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Increasing Versatility of PPIs: The Place of Orally Disintegrating Lansoprazole

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Proton pump inhibitors (PPIs) have, since their introduction in the 1990s, become integral and versatile agents in the therapeutic armamentarium of general practitioners and specialists alike.

Currently available PPI compounds. The five compounds currently available in this class in Canada are esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Losec® and generics), pantoprazole (Pantoloc®) and rabeprazole (Pariet®).

Indications. PPIs are indicated for a broad range of conditions; however, the indications vary substantially from agent to agent.[1-6] For example, while all five agents are indicated for the treatment of gastroesophageal reflux disease (GERD), only lansoprazole, pantoprazole and esomeprazole are indicated to prevent NSAID-associated GU with ongoing NSAID therapy. All but rabeprazole are indicated for the healing of NSAID-associated gastric ulcers. Among the PPIs, lansoprazole has the broadest spectrum of indications; it can be used to treat reflux esophagitis (including those cases associated with Barrett's esophagus and those cases for whom histamine H_2-receptor antagonists are not currently effective), duodenal ulcers (DU), gastric ulcers (GU), NSAID-associated GU, and Zollinger-Ellison Syndrome. Lansoprazole is also the only agent indicated for pediatric use (patients aged 1 to 17 years). All PPIs are indicated for *H. pylori* eradication when given in association with antibiotic therapy.

Available formulations. The available formulations of these agents are shown in Table 1. For four of the six agents, the primary formulation is an oral tablet. Lansoprazole's primary formulation is an oral capsule containing active granules. The capsular formulation of lansoprazole makes it more versatile than standard tablets. The granules can be removed from the capsule and mixed into certain soft foods (*e.g.*, yogurt, apple sauce) or into selected beverages. They can also be flushed through a nasogastric tube. This has facilitated the use

TABLE 1 PPI Formulations Available in Canada

Administration option includes	Apo-omeprazole	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Capsule granules*	✓		✓			
Sprinkled on select soft food			✓			
Mixed into select beverage			✓			
Granules flushed through a nasogastric tube with apple juice			✓			
Tablets		✓***		✓†	✓**	✓
Disintegrating tablet			✓ (FasTab®)			
IV formulation			✓ (NOC)		✓	

Adapted from the product monographs for apo-omeprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

*Do not crush or chew; **Do not split tablets; ***May be mixed into soft foods or dissolved in water and administered as a drink / be flushed through an NG tube; †Available formulations include multiple unit pellet system that can be dissolved in water and administered through an NG tube

of PPIs in patients who have difficulty with oral medications (*e.g.*, dysphagia, or difficulty swallowing tablets/capsules).

Omeprazole is available in two oral formulations: regular capsules and the multiple unit pellet system (MUPS), which can be dissolved in water and taken by mouth from a syringe or cup or flushed through a nasogastric tube. The generic omeprazole is only available in capsules. Esomeprazole tablets can also be dissolved into water and the component pellets swallowed from a cup or flushed through a nasogastric tube.

For in-hospital use, lansoprazole and pantoprazole are approved by Health Canada as intravenous (i.v.) formulations. However, to date, only pantoprazole i.v. is available in Canada, as the makers of lansoprazole i.v. have yet to market that formulation in this country.

The most recent addition to the list of PPI formulations available in Canada is the lansoprazole orally disintegrating tablet (Prevacid FasTab®).

In June of 2006, a group of specialists with an interest in PPI therapy met to discuss the characteristics of the new orally disintegrating formulation of lansoprazole and define the clinical settings and patient types in which this formulation would be most beneficial. In the discussion of each setting, the participants discussed the advantage to the patient, to the healthcare professionals and to the healthcare system in general. The remainder of this review will focus on the use of the orally disintegrating tablet for adult patients. A subsequent specialist panel will discuss pediatric use of this formulation in more detail.

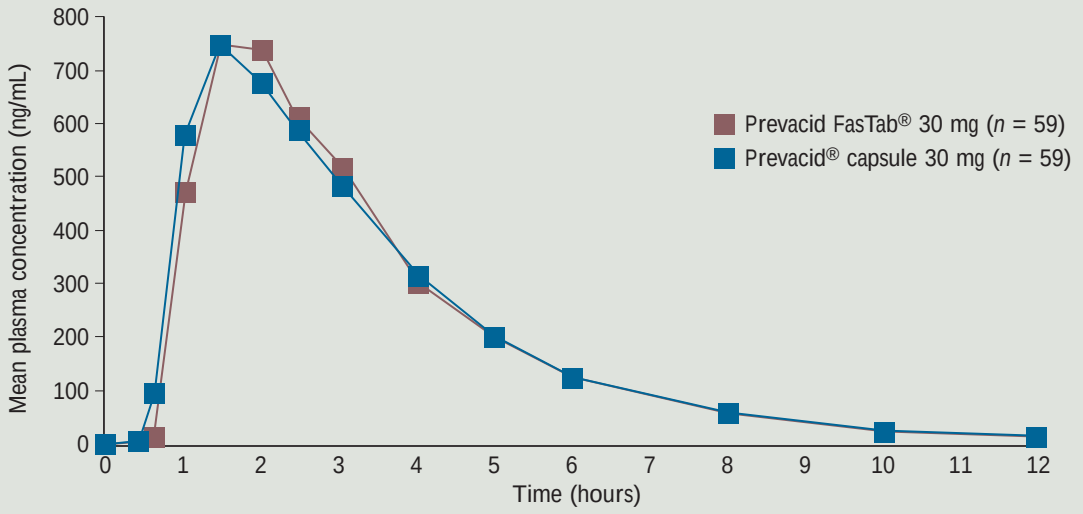
LANSOPRAZOLE ORALLY DISINTEGRATING TABLET: OVERVIEW

Before discussing the particular characteristics of the orally disintegrating lansoprazole tablet, the panel briefly reviewed the efficacy and safety records of the compound itself.

Evidence with lansoprazole capsules. In clinical trials, lansoprazole has demonstrated a rapid onset of action. Oral administration of lansoprazole capsules results in an increase of gastric pH to greater than 4 within 130 minutes.[7] This rapid onset of action has important clinical implications. In a comparative trial versus omeprazole in erosive esophagitis, lansoprazole-treated patients were significantly less likely to experience daytime heartburn on the first day of therapy.[8]

In placebo- or active-controlled, randomized studies, lansoprazole has proven to be effective in treating a number of different conditions, including GERD,[9] gastric ulcers,[10] duodenal ulcers,[11] functional dyspepsia,[12] reflux symptoms and esophagitis associated with Barrett's esophagus,[13] NSAID-associated GU[14] and Zollinger-Ellison Syndrome.[15]

FIGURE 1 Bioequivalence of Lansoprazole Oral Capsule and Orally Disintegrating Tablet



Adapted from Freston JW et al. *Aliment Pharmacol Ther* 2003;17:361-7.

In pediatric populations, lansoprazole has also been proven effective for GERD in children[16,17] and adolescents.[18,19] The flavoured oral suspension of lansoprazole has also been associated with enhanced tolerability in children.[20] The suspension is not, however, available in Canada.

In addition to its rapid onset of action and effectiveness in treating various conditions in various populations, lansoprazole's beneficial effects have also been shown in maintenance therapy. Among patients who had been healed of erosive esophagitis, 79% of those treated with maintenance lansoprazole (15 mg) remained healed over one year, compared to only 24% of those in the placebo group.[21] Lansoprazole has also been shown to be effective in maintenance treatment of healed NSAID-related ulcers.[22]

Clinical characteristics. The actual dissolution time of the oral disintegrating tablet is usually less than 60 seconds.[1] The tablet itself is strawberry flavoured, which may enhance its acceptability.[20] The tablet dissolves in the mouth, releasing easy-to-swallow microgranules. Prevacid FasTab® can be used without water, and should not be swallowed or chewed.

Comparative pharmacokinetics/pharmacodynamics. Given that the majority of the efficacy and safety data accumulated has been with the oral-capsule formulation, it was essential that the orally disintegrating tablet demonstrate bioequivalence to the oral capsule.

In an open-label, crossover study of 120 healthy subjects, lansoprazole administered as the orally disintegrating tablet was bioequivalent to the intact capsule formulation with respect to Cmax, AUCt and AUCinfinity (Figure 1).[23] In addition, direct oral administration of the orally disintegrating tablet has been compared to dissolution of that tablet in water. These two methods were also shown to be bioequivalent.[24]

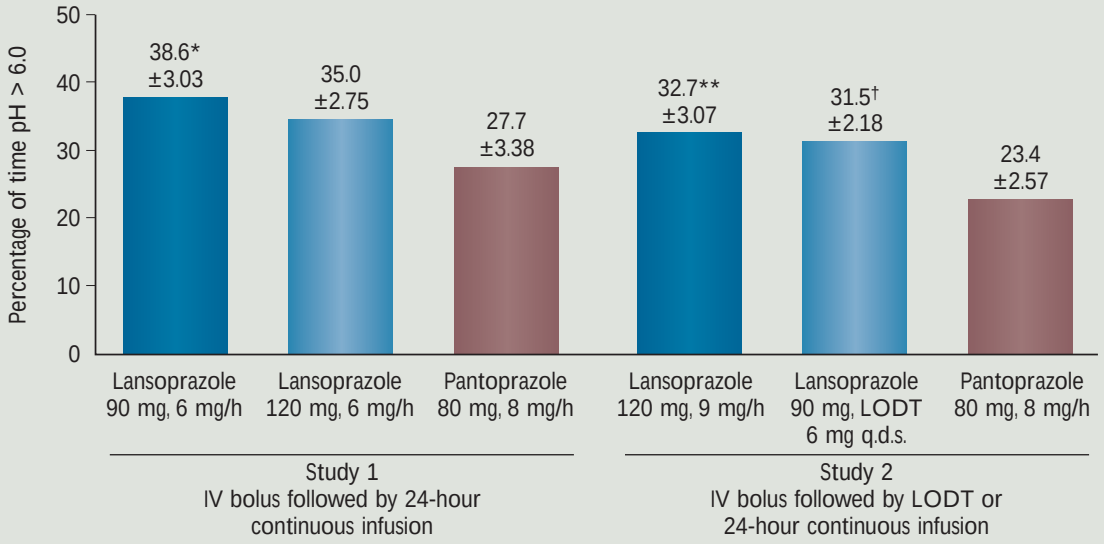
Clinical-trial evidence. A recent publication reported the results of two crossover trials comparing various regimens of lansoprazole orally disintegrating tablet and i.v. lansoprazole vs. i.v. pantoprazole.[25] The primary goal of treatment was sustaining intragastric pH greater than 6.0.

The investigators of this relatively small project found that while all the regimens resulted in robust gastric acid suppression, lansoprazole regimens (including the orally disintegrating tablet) were superior to the pantoprazole regimens over the study period (Figure 2).[25]

ORALLY DISINTEGRATING TABLET: PLACE IN THERAPY AND BENEFITS OF USE

The lansoprazole orally disintegrating tablet is a useful addition to the available PPI formulations. It is the same effective, fast-acting drug that is

FIGURE 2 Equivalent Efficacy of Orally Disintegrated Lansoprazole, i.v. Lansoprazole and i.v. Pantoprazole



*Lansoprazole 90 mg, 6 mg/h vs. pantoprazole 80 mg, 8 mg/h (p = 0.009)
**Lansoprazole 120 mg, 9 mg/h vs. pantoprazole 80 mg, 8 mg/h (p = 0.002)
†Lansoprazole 90 mg, LODT 60 mg q.d.s. vs. pantoprazole 80 mg, 8 mg/h (p = 0.013)

Adapted from Metz DC et al: *Aliment Pharmacol Ther* 2006; 23(7):985-95.

already in widespread use in capsule form, but features an alternative convenient method of administration that may lead to greater therapeutic compliance. The orally disintegrating tablets cost the same as lansoprazole capsules.[26]

Lansoprazole orally disintegrating tablets will be of value for patients with dysphagia and those who receive their medication via a gastric or enteral tube (detailed below and in Figure 3). Although approved for use in young children, it should be used in the form of a suspension for those younger than five years.

While the orally disintegrating tablet is indicated for the treatment of GERD in children 1 to 17 years of age, the data in children under the age of five years are few, as are the indications for use in that age group. One should therefore consider consultation with a specialist in pediatric gastroenterology before using a PPI in young children.

The orally disintegrating tablet will be a valuable option for adult patients with DU, GU, reflux esophagitis (including those with Barrett's esophagus and those for whom histamine H_2-receptor antagonists are not currently effective), as well as patients who require healing of NSAID-induced GU, to reduce the risk of NSAID-induced GU, those with symptomatic GERD, and those with *H. Pylori*. Zollinger-Ellison Syndrome is also treatable with the orally disintegrating lansoprazole tablet.

Which patients will benefit most from the lansoprazole orally disintegrating tablet and why?

The key benefit that patients will derive from using this formulation (beyond the efficacy in symptom reduction associated with the compound itself) is greater ease of use.

In the general practice setting, the new formulation will be used for all of its above-listed indications, and will likely, as well, be of benefit to patients with dysphagia. This will be important to older patients, as an estimated 15% to 40% of people aged 60 years and older have some problems with swallowing.[27] Patients without swallowing difficulties, but who demonstrate a reluctance to take pills, may be more willing to use the orally disintegrating tablet. This unique formulation has been shown to be preferred over traditional formulations.[28] The blister-type packaging of 30 individual tablets, which can be easily carried, also offers convenience for people "on the go."

Children, both in subspecialist practice and in a hospital setting, are a group for whom orally disintegrating lansoprazole tablets can provide attractive benefits. This formulation is easier for caregivers to administer and, due to the strawberry taste of the agent, may be generally

acceptable to younger children if given in a liquid suspension.[20]

Cancer patients and palliative-care patients who may have swallowing difficulties, due to mucositis or strictures, may find the orally disintegrating lansoprazole to be a useful alternative to taking medication by using a feeding tube.

In a hospital setting, there are other patients suited for orally disintegrating tablets, including: patients with upper GI bleeds who are hemodynamically stable and not vomiting. Lansoprazole orally disintegrating tablets may be a less expensive and easier to use alternative to intravenous preparations. Future research with the orally disintegrating tablet should be conducted to assess its role in acutely bleeding patients, pre- and post-op patients; transplant patients; and patients in need of ICU prophylaxis.

A further benefit to all patients is that minimal drug-drug interactions have been reported with lansoprazole capsules.[29] The bioequivalence of the orally disintegrating lansoprazole tablet indicates that it should offer the same safety profile, and the drug may be given concomitantly with antacids.[1]

The long-term safety data for lansoprazole also demonstrate that the drug is well tolerated.[13] In the pediatric population, safety and effectiveness in treating pediatric GERD with the original capsule formulation has been established in the short term (up to 12 weeks).[18]

What are the benefits of the lansoprazole orally disintegrating tablet for health-care professionals? For the general practitioner, this agent in this formulation has a wide range of indications, and offers ease of use for the prescriber and user. Given comparable efficacy and safety data among PPIs, the selection of a PPI should be based on current indications and patient choice.

The literature suggests patient preference for the orally disintegrating formulation of lansoprazole,[28] and this may translate into improved compliance, possibly resulting in improved outcomes.

As with general practitioners, gastroenterologists will find this formulation to be especially useful in a variety of patients.

The prevalence of patients with dysphagia (neurological, motility-related or obstructive) is higher in hospitals and long-term care facilities than in the community. The orally disintegrating tablet should be a valuable addition to hospital formularies as a more convenient way to administer PPI therapy. Previous PPI treatment in this patient group may have required either i.v. therapy or other formulations that require additional preparation time.

As an alternative to the preparation of the currently available PPI suspensions, the orally disintegrating tablet may save time for hospital staff (*i.e.,* nurses, pharmacists). If a PPI solution is required, such a preparation with orally disintegrating lansoprazole is accomplished efficiently and with potential cost savings.

An additional benefit for pharmacists is that the orally disintegrating tablet comes in easily-stored blister packs, facilitating dispensing in community and hospital settings.

What are the benefits of lansoprazole orally disintegrating tablets for the health-care system? Benefits to the health-care system should result in part from patient preference, possibly leading to improved compliance. Greater adherence may result in improved outcomes and a reduction in demand on health-care resources, including:

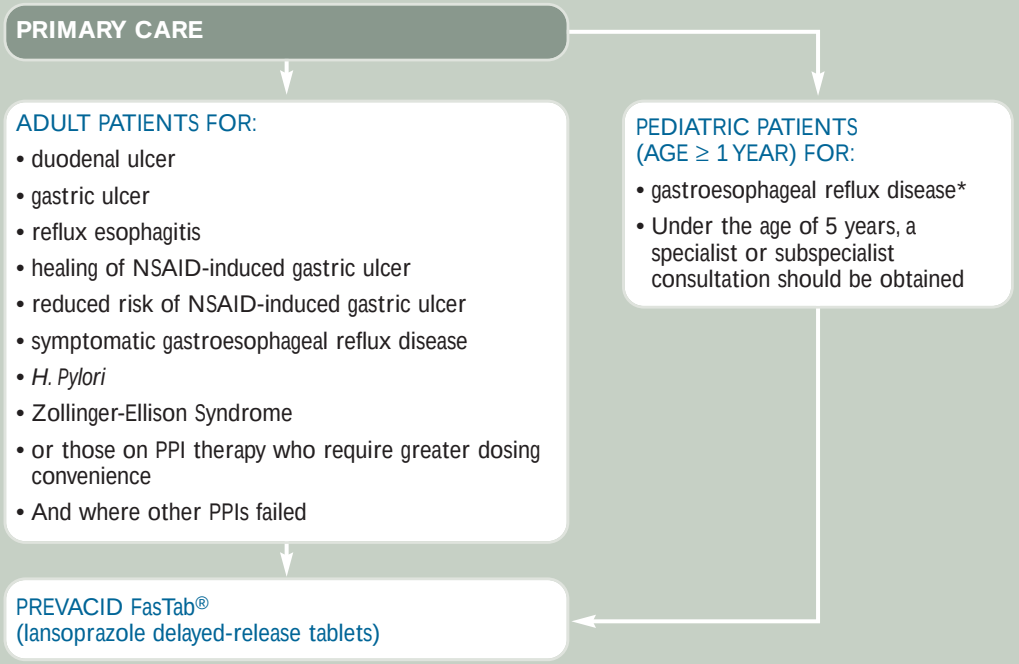
- greater availability of nursing time due to savings in medication preparation and administration time;
- cost savings related to staffing and administration of drug.
- less inappropriate use of intravenous therapy; and
- fewer hospitalizations for NSAID-related GI bleeds.

CONCLUSION

The lansoprazole orally disintegrating tablet is a useful addition to the currently available PPI formulations. The key benefits of the new formulation are:

- efficacy, convenience and ease of use;
- patient preference for this formulation (may improve compliance);
- ease of administration in the pediatric population (age ≥ 1). Under the age of 5 years, a specialist or subspecialist consultation should be obtained;
- a wide range of indications;

FIGURE 3 Prevacid FasTab® in the Primary Care Setting



* Specific recommendations for pediatric patients are to be presented in a separate document. For pediatric patients in whom therapy with Prevacid FasTab® is thought to be an option, consider referral to a specialist in pediatric gastroenterology.

FIGURE 4 Prevacid FasTab® in the Specialist Setting

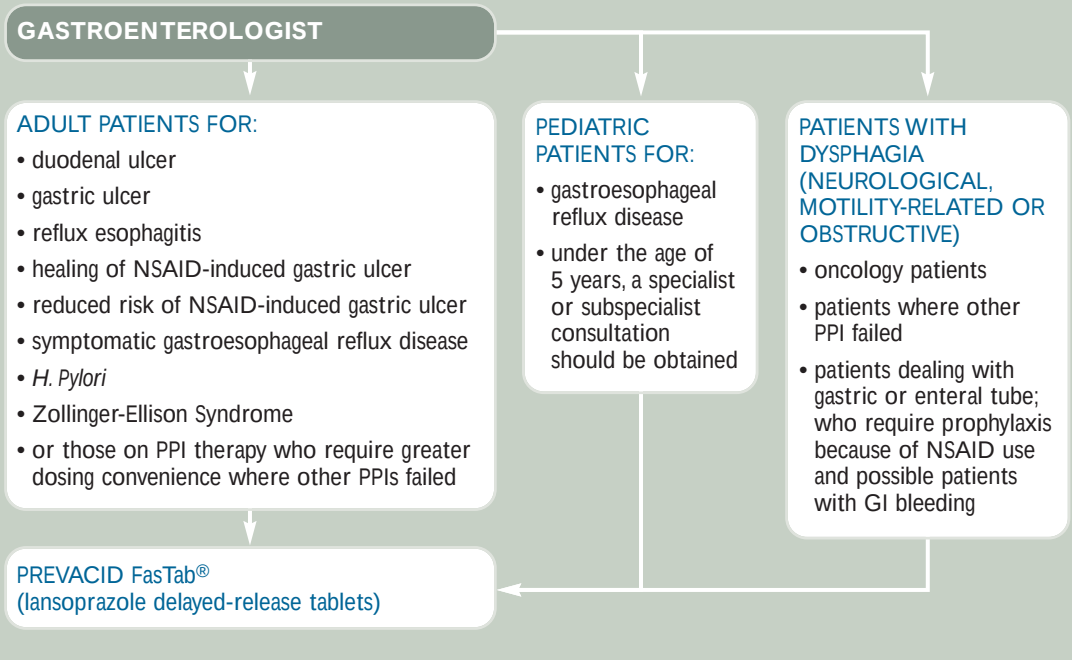
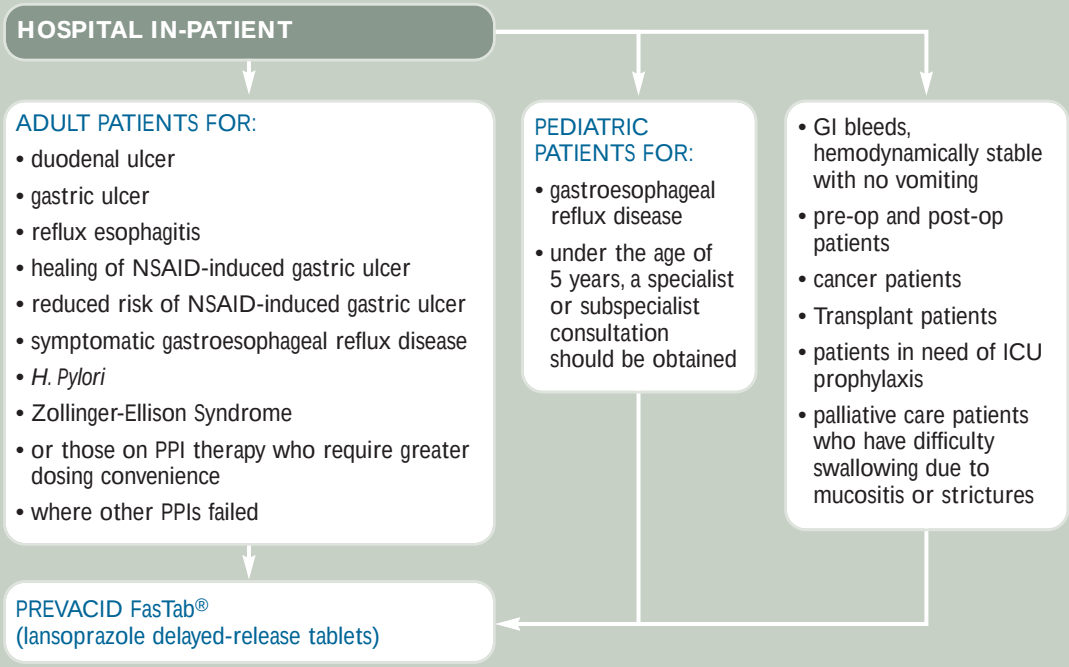


FIGURE 5 Prevacid FasTab® in the Hospital Setting



- a wide range of uses, including use in children, adolescents, the elderly, critical-care patients, patients with dysphagia and more;
- safety;
- drug interactions occur rarely; and
- cost savings.

A graphic rendition of the recommended patients in whom to use lansoprazole orally disintegrating tablets is available. Please see figures 3, 4 and 5.

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