HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 April 2011

METEOXANE, capsules
B/60 (CIP code: 306 693-3)

Applicant: IPRAD

Simethicone
Hydrated phloroglucinol

ATC code: A03AX (OTHER DRUGS FOR FUNCTIONAL BOWEL DISORDERS)

Date of Marketing Authorisation: Initial MA 11/10/1971 (validated on 15/04/1996), most recent modification of MA on 30/04/2003

Reason for request: Re-assessment of actual benefit in line with article R. 163-21 of the French Social Security Code.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

Simeticone
Hydrated phloroglucinol

1.2. Indication

"Secondary treatment of functional manifestations of intestinal disorders, particularly bloating and diarrhoea."

1.3. Dosage

See SmPC

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

A	Alimentary tract and metabolism
A03	drugs for functional gastrointestinal disorders
A03AA	drugs for functional bowel disorders
A03AX13	Silicones

2.2. Medicines in the same therapeutic category

Antispasmodics belonging to the musculotropic class are presented in APPENDIX 1.

2.3. Medicines with a similar therapeutic aim

Other medicines used in functional disorders of the digestive tract, in particular non-opioid analgesics.

3. REMINDER OF THE TRANSPARENCY COMMITTEE'S OPINIONS

Opinion dated 06 February 2008 (renewal of inclusion)

In the indication "FBD", the TC concluded:
"Considering the role of this product in the strategy of treatment, the Transparency Committee took the view that the current benefit provided by METEOXANE was low".

4. UPDATE ON DATA MADE AVAILABLE SINCE PREVIOUS OPINION

4.1 Efficacy

The applicant has provided a new placebo-controlled study (the IPR-MET-7 study). This was a comparative, randomised, double-blind trial investigating efficacy and tolerance in painful flare-ups of irritable bowel syndrome. In total, 413 patients were randomised into the study (201 in the METEOXANE arm and 212 in the placebo arm).

The primary efficacy endpoint was patient-evaluated abdominal pain from day 0 (first visit [V1]) to day 7 (-1 day, + 2 days) (second visit [V2]).

The criterion of judgement was relative reduction in pain intensity as reported by patients, noted on a visual analogue scale (VAS) at the inclusion visit (V1) and at the second visit V2. The primary efficacy endpoint was patient-reported relative reduction in pain intensity (expressed as ITT), noted on a VAS at V1 and V2.

Mean reduction in pain intensity observed between V1 and V2 was -31.5 ± 24.5 in the METEOXANE arm and -31.0 ± 26.4 in the placebo arm (NS). Mean reduction observed in relative reduction in pain intensity was therefore -50.6 ± 39.4% in the METEOXANE arm and -47.9 ± 41.6% in the placebo arm; this difference between the two arms was not statistically significant.
Overall, no difference was seen between METEOXANE and placebo in terms of relative reduction in pain intensity following treatment.

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4.2 Adverse effects

The tolerance profile was similar in the two arms. The overall incidence of adverse events was 3.2%: 3.5% in the METEOXANE arm versus 2.9% in the placebo arm (NS).
The most commonly observed adverse events were gastroenteritis and nausea, which only occurred in the METEOXANE arm with an incidence of 1.0%.
No serious adverse events occurred during the study.
The AFSSAPS Department of Pharmacovigilance has received no new data about the tolerance of this proprietary medicinal product in use. Some prescription errors, involving confusion between METEOXANE and METHOTREXATE (dispensing of METHOTREXATE when METEOXANE had been prescribed) have been reported. These reports have been taken up by the Drug Errors section of AFSSAPS.
The SmPC mentions the possibility of allergic reactions.

5. DRUG USAGE DATA

According to data from IMS (CMA August 2010), 1,113,000 prescriptions for METEOXANE were recorded.
The distribution of these prescriptions was as follows:

other intestinal diseases	14%
digestive tract symptoms	15%
infectious diseases of the intestines	22%
other	49%

6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of actual benefit

Functional bowel disorders (FBDs) are problems with transit disorder (diarrhoea, constipation or both) associated with abdominal pain and bloating (meteorism). Diagnosis of FBD is primarily a diagnosis of exclusion, which is suggested after ruling out underlying organic disease.
The primary objective of management of FBD is normalisation of transit disorder, mainly using lifestyle and dietary measures, and the reduction of pain.
These disorders are characterised by repeated flare-ups. Functional bowel disorders are not serious but can lead to a marked deterioration in quality of life.
These proprietary medicinal products are intended to provide symptomatic treatment.
The efficacy/tolerance ratio is low.
These proprietary medicinal products are first-line medicinal products, assuming that diet and lifestyle measures are being followed.
There are treatment alternatives: other antispasmodics.

Public Health Benefit: irritable bowel syndrome is a common condition that affects significantly quality of life but which does not meet the criteria for severity. It is a minor public health burden.

The available data show that these proprietary medicinal products have a low level of impact on reduction of symptoms, and do not show that they have an impact in terms of improvement of quality of life.
Although the availability of these proprietary medicinal products as part of a range of treatments could theoretically enable patients to avoid having to take other classes of treatment that involve more risks (such as antidepressants), it is not possible to state that this product has a public health benefit.

The actual benefit of these proprietary medicinal products is low.

6.2. Therapeutic use

Functional bowel disorders (FBDs) are defined using the current international criteria (Rome III)[9] as symptoms that have been present for more than six months and that occur on at least three days per month at quarterly assessment. The main presenting complaint is abdominal

pain, which is usually relieved by defecation. The second complaint is digestive disorders.[1] There have been successive consensus decisions about the diagnostic criteria for FBDs (the current criteria being Rome III[2]).

Diagnosis of FBD is primarily a diagnosis of exclusion that is suggested after ruling out underlying organic disease (mainly Crohn's disease and colon cancer).
The primary objective of management of FBD is normalisation of transit disorder and reduction of pain.

The strategy of treatment aims to relieve the primary symptom (constipation, diarrhoea or pain).

The treatment of FBDs is primarily based on lifestyle and dietary measures:

- avoiding foods that are likely to aggravate symptoms;
- taking regular physical exercise;
- if constipation is present, increasing the amount of fibre in the diet;[3,4]
- if diarrhoea is present, reducing intake of fibre, indigestible carbohydrates, fruit and caffeine.

Outcomes using these measures are often less than optimal, and can be improved using therapeutic education.
If these measures are insufficient, antispasmodics can be prescribed.
Antispasmodics appear to be the first-line treatment used in primary care, particularly when abdominal pain and bloating are the main symptoms.[5]

6.3. Target population

Irritable bowel syndrome and functional bowel disease are the most common causes of functional bowel disorders.
The prevalence of irritable bowel syndrome depends largely on the country and diagnostic criteria used in studies, and varies between 1% and 20%.[6]
Two studies have evaluated the prevalence of irritable bowel syndrome in France:

- in one study, which was based on a self-administered questionnaire answered by 20,000 patients,[7] the prevalence of irritable bowel syndrome using the Rome II criteria was 4.7% [4.36%-5.04%];
- in a study based on telephone questioning of 8,221 patients,[8] 23% of those asked stated that they had had abdominal pain over the previous 12 months. The prevalence of irritable bowel syndrome has been estimated at 12% using the Manning criteria (with no reference to duration of symptoms; 2.5% when duration was taken into account), 2.1% using Rome I and 1% using Rome II.

No epidemiological studies have been identified to evaluate the prevalence of irritable bowel syndrome using the currently applicable Rome III criteria.[9] The prevalence of irritable bowel syndrome according to the Rome III should be higher than that identified using the Rome II

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[1] Ducrotté P. Irritable bowel syndrome: dietary and pharmacological therapeutic options. Gastroenterol clin biol. 2009; 33: suppl 1:s68-78.
[2] Drossman DA, guest editor. The functional gastrointestinal disorders and the Rome III process. Gastroenterology 2006; 130: 1377-90.
[3] Mertz H-R. Irritable bowel syndrome. N Engl J Med 2003; 349: 2136 -2146.
[4] Spiller RC. Treatment of irritable bowel syndrome. Curr treat options gastroenterol. 2003; 6: 329-337.
[5] Spiller R, Aziz Q, Creed F, Emmanuel A, Houghton L, Hungin P et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut 2007; 56: 1770-1798.
[6] Dapoigny M. Irritable bowel syndrome: epidemiology/economic burden. Gastroenterol Clin Biol 2009; 33 (suppl.1): 3-8.
[7] Dapoigny M. Irritable bowel syndrome in France: a common, debilitating, costly disorder. European Journal Gastroenterology Hepatology 2004, 16: 995-1001.
[8] Bommelaer G, Poynard T, Le Pen C, Gaudin AF et al. Prevalence of irritable bowel syndrome (IBS) and variability of diagnosis criteria. Gastroenterol Clin Biol 2004; 28: 554-61.
[9] Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006; 130: 1480-1491.

criteria, as the Rome III criteria are less restrictive in terms of time since onset of symptoms (in Rome III, symptom onset needs to be at least six months prior to diagnosis, compared with one year for Rome II).
According to Dapoigny,[6] the prevalence of irritable bowel syndrome in the general adult population can currently be estimated at around 8%.
Considering that the prevalence of irritable bowel syndrome is between 4% and 8% of the general adult population in France, the target population for METEOXANE in this indication is estimated at between 2 and 4 million people.

6.4. Transparency Committee recommendations

The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indication and at the dosage in the MA.

6.4.1 Packaging: Appropriate for the prescription conditions

6.4.2 Reimbursement rate: 15%

APPENDIX 1: Proprietary medicinal products in the class "antispasmodics"
AB attributed by the Transparency Committee

Indications that are not affected by the present re-assessment are given *in italics*

PROPRIETARY MEDICINAL PRODUCT	INN	INDICATIONS	CURRENT BENEFIT	OPINION DATE (FBD)
DEBRIDAT	Trimebutine (maleate)	Symptomatic treatment: - of pain connected with functional disorders of the digestive tract; - of pain, digestive disorders and intestinal discomfort connected with functional bowel disorders. *- of pain connected with functional disorders of the biliary tract;*	low	6 April 2011
DICETEL	Pinaverium bromide	- Symptomatic treatment of pain, digestive disorders and intestinal discomfort connected with functional bowel disorders. *- Symptomatic treatment of pain connected with functional disorders of the biliary tract;* *- Preparation for barium enema*	low	6 April 2011
METEOSPASMYL	Alverine citrate / simethicone	Symptomatic treatment of functional manifestations of intestinal disorders, particularly bloating	low	6 July 2011
METEOXANE	Simethicone / hydrated phloroglucinol	Secondary treatment of functional manifestations of intestinal disorders, particularly bloating and diarrhoea	low	6 April 2011

SPASFON	Phloroglucinol Trimethylphloroglucinol	Symptomatic treatment of pain connected with functional disorders of the digestive tract. *Symptomatic treatment of pain connected with functional disorders of the biliary tract*. *Treatment of acute pain and spasm in the urinary tract: renal colic.* *Symptomatic treatment of painful spasms in gynaecology.* *Adjuvant treatment for contractions during pregnancy, in combination with rest (indication does not apply to solution for injection)*	low	22 June 2011
VISCERALGINE	Tiemonium (methylsulfate)	Symptomatic treatment of acute pain connected with functional disorders of the digestive tract. *Symptomatic treatment of acute pain connected with functional disorders of the biliary tract.* *Symptomatic treatment of pain and spasm in the urinary tract.* *Symptomatic treatment of acute pain in gynaecology.*	low	6 April 2011

GENERIC GROUP "MEBEVERINE" 100 MG - 200 MG ORIGINATOR PRODUCT DUSPATALIN *				
PROPRIETARY MEDICINAL PRODUCT	**INN**	**INDICATIONS**	**CURRENTBENEFIT**	**DATE OF OPINION**
DUSPATALIN: removed on 31 March 2010 *	mebeverine (hydrochloride)	- Symptomatic treatment of intestinal pain and discomfort connected with functional disorders of the digestive tract *- Symptomatic treatment of intestinal pain and discomfort connected with functional disorders of the biliary tract*	low	31 March 2010

* Because DUSPATALIN, the originator drug of the group of generics, is no longer on the reimbursement list, the Transparency Committee is re-evaluating the AB of generics on the reimbursement list.

PROPRIETARY MEDICINAL PRODUCT	**INN**	**INDICATIONS**	**AB (FBD)**	**DATE OF OPINION**
COLOPRIV	mebeverine (hydrochloride)	- Symptomatic treatment of intestinal pain and discomfort connected with functional disorders of the digestive tract *- Symptomatic treatment of intestinal pain and discomfort connected with functional disorders of the biliary tract*	Insufficient*	6 April 2011
MEBEVERINE HYDROCHLORIDE MYLAN			Insufficient*	6 April 2011
MEBEVERINE BIOGARAN			Insufficient*	6 April 2011
MEBEVERINE EG			Insufficient*	6 April 2011
MEVERINE QUALIMED			Insufficient*	6 April 2011
MEBEVERINE TEVA			Insufficient*	6 April 2011
MEBEVERINE ZYDUS			Low	6 April 2011
SPASMOPRIV			Low	6 April 2011

*The Transparency Committee is aware that some mebeverine-based proprietary medicinal products include an excipient that is known to have a harmful effect, which seems to have caused serious adverse effects. The Committee considers that these proprietary medicinal products should not be recommended for reimbursement.