HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 September 2011

GAVISCON PEPPERMINT, chewable tablet
B/20 (CIP code: 367 909-6)

GAVISCON, oral suspension
250 ml bottle (CIP code: 322 850-2)

GAVISCON, oral suspension
B/24 sachets (CIP code: 330 952-5)

GAVISCON INFANT, oral suspension in a bottle
150 ml bottle (CIP code: 337 536-7)

Applicant: RECKITT BENCKISER HEALTHCARE FRANCE

sodium alginate
sodium bicarbonate

Date of Marketing Authorisation:

- GAVISCON PEPPERMINT, tablet: 18 April 2005
- GAVISCON, oral suspension in a bottle: 19 June 1979
- GAVISCON, oral suspension in a sachet: 6 May 1988
- GAVISCON INFANT, oral suspension in a bottle: 5 September 1994

Reason for request: Renewal of inclusion in the list of medicines refundable by National Health Insurance.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

GAVISCON, oral suspension in a sachet or in a bottle
Sodium alginate 500 mg
Sodium bicarbonate 267 mg
For 10 ml

GAVISCON Peppermint, chewable tablet
Sodium alginate 500 mg
Sodium bicarbonate 267 mg
Calcium carbonate 160 mg

GAVISCON Infant, oral suspension in a bottle
Sodium alginate 500 mg
Sodium bicarbonate 26.7 mg
Per ml

1.2. Indications

GAVISCON PEPPERMINT:
"Treatment of the symptoms of gastro-oesophageal reflux, such as acid regurgitation, pyrosis and impaired digestion (due to the reflux) like, for example, after meals or during pregnancy, or in cases of oesophagitis."

GAVISCON, oral suspension and GAVISCON INFANT:
"Symptomatic treatment of gastro-oesophageal reflux. "

1.3. Dosage

Cf. SPC

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

A	Alimentary tract and metabolism
A02	Antacids, drugs for peptic ulcer and antiflatulents
A02BX	Other drugs for peptic ulcer and gastro-oesophageal reflux
A02BX13	Alginic acid

2.2. Medicines in the same therapeutic category

- SODIUM ALGINATE/BIOGARAN SODIUM BICARBONATE, oral suspension, 250 ml bottle
- SODIUM ALGINATE/EG SODIUM BICARBONATE, oral suspension, 250 ml bottle
- SODIUM ALGINATE/SANDOZ SODIUM BICARBONATE, oral suspension, 250 ml bottle
- SODIUM ALGINATE/TEVA SODIUM BICARBONATE, oral suspension, 250 ml bottle
- TOPAAL (alginic acid, aluminium hydroxide, magnesium hydrocarbonate, silica), oral suspension, 210 ml bottle

These proprietary medicinal products offer a low actual benefit (AB).

2.3. Medicines with a similar therapeutic aim

These are the other medicinal products used in the treatment of the symptoms of gastro-oesophageal reflux:

- **Antacids**
- GELOX (monmectite, aluminium hydroxide and magnesium hydroxide)
- GASTROPULGITE (activated Attapulgite Mormoiron, aluminium hydroxide magnesium carbonate co-dried gel)
- MOXYDAR (hydrated aluminium oxide, magnesium hydroxide, aluminium phosphate, guar gum coated)
- PHOSPHALUGEL (aluminium phosphate)
- ROCGEL (hydrated aluminium oxide).

These proprietary medicinal products have a low actual benefit (actual benefit).

Also indicated in the symptomatic treatment of regurgitation in infants: GELOPECTOSE (pectin, cellulose, colloidal silica), non-refundable product.

- **H2-receptor antagonists**
- TAGAMET (cimetidine) 200 mg, film-coated tablet and effervescent tablet and its generics
- RANIPLEX and AZANTAC (ranitidine) 75 mg, film-coated tablet and effervescent tablet and its generics
- PEPDINE (famotidine) 20 mg, film-coated tablet and its generics

These proprietary medicinal products have a low actual benefit (AB).

- **Proton-pump inhibitors**
- EUPANTOL 20 mg, gastro-resistant tablet
- EUPANTOL 40 mg, gastro-resistant coated tablet
- INEXIUM 10 mg, gastro-resistant granules for oral suspension
- INEXIUM 20 mg, gastro-resistant tablet
- INEXIUM 40 mg, gastro-resistant tablet
- INIPOMP 20 mg, gastro-resistant tablet
- INIPOMP 40 mg, gastro-resistant coated tablet
- LANZOR 15 mg, gastro-resistant hard capsule
- LANZOR 30 mg, gastro-resistant hard capsule
- MOPRAL 10 mg, gastro-resistant microgranule in hard capsule
- MOPRAL 20 mg, gastro-resistant microgranule in hard capsule
- OGAST 15 mg, gastro-resistant hard capsule
- OGAST 30 mg, gastro-resistant hard capsule
- OGASTORO 15 mg, orodispersible tablet
- OGASTORO 30 mg, orodispersible tablet
- PARIET 10 mg, gastro-resistant tablet
- PARIET 20 mg, gastro-resistant tablet
- ZOLTUM 10 mg, gastro-resistant microgranule in hard capsule
- ZOLTUM 20 mg, gastro-resistant microgranule in hard capsule

and their generics.

These proprietary medicinal products have a substantial actual benefit (AB).

3. REMINDER OF THE PREVIOUS TRANSPARENCY COMMITTEE OPINION

Reminder of the opinion of 18 April 2007 (renewal of inclusion):

The actual benefit of the proprietary medicinal product GAVISCON INFANT, oral suspension remains substantial in the MA indication.

Reminder of the opinion of 13 May 2009 (reassessment of the actual benefit (AB) – this opinion did not concern GAVISCON INFANT):

The actual benefit (AB) of these proprietary medicinal products is low in the MA indications.

4. UPDATE ON THE DATA AVAILABLE SINCE THE PREVIOUS OPINION

4.1. Efficacy

The applicant has provided a new study (Study 2010-019563-11).

Study objective and schedule: This is a randomised, double-blind, double-placebo controlled study comparing GAVISCON oral suspension with omeprazole 20 mg in patients with untreated gastro-oesophageal reflux (GOR). The objective of the study was to demonstrate the non-inferiority of GAVISCON oral suspension in comparison with omeprazole 20 mg in terms of the time required to obtain a period of 24 consecutive hours without pyrosis. It should be noted that the efficacy of PPI in GOR is not immediate and requires treatment for 4 weeks. In this study, because of its treatment schedule, the effect of omeprazole could have been underestimated.

The non-inferiority hypothesis was validated if the difference in the time required to obtain relief over 24 consecutive hours without pyrosis between GAVISCON and omeprazole 20 mg did not exceed half a day. For an α risk of 5% and a β risk of 95%, the number of subjects needed was 88 per group.

The study was carried out in patients followed up in primary care practices.

GAVISCON oral suspension had to be administered at a daily dosage of 10 ml four times a day after the three main meals and in the evening at bedtime. Omeprazole 20 mg gastro-resistant microgranules had to be administered orally at the daily dosage of 20 mg in the morning. These treatments were administered for a maximum period of 14 days.

Inclusion criteria: men and women aged from 18 to 60 years, having between two and six GOR episodes per week with pyrosis, with or without regurgitation, untreated for at least two months with an alginate/antacid combination or with a proton-pump inhibitor (PPI).

Non-inclusion criteria, in particular:
- patients having primarily atypical symptoms, whether digestive or extra-digestive,
- being followed up for a stomach or duodenal ulcer,
- having had an operation on the upper digestive tract,
- suffering from a neoplastic disease of the upper digestive tract or ENT.

The primary efficacy endpoint was the average time taken to obtain a pyrosis-free period of 24 consecutive hours, as assessed by the doctor on D7 with the aid of the patient.

This average period was determined from the time elapsed between the first dose and the date on which pyrosis-free relief lasting 24 consecutive hours was obtained, based on the self-questionnaire completed by the patient from D1 to D7. This is not the criterion normally used, which is 4-week relief from pyrosis. The time allowed for collating data on the assessment criterion (7 days) is therefore too short.

Results:

A total of 278 patients were included. Two non-assessable patients were excluded from the analysis. Among the included patients, 135 patients received GAVISCON and 141 were treated with omeprazole.
The average time for a 24-hour pyrosis-free period to appear was, for the patients with a pyrosis-free period of at least 24 hours on D7: 1.4 ± 1.5 days in the GAVISCON group as against 1.4 ± 1.6 days in the omeprazole group (ANOVA, p = 0.97).

4.2. Adverse effects

The overall incidence of adverse events was comparable between the groups: 12.6% in the GAVISCON group versus 14.2% in the omeprazole group (p = 0.70).

The adverse events are presented in Table 1.

Table 1 Overall incidence of adverse events (> 0.5%)

	GAVISCON N = 135 (%)	**Omeprazole N = 141 (%)**	**Total N = 276 (%)**	***p***
Patients with at least one AE	17 (12.6)	20 (14.2)	37 (13.4)	0.70
D0 to D7	12 (9.1)	13 (9.2)	25 (9.2)	0.97
D7 to D14	7 (5.5)	8 (5.8)	15 (5.6)	0.91
Nausea	3 (2.2)	2 (1.4)	5 (1.8)	
Constipation	3 (2.2)	1 (0.7)	4 (1.5)	
Nasopharyngitis	2 (1.5)	2 (1.4)	4 (1.5)	
Meteorism	1 (0.7)	2 (1.4)	3 (1.1)	
Diarrhoea	1 (0.7)	1 (0.7)	2 (0.7)	
Abdominal pain	1 (0.7)	1 (0.7)	2 (0.7)	
Rhinitis	1 (0.7)	1 (0.7)	2 (0.7)	
Cough	0 (0.0)	2 (1.4)	2 (0.7)	

Conclusion

In a non-inferiority study that included 278 patients and comparing GAVISCON oral suspension with omeprazole 20 mg, the average time to the appearance of a 24-hour pyrosis-free period on D7, in patients with untreated gastro-oesophageal reflux (GOR) was 1.4 ± 1.5 days in the GAVISCON group and 1.4 ± 1.6 days in the omeprazole group (ANOVA, p = 0.97). The very short time (7 days) for collating data on the primary efficacy endpoint is insufficient either to consider the true effect of omeprazole, or to assess GAVISCON based on the usual criterion, namely relief from pyrosis at 4 weeks.

Caution needs to be exercised in interpreting the results of this study because:
- while the study may be presented as a non-inferiority study, the statistical analysis carried out is that of a superiority study,
- no reasoning is given for the choice of the value of the non-inferiority limit,
- the study does not have a third placebo arm, even though it would have been ethically acceptable.

The appearance of adverse events was comparable between the two groups and was unremarkable in nature.

5. DRUG USAGE DATA

According to the IMS data (cumulative rolling prescription volume to February 2011), these proprietary medicinal products were the subject of 1,775,000 prescriptions, especially for gastro-oesophageal reflux (48% of the prescriptions), gastritis and duodenitis (8.3%), diaphragmatic hernia (3.7%), and dyspepsia (2.1%). The average daily dosage was 2.7 tablets.

6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Reassessment of the actual benefit

- In adults

GOR is regarded as a disease when the episodes of pyrosis occur at least weekly. GOR can erode the quality of life and lead to oesophagitis, which exposes the sufferer to the risk of oesophageal stricture, gastric bleeding and Barrett's oesophagus.
Postural measures, stopping smoking, cutting out alcohol, a low-fat diet and weight loss may be proposed as a first step in managing the condition.
Antacids and alginates have a demonstrable but limited effect on the symptoms of GOR.[1]
The available data are insufficient to be able to quantify the efficacy of this otherwise well tolerated proprietary medicinal product. The efficacy/tolerance ratio of this product is therefore moderate in this indication.

GAVISCON proprietary medicinal products fall into the category of symptomatic treatment.

There are alternatives to these proprietary medicinal products: antacids, H2-antagonists and finally PPIs, especially effective for the symptomatic treatment of GOR if the symptoms are typical and close together in time.

The actual benefit (AB) of these proprietary medicinal products remains low.

- In infants

GOR symptoms are generally not serious, but untreated GOR can mean an erosion of the quality of life and complications: pharyngeal conditions, oesophagitis, peptic stricture, Barrett's oesophagus, and more rarely gastric bleeding.
Repercussions for the growth of the child, chronic respiratory or ENT manifestations and malaise may also be observed. Erosive oesophagitis or oesophagitis ulcerated by GOR is a rare and serious condition, especially when the children present a neurological condition or after surgery for oesophageal atresia.

This proprietary medicinal product is intended as a symptomatic treatment.

Even though there are few recent data confirming it, the efficacy/adverse effects ratio of this proprietary medicinal product is high in this indication.

This proprietary medicinal product is a first-line medicine for the symptomatic treatment of GOR in infants.

There are alternatives to this proprietary medicinal product.

The actual benefit of these proprietary medicinal products is substantial.

[1] Gastro-oesophageal reflux in adults: diagnosis and treatment. SNFGE consensus conferences, 1999

6.2. Therapeutic use

In adults, the treatment of GOR relies, first and foremost, on diet and lifestyle and on postural measures.

The first measure involves raising the head of the patient's bed by 10 to 15 cm.
Stopping smoking, giving up alcohol, a low-fat diet and losing weight may also be proposed.

If these measures are not enough, drug treatment may then be indicated.

In infants, the parents' reassurance and the introduction of lifestyle and dietary measures (division of meals to reduce their volume, giving them thickened formula in their feeding bottle) are generally enough in children up to 36 months. The outcome is most often favourable, with the symptoms being reduced or disappearing altogether when the child starts walking. Straightforward possetting (from 28 days to 18 months) does not justify treatment with PPIs.

Alginates and gastric antisecretory drugs have their place in the treatment of moderate and spread-out episodes of GOR.[2]

Alginates form a gel that floats on the surface of the stomach contents, effectively forming a physical barrier, reducing the number and average duration of the GOR episodes.
They should be taken after meals and possibly at bedtime.

Half-dose proton-pump inhibitors are indicated in the symptomatic treatment of gastroduodenal reflux and associated symptoms (pyrosis, gastric regurgitation, painful swallowing).
Closely-spaced typical symptoms (once a week or more), with no alarm features, require continuous treatment for about 4 weeks.
If the treatment is successful it should be stopped.

It was not shown that antacids+alginates are any more effective than antacids alone in treating the symptoms of gastro-oesophageal reflux (GOR). The most recent of the studies comparing alginates+antacids with antacids on their own dates back to 1980. These studies showed contrasting results, so that it is impossible to assert that alginates+antacids are superior to antacids alone.[3]

The Afssaps 2007 guidelines stipulate "that in cases of symptomatic treatment for GOR, when the rules on lifestyle and diet have not shown themselves to be effective, during the initial short-term treatment: if the symptoms are typical and spread out (less than once a week), it is recommended to use any fast-acting (Grade A) treatment as and when required.

- either an antacid,
- or an alginate,
- or an H2-antagonist (cimetidine 200-600 mg/day, ranitidine 75-225 mg/day, famotidine 10-20 mg), in one to three daily intakes.

PPIs are not recommended, because their effect is not immediate.
If the symptoms are typical and close together (once a week or more), it is recommended to prescribe a half-dose PPI (except for full-dose omeprazole) (Grade A) generally for 4 weeks. If that proves ineffective, an upper digestive tract endoscopy should be performed (Professional Agreement)[4]".

[2] spaced-out episodes: once or twice a week
[3] NICE (August 2004). Dyspepsia – management of dyspepsia in adults in primary care.
[4] AFSSAPS Good Practice Guidelines: Gastric antisecretory agents in adults; 2007

6.3. Transparency Committee recommendations

The transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services.

The transparency Committee would like to see data confirming the efficacy of GAVISCON in the treated paediatric population at the next renewal of inclusion.