lansoprazole is to be reconstituted in 5 mL Sterile Water for Injection, USP in preparation of use. Reconstitution yields a solution with a concentration of 6 mg/mL with a pH of approximately 11 that is stable for 7 hours when stored at 25°C (77°F). Before administration to the patient, further dilution in 50 mL of 0.9% Sodium Chloride is required. This solution has a pH of approximately 10.2. TAP states the solution should be administered 7 hours of reconstitution and stored at 25°C (77°F). I.V. lansoprazole should not be mixed with other drugs or diluents due to incompatibilities. The intravenous line should be flushed before and after administration.

#### IX. Use in Special Populations

##### A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The pivotal and supportive studies were not powered to establish equivalence between the oral and I.V. lansoprazole formulations in subsets based on gender. When analyses of median BAO and MAO values by subgroup were performed, no clinically significant differences were observed between male and female subjects.

The safety profile for I.V. lansoprazole was similar for females and males. A similar pattern of adverse events experienced by females and males was seen in the pivotal and supportive trials. Similar percentages of females and males reported treatment-emergent adverse events and treatment-related adverse events. The following table displays the number of subjects in the combined pivotal and supportive studies reporting adverse events summarized by gender and treatment group.

# CLINICAL REVIEW

## Clinical Review Section

**TABLE 29 - All Treatment-Emergent and Treatment-Related Adverse Events by Group and Gender in the Combined Pivotal and Supportive U.S. Studies**

	Group n (%)					
	Oral Lansoprazole 30 mg		IV Placebo		IV Lansoprazole 30 mg	
	Female (N=45)	Male (N=139)	Female (N=23)	Male (N=68)	Female (N=55)	Male (N=244)
<b>All Treatment-Emergent Adverse Events</b>	7 (16%)	24 (17%)	10 (43%)	9 (13%)	18 (33%)	65 (27%)
<b>Treatment-Related Adverse Events</b>	0	1 (1%)	1 (4%)	1 (1%)	4 (7%)	10 (4%)

(Reference: Table 9.1a, page 29, ISS, Electronic Submission)

The following table displays the most frequent treatment emergent adverse events by gender.

**TABLE 30 - Most Frequently<sup>a</sup> Reported Treatment-Emergent Adverse Events by Group and Gender in the Combined Pivotal and Supportive U.S. Studies**

	Group n (%)					
	Oral Lansoprazole 30 mg		IV Placebo		IV Lansoprazole 30 mg	
	Female (N=45)	Male (N=139)	Female (N=23)	Male (N=68)	Female (N=55)	Male (N=244)
<b>COSTART Term</b>						
<b>Any Event</b>	7 (16%)	24 (17%)	10 (43%)	9 (13%)	18 (33%)	65 (27%)
Headache	2 (4%)	6 (4%)	5 (22%)	4 (6%)	10 (18%)	11 (5%)
Injection Site Pain	0	2 (1%)	1 (4%)	0	6 (11%)	13 (5%)
Pharyngitis	3 (7%)	5 (4%)	1 (4%)	0	3 (5%)	12 (5%)
Injection Site Inflammation	0	1 (1%)	0	0	2 (4%)	16 (7%)
Nausea	3 (7%)	7 (5%)	0	1 (1%)	2 (4%)	14 (6%)

<sup>a</sup> reported by more than 2% of subjects

Given that this is a new formulation of an established drug, the applicants analysis based on gender is adequate.

**B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

The following table displays the breakdown of demographic subgroups in the pivotal and supportive trials.

## CLINICAL REVIEW

### Clinical Review Section

**TABLE 31 - Demographic and Baseline Characteristics in U.S. Studies of Lansoprazole for Injection (Combined Pivotal<sup>a</sup> U.S. and Supportive<sup>b</sup> U.S. Studies)**

Variable	All Subjects (N=190)	I.V. lansoprazole 10 mg (N=70)
<b>Race</b>		
Caucasian	147 (77%)	127 (75%)
Black	8 (4%)	8 (5%)
Other	35 (18%)	35 (21%)
<b>Age (years)<sup>c</sup></b>		
Mean (SD)	38.6 (12.8)	37.5 (12.2)
Minimum-Maximum	18-78	19-78

a U.S. Studies M01-308 and M01-307.

b U.S. Studies M95-306 and M96-486.

c At baseline.

(Reference: Table 6.0b, Page 29, ISE, Electronic Submission)

The applicant did carry out subgroup analyses were for race (Caucasian and Non-Caucasian), and age (less than 65 years and at least 65 years) for combined data from Studies M01-308 and M01-307. Due to small sample sizes in the Non-Caucasian (n=5) and geriatric (>65 years of age, n=9) groups, these analyses consisted of descriptive statistics (including minimum, median, maximum, and mean) rather than formal statistical tests. Pharmacodynamic parameters were not analyzed controlling for age, gender, race, or any social history variable because the small numbers involved.

There was a paucity of subjects over 65 years of age. Only three subjects had BAO values and only four subjects had MAO values who were 65 years or older. These small numbers did not permit statistical analysis to demonstrate the equivalence of I.V. lansoprazole to oral lansoprazole in the elderly.

TAP conducted an analysis of adverse events based on age. The following table displays the adverse events by age.

**TABLE 32 - All Treatment-Emergent and Treatment-Related Adverse Events by Group and Age in the Combined Pivotal and Supportive U.S. Studies**

	Group n (%)					
	Oral Lansoprazole 30 mg		I.V. Placebo		I.V. Lansoprazole 30 mg	
	<65 years (N=175)	≥65 years (N=9)	<65 years (N=87)	≥65 years (N=4)	<65 years (N=294)	≥65 years (N=5)
All Treatment-Emergent Adverse Events	31 (18%)	0	16 (18%)	3 (75%)	81 (28%)	2 (40%)
Treatment-Related Adverse Events	1 (1%)	0	1 (1%)	1 (25%)	14 (5%)	0

(Reference: Table 6.0c, Page 30, ISE, Electronic Submission)

The pattern of adverse events experienced by older subjects (at least 65 years) compared to younger (less than 65 years) subjects was similar in the combined pivotal and supportive studies. Slightly higher percentages of older subjects reported treatment-emergent adverse events than younger subjects in those who received I.V. lansoprazole. However, no older I.V. lansoprazole-treated subject had a treatment-related adverse event. Due to the small numbers, no significant

## CLINICAL REVIEW

### Clinical Review Section

conclusion can be made. A summary of treatment-emergent adverse events reported by I.V. lansoprazole-treated subjects with an incidence of at least 5% (and more than one subject) in either age group is presented in the following table.

**TABLE 33 - Most Frequently<sup>a</sup> Reported Treatment-Emergent Adverse Events by Group and Age in the Combined Pivotal and Supportive U.S. Studies**

COSTART Term	Group n (%)					
	Oral Lansoprazole 30 mg		I.V. Placebo		I.V. Lansoprazole 30 mg	
	<65 years (N=175)	≥65 years (N=9)	<65 years (N=87)	≥65 years (N=4)	<65 years (N=294)	≥65 years (N=5)
Any Event	31 (18%)	0	16 (18%)	3 (75%)	81 (28%)	2 (40%)
Headache	8 (5%)	0	8 (9%)	1 (25%)	21 (7%)	0
Injection Site Pain	2 (1%)	0	0	1 (25%)	19 (6%)	0
Injection Site Inflammation	1 (1%)	0	0	0	18 (6%)	0
Nausea	10 (6%)	0	1 (1%)	0	16 (5%)	0

<sup>a</sup> Reported by 5% (and more than one subject) of lansoprazole-treated subjects in either age group. (Reference: Table 9.1f, Page 81, ISE, Electronic Submission)

As with the other subset analyses, these studies were not powered to allow formal statistical testing based on racial group. In the subgroup analyses of pharmacodynamic parameters, no clinically significant differences were observed between male and female subjects and between Caucasian subjects and subjects of other races. In regards to adverse events, safety profile between races was similar. The following table displays a summary of treatment-emergent adverse events reported by I.V. lansoprazole-treated subjects with an incidence of at least 5% (and more than one subject) in either race group.

**TABLE 34 - All Treatment-Emergent and Treatment-Related Adverse Events by Group and Race in the Combined Pivotal and Supportive U.S. Studies<sup>a</sup>**

	Group n (%)					
	Oral Lansoprazole 30 mg		I.V. Placebo		I.V. Lansoprazole 30 mg	
All Treatment-Emergent Adverse Events	27 (19%)	4 (10%)	14 (26%)	5 (13%)	69 (33%)	14 (15%)
Treatment-Related Adverse Events	1 (1%)	0	2 (4%)	0	12 (6%)	2 (2%)

(Reference: Table 9.1E, ISS, Electronic Submission)

The following table displays the most frequent adverse events by race.

**TABLE 35 - Most Frequently<sup>a</sup> Reported Treatment-Emergent Adverse Events by**

# CLINICAL REVIEW

## Clinical Review Section

### Group and Race in the Combined Pivotal and Supportive U.S. Studies

	Group (%)					
	Oral Lansoprazole 30 mg		I.V. Placebo		I.V. Lansoprazole 30 mg	
	Caucasian (N=143)	Other Races (N=41)	Caucasian (N=53)	Other Races (N=38)	Caucasian (N=207)	Other Races (N=92)
<b>Any Event</b>	27 (19%)	4 (10%)	14 (26%)	5 (13%)	69 (33%)	14 (15%)
Injection Site Pain	2 (1%)	0	1 (2%)	0	18 (9%)	1 (1%)
Headache	5 (3%)	3 (7%)	4 (8%)	5 (13%)	17 (8%)	4 (4%)
Injection Site Inflammation	1 (1%)	0	0	0	17 (8%)	1 (1%)
Nausea	10 (7%)	0	1 (2%)	0	15 (7%)	1 (1%)
Pharyngitis	6 (4%)	2 (5%)	1 (2%)	0	13 (6%)	2 (2%)

a Reported by 5% (and more than one subject) of lansoprazole-treated subjects in either race group.  
(Reference: Table 9.1f, ISSE, Electronic Submission)

Caucasians experienced a higher frequency of adverse events than other racial groups in these trials, but no conclusions can be drawn due to the small numbers. The current oral lansoprazole label states that Asians have an increase in the AUC when compared to patients in the U.S. However, since the approval of oral lansoprazole no safety or efficacy differences in various ethnic subgroups have come to light.

#### C. Evaluation of Pediatric Program

Oral lansoprazole is currently approved for use in children age 1 to 11 years of age. The applicant has not included any data involving the use of I.V. lansoprazole in pediatric patients in this submission. [ ]

#### D. Comments on Data Available or Needed in Other Populations

[ ] Also, although oral lansoprazole has been studied in patients with hepatic and renal impairment, it may be useful to have similar data for the I.V. formulation.

## X. Conclusions and Recommendations

### A. Conclusions

The applicant's submission demonstrates a favorable risk/benefit profile for I.V. lansoprazole for short term use in patients with erosive esophagitis who cannot take oral medication. Efficacy is based on an established pharmacodynamic parameters. In two pivotal and two supportive trials, I.V. lansoprazole met pre-specified criteria for equivalence. The applicant also has demonstrated that I.V. lansoprazole has an acceptable safety profile. The adverse events in the pivotal and supportive studies were similar to what is seen with oral lansoprazole. The data is limited by the applicant's decision not integrate data from non-U.S. studies in the safety database. This made review of this data problematic. However, despite this limitation sufficient data was submitted to establish that I.V. lansoprazole is safe.

## CLINICAL REVIEW

### Clinical Review Section

#### B. Recommendations

This medical officer recommends approval for I.V. lansoprazole for use in adults for the indication of short-term treatment (up to 7 days) of all grades of erosive esophagitis when patients are unable to take the oral formulations. Approval is not recommended  $\left[ \begin{array}{l} \text{without further data utilizing I.V. lansoprazole in that population.} \end{array} \right.$

## XI. Appendix

#### A. References

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9. A Randomized, Open-Label, Crossover, Single-Center Study to Evaluate the Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Doses of Intravenous Lansoprazole in Healthy Subjects. TAP Study No. M96-486, TAP Report No. R&D/00/225, 2000. This report was previously submitted to the IND on April 12, 2001 (Amendment No. 24), Vol. 1, Page 1.
10. A Randomized, Placebo-Controlled, Multi-Center Study to Evaluate the Pharmacodynamics of Intravenous Lansoprazole to that of Oral Lansoprazole in Subjects with Erosive Esophagitis. TAP Study No. M01-308, TAP Report No. TAP-02-000891-2.0, November 12, 2002.
11. A Phase 1, Open-Label, Single-Center Study to Evaluate the Pharmacokinetics and Pharmacodynamics of 30 mg Intravenous Lansoprazole and 30 mg Oral Lansoprazole in Healthy Subjects. TAP Study No. M01-307, TAP Report No. TAP-02-000436-1.0, October 7, 2002.

**CLINICAL REVIEW**

Clinical Review Section

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