HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

16 SEPTEMBER 2020

The legally binding text is the original French opinion version

pantoprazole

EUPANTOL 20 mg gastro-resistant tablets
EUPANTOL 40 mg gastro-resistant tablets
EUPANTOL 40 mg powder for solution for injection (IV)
INIPOMP 20 mg gastro-resistant tablets
INIPOMP 40 mg gastro-resistant tablets
INIPOMP 40 mg powder for solution for injection (IV)

Reevaluation

Key points

Favourable opinion for maintenance of reimbursement in the MA indications.

Role in the care pathway?

PPIs retain a major role in the treatment of gastroduodenal ulcers and gastro-oesophageal reflux disease (GOR):

In the treatment of gastroduodenal ulcers (GDU)

The Committee reiterates that a diagnosis of gastroduodenal ulcer must be confirmed endoscopically and the treatment depends on the presence or otherwise of *H pylori* infection.

In GDU without *H pylori* infection, the prescription duration must comply with the MA dosages, i.e., 4 to 8 weeks, with the exception of certain rare and serious gastric ulcers that may require longer treatment durations.

In GDU with *H pylori* infection, the prescription duration must comply with the current guidelines and revision of MAs that do not comply with these guidelines appears to be justified.

Clinical situations warranting long-term treatment are rare in the case of GDU: idiopathic forms, failure to eradicate *H. pylori*, Zollinger-Ellison syndrome, long-term treatment with NSAIDs in patients at risk of upper gastrointestinal complications.

GDU without *HELICOBACTER PYLORI* infection

In the event of a duodenal ulcer, initial treatment is based on antisecretory therapy (PPI or anti-H2), prescribed at full doses for a period of 4 weeks. Long-term treatment reduces the frequency of relapses, bleeding complications and perforations.

In the event of a gastric ulcer, the initial treatment duration of 4 to 8 weeks can be prolonged if there are factors delaying healing, such as the ulcer size.

GDU associated with *HELICOBACTER PYLORI* infection

H. pylori infection must be demonstrated before any eradication treatment is initiated.

PPIs remain first-line medicinal products. The recommended treatment combines antibiotic therapy with a PPI. The choice of antibiotic depends on the performance of an antibiogram on the gastric biopsy cultures. Eradication of *H. pylori* must be checked after each treatment line, at least 4 weeks after the discontinuation of antibiotic therapy and at least 2 weeks after the discontinuation of PPI therapy. The treatment algorithm in adults includes two possible scenarios, depending on whether or not an antibiotic susceptibility study is available (see 2017 guidelines in force). H2 receptor antagonists are recommended if PPI treatment has failed.

In pregnant or breastfeeding women, PPI treatment must be delayed, since treatment is not an emergency.

Prevention and treatment of upper gastrointestinal lesions induced by NSAIDs, including gastroduodenal ulcers

◗ **Treatment of lesions induced by NSAIDs**: in patients with upper gastrointestinal lesions induced by NSAIDs in whom continued treatment is justified, full-dose PPI treatment is recommended for 4 to 8 weeks (except esomeprazole, at half doses).

◗ **Prevention of lesions induced by NSAIDs**

The routine prescription of a PPI in combination with NSAIDs is only justified, in accordance with the MA, in the following at-risk situations:

- age 65 years or over;
- history of gastric or duodenal ulcer. In this case, it is necessary to investigate for and treat any H. pylori infection;
- combination with an antiplatelet drug (in particular, low-dose aspirin and clopidogrel) and/or a corticosteroid and/or an anticoagulant (reiterating, however, that these combinations should, in principle, be avoided).

In these high-risk patients and for whom NSAID treatment is necessary, PPIs are still the first-line preventive treatment. They are prescribed at half doses (except omeprazole, at full doses).

New data do not call into question this strategy restricting routine co-prescription of PPIs with NSAIDs to these at-risk patients only.

Preventive PPI therapy should be discontinued at the same time as NSAID treatment.

Case of <u>off-label</u> USE in cardiology in adults to prevent upper gastrointestinal complications of antiplatelet drugs and oral anticoagulants

The use of PPIs is an off-label use in these situations. The results of a recent controlled, randomised study (COMPASS safety study in 17,000 patients) determined that there is no benefit of routine use of PPIs in patients at low risk of gastrointestinal complications (no history of gastroduodenal ulcers, gastrointestinal bleeding and/or perforations, etc.).

In patients at high risk of complications, according to expert opinion and based on the literature review carried out, a preventive effect seems likely, remembering that their use is currently off-label.

In sum, the Committee considers that this use is not justified in low-risk patients. In patients at high risk of gastrointestinal complications (history of GDU, gastrointestinal bleeding and/or perforations), **additional data are required given that a benefit appears likely.**

Zollinger-Ellison syndrome

PPIs remain the first-line treatment. The IV route is envisaged when the oral route is impossible.

Prevention and treatment of ulcer-associated upper gastrointestinal bleeding (INEXIUM solution for injection only)

INEXIUM for injection is the only PPI indicated in adults for the prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. A recent consensus group recommends that patients with bleeding ulcers with high-risk signs who have undergone successful endoscopic treatment should receive high-dose PPI treatment (intravenous loading dose followed by continuous infusion) for 3 days. In these high-risk patients, continuous oral PPI treatment taken twice daily for 14 days, then once daily for a duration that depends on the nature of the bleeding lesion, is suggested.

In the symptomatic treatment of GOR

Treatment is based on the implementation of lifestyle and dietary measures and, if these are inadequate, medicinal treatment with an antacid, alginate, anti-H2 or PPI.

The Committee highlights the fact that patients with GOR without clinical symptoms or oesophageal lesions do not require medical treatment. Prescription of a PPI should only be considered in the presence of symptoms suggestive of GOR (pyrosis, post-prandial gastric burning, acid regurgitation), and in addition to lifestyle and dietary measures, for a maximum initial period of 4 weeks.

The benefit of continued treatment must then be systematically reviewed after 4 weeks of treatment based on relief of the patient, the persistence of GOR symptoms, the adverse effects reported and the results of upper gastrointestinal endoscopy.

The benefit of continuing the prescription beyond 4 weeks must be reviewed on a case-by-case basis, in consultation with patients, and taking into account risks related to polymedication, interactions with other medicines, and uncertainties relating to the long-term safety and efficacy. The Transparency Committee reiterates that, in the event of long-term use, the main important risk determined with a good level of evidence (see COMPASS study results) is the development of gastrointestinal infections. Observational studies have suggested a possible link between long-term use of PPIs and excess mortality and/or several serious risks (excess mortality, cardiovascular effect, dementia, rebound effect, cancer, in particular) but the causal relationship has not been determined. The extensive use of PPIs - in accordance with the MA or off-label - poses the problem of the risk of adverse effects, particularly in elderly, often fragile patients, in a context of multiple conditions and polymedication, or in the event of long-term treatments. Information to promote good practice with this medicinal product is provided in a good practice guide.

Finally, the Committee reiterates that the only clinical situations justifying long-term treatment are: GOR with Los Angeles grade C or D oesophagitis, Barrett's oesophagus, documented non-erosive GOR responding to PPIs.

PPIs are not recommended to relieve isolated extra-gastrointestinal signs that may be related to GOR, such as ENT symptoms, chronic cough, asthma or non-cardiac chest pain. There is no benefit of prescribing them in these situations, except in the event of documented GOR, but not as a test treatment or therapeutic test.

Current marketing authorisations differentiate between PPI doses depending on the presence or otherwise of oesophagitis. However, in routine practice and in incident patients, endoscopy is not systematically justified or performed. Hence, and if endoscopy cannot be rapidly performed, the Committee recommends initiating full-dose PPI treatment for a maximum duration of 4 weeks. Then, if continued treatment is warranted, the minimum effective dose (generally a half dose) should be sought, and administered for as short a time as possible.

Other situations

◗ **Case of PPI use in children:**

The efficacy and safety data are not very abundant and are of poor methodological quality.

No PPIs have an MA in children under the age of 1 year and weighing under 10 kg. Beyond the age of 1 year:

- omeprazole (MOPRAL and ZOLTUM 10 mg capsules, identical to the adult form) and esomeprazole (INEXIUM granules in 10 mg sachets, specifically for children and patients with swallowing difficulties) are indicated in children from the age of 1 year in erosive oesophagitis.

- esomeprazole is also indicated in symptomatic GOR from the age of 1 year.

- omeprazole (MOPRAL and ZOLTUM 10 and 20 mg capsules), esomeprazole (INEXIUM 10, 20 and 40 mg) and pantoprazole (EUPANTOL and INIPOMP 20 mg) are indicated in erosive reflux oesophagitis (healing treatment and prevention of relapses), from the age of 11-12 years.

Esomeprazole (INEXIUM 10 and 20 mg) is the only PPI indicated in the maintenance treatment of GOR-associated oesophagitis from the age of 12 years. Esomeprazole is also indicated in children over the age of 4 years in combination with antibiotics in the treatment of duodenal ulcer caused by H. pylori infection.

Their role in the care pathway is currently as follows:

- **in duodenal ulcers caused by H *pylori* infection:**

  o no good-quality data have been found. But the expected efficacy is the same as that observed in adults.

  o It is a first-line treatment that must be prescribed in accordance with current guidelines, as in adults. They are recommended as a first-line treatment in children over the age of 4 years and adolescents in combination with an antibiotic.

- **in the symptomatic treatment of GOR:**

  o their prescription in babies from the age of 1 year and young children is only beneficial if the GOR is complicated and, in particular, combined with oesophagitis. In the event of physiological GOR (with regurgitation), PPIs have no demonstrated efficacy. In the event of recurrent vomiting, it is necessary to investigate the cause.

Special recommendations

In response to the French Department of Social Security referral, available in the annex to the reevaluation report, and considering the confirmed and major role of PPIs in the care pathway for gastroduodenal ulcers and GOR, in both adults and children, with an efficacy/adverse effects ratio that remains high, and despite the identified off-label uses**, the Committee does not favour restricting the reimbursement duration of PPIs.**

The use data in France indicate that PPIs may be used excessively. The study conducted by the CNAMTS (National health insurance fund for salaried workers) in 2015 confirmed the observations already made in 2009. PPIs are not always prescribed in accordance with their MA indications, in particular for the prevention of gastroduodenal lesions due to NSAIDs in patients not considered to be at risk, as well as in patients receiving long-term antiplatelet or anticoagulant therapy for a cardiovascular or neurovascular event.

Any long-term prescription of a PPI must be the subject of regular reevaluation of its benefit (efficacy, quality of life, investigation for adverse effects and interactions with other medicinal products).

The Committee therefore encourages the promotion of broad good practice initiatives among health professionals and patients before considering delisting measures, particularly since some PPIs are available over-the-counter. The Committee proposes that the good practice guide for these medicinal products be updated and circulated and that its impact be boosted by working in collaboration with healthcare professionals and patients. The objective is to evolve practices, in particular to tackle the misuse that has been once more observed with this medicinal products for the prevention of gastroduodenal lesions due to NSAIDs in patients who are not at risk (unjustified off-label use), to reiterate the need to comply with the use durations for these medicinal products, particularly in the event of GOR and to reduce their long-term use when this is medically unjustified, particularly in the oldest patients at iatrogenic risk due to polymedication, and in young patients in whom the situations justifying their prescription should be rare.

The Committee draws the attention of the authorities in charge of marketing authorisations (ANSM) and MA holder pharmaceutical companies to the fact that the current MA dosages of PPIs in the event of gastroduodenal ulcer with H. pylori do not comply with the 2017 guidelines in force (treatment duration and choice of combinations). A revision of MAs therefore appears to be necessary and will be requested by the HAS.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Gastro-oesophageal reflux disease, gastroduodenal ulcers and Zollinger-Ellison syndrome can cause a sometimes marked deterioration in quality of life.

◗ These medicinal products are:
- part of a curative treatment regimen for erosive oesophagitis associated with gastro-oesophageal reflux disease and eradication of *Helicobacter pylori* to heal duodenal ulcers, and for Zollinger-Ellison syndrome,
- part of a preventive treatment regime, in the maintenance treatment of reflux-associated oesophagitis and gastroduodenal ulcer relapse,
- part of a symptomatic treatment regimen in the treatment of gastro-oesophageal reflux disease, associated or otherwise with oesophagitis.

◗ The efficacy/adverse effects ratio remains high.

◗ PPIs remain a first-line treatment in the context of the MA indications and dosages.

◗ There are medicinal alternatives, in particular other PPIs.

Public health impact

Considering:
- the seriousness and prevalence of gastro-oesophageal reflux disease, gastroduodenal ulcers and Zollinger-Ellison syndrome,
- the medical need partially met by PPIs,
- the response provided by this PPI, like other PPIs, to the needs identified in the treatment of gastroduodenal ulcers and Zollinger-Ellison syndrome and the expected improvement in patients' quality of life in the event of symptomatic gastro-oesophageal reflux,
- the current uncertainties with respect to the safety profile of PPIs in the event of long-term treatment,
- and due to misuse identified as being widespread,

on the basis of currently available data, the proprietary medicinal products INIPOMP and EUPANTOL, like other PPIs, are not likely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of INIPOMP and EUPANTOL remains substantial in the MA indications.

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list and/or the retail formulary list of reimbursed proprietary medicinal products approved for use in the MA indications and dosages.