



HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

6 April 2011

**DEBRIDAT CHILD AND INFANT 4.8 mg/mL, granules for oral suspension, in a bottle
B/1 (CIP code: 341 048-3)**

**DEBRIDAT, granules for oral suspension, in a bottle
B/1 (CIP code: 302 825-2)**

**DEBRIDAT, granules for oral suspension in sachet
B/30 (CIP code: 335 956-9)**

**DEBRIDAT 100 mg, film-coated tablet
B/30 (CIP code: 339 046-7)**

**DEBRIDAT 200 mg, film-coated tablet
B/30 (CIP code: 359 194-1)**

Applicant: PFIZER

trimebutine (maleate)

ATC code: A03AA05 (drugs for functional bowel disorders)

List II

Dates of Marketing Authorisation:

DEBRIDAT CHILD AND INFANT 4.8 mg/mL, granules for oral suspension, in a bottle: Initial MA 04/06/1996

DEBRIDAT, granules for oral suspension, in a bottle: Initial MA 04/09/1975 (validated on 13/12/1989)

DEBRIDAT, granules for oral suspension in sachet: Initial MA 04/09/1975 (validated on 13/12/1989)

DEBRIDAT 100 mg, film-coated tablet: Initial MA 08/07/1974 (validated on 10/01/1989)

DEBRIDAT 200 mg, film-coated tablet: Initial MA 03/05/2002

Reason for request: Re-assessment of actual benefit (AB) in compliance with article R. 163-21 of the French Social Security Code in the symptomatic treatment of functional bowel disorders.

The indication "pain related to functional disorders of the biliary tract" is not affected by the re-assessment of the AB in the present opinion.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Trimebutine (maleate)

1.2. Indications

"Symptomatic treatment:

- of pain connected with functional disorders of the digestive tract and biliary tract;
- of pain, digestive disorders and intestinal discomfort connected with functional bowel disorders. "

1.3. Dosage

See SPC

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
A03AA05	Trimebutine

2.2. Medicines in the same therapeutic category (refundable)

Antispasmodics in 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 6 February 2008 (renewal of inclusion):

In the indication "FBD", the TC concluded:

"Functional bowel disorders

Functional bowel disorders are problems with digestion (diarrhoea, constipation or both) associated with abdominal pain and bloating (meteorism), with no organic cause. These disorders become chronic and are characterised by flare-ups. Functional bowel disorders are not serious and do not lead to a marked deterioration in quality of life.

These proprietary medicinal products are intended to provide symptomatic treatment.

The efficacy/adverse effects ratio is low.

These proprietary medicinal products are used in first-line treatment.

There are treatment alternatives.

The actual benefit of these medicinal products is low".

4. UPDATE ON DATA MADE AVAILABLE SINCE PREVIOUS OPINION

4.1. Efficacy

No new efficacy data has been sent by the applicant. The previous opinion was based on the meta-analysis by Poynard, published in 2001.¹ This meta-analysis evaluated the efficacy of six antispasmodics (including mebeverine, pinaverium and trimebutine, which are all marketed in France) in the treatment of functional bowel disorders (FBDs). Trimebutine was observed to be significantly superior to placebo in providing overall improvement in symptoms. However, no significant difference was observed in effect on abdominal pain.

The Cochrane 2005 meta-analysis² evaluated the efficacy of the antispasmodics (including mebeverine, pinaverium and trimebutine) in the treatment of FBDs. Trimebutine was observed to have minimal benefit over placebo for abdominal pain (RR=1.32 [1.07; 1.64]), with no statistically significant difference for overall improvement in symptoms.

The results of these meta-analyses are difficult to interpret (the trials are old, the methodology is questionable, they are small and the length of follow-up is generally too short).

4.2. Adverse effects

Tolerance data for the period 1 May 2008 to 31 May 2009³ do not provide any new information that could alter DEBRIDAT's tolerance profile.

The Pharmacovigilance Unit at AFSSAPS has been informed of three serious cases of deliberate overdose, including one death, involving DEBRIDAT alone or in combination with other drugs. One of these cases is about to be published.

This notification is subject to additional investigation and no specific measures have yet been taken as a result of it.

The SPC states that "in clinical studies, skin reactions have been described in rare cases. Granules for oral suspension: because of the presence of sunset yellow colouring, there is a risk of allergic reaction".

¹ Poynard T. et al. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther.* 2001; 15:355-61.

² Quartero AO, Meineche-Schmidt V, Muris J, Rubin G, de Wit N. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD003460. DOI:10.1002/14651858.CD003460.pub2.

³ PSUR (Periodic Safety Update Report) for the period 1 May 2008 to 31 May 2009

5. DRUG USAGE DATA

According to the EPPM [Ongoing Study into Medical Prescription] panel at IMS Health, prescriptions of trimebutine account for over 2.92 million prescriptions annually (cumulative total at August 2010).

Independent generalist physician were the main prescribers (92% of all prescriptions), followed by paediatricians (5%) and independent gastro-enterologists (3% of prescriptions).

In 2010, DEBRIDAT represented 70% of all trimebutine prescriptions, with over 2 million prescriptions in total. Around 1/3 of prescriptions were for 200 mg tablets or granules for oral suspension for infants.

The most common dosage prescribed was 600 mg per day (52% of prescriptions) i.e. three tablets once daily or one tablet three times daily, or 1.5 tablets twice daily, which is in line with the SPC.

The diagnosis associated with the prescription was, in 32% of cases, diarrhoea or gastroenteritis presumed to be of infectious origin. The other diagnoses are given in the table below:

	Annual prescriptions	% of annual prescriptions
Diarrhoea and gastroenteritis, presumed to be of infectious origin	662,100	32.40
Abdominal pain, other and not stated	462,432	22.63
Intestinal diseases	129,330	6.33
Constipation	119,889	5.87
Functional intestinal disorders, not otherwise stated	97,067	4.75

6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of actual benefit

Functional bowel disorders (FBDs) are problems with digestion (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 digestion, 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 deterioration in quality of life.

These proprietary medicinal products are intended to provide symptomatic treatment.

The efficacy/adverse effects ratio is low.

These proprietary medicinal products are first-line medicinal products, assuming that diet and lifestyle measures are being followed.

There are therapeutic alternatives: other antispasmodics.

Public Health Benefit: irritable bowel syndrome is a common condition that affects 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 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 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 these proprietary medicinal products have 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)¹² 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.⁴ There have been successive consensus decisions about the diagnostic criteria for FBDs (the current criteria being Rome III⁵).

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 digestion and reduction of pain.

Treatment strategies aim 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.^{6,7}
- if diarrhoea is present, reducing intake of fibre, indigestible carbohydrates, fruit and caffeine.

⁴ Ducrotté P. Irritable bowel syndrome: dietary and pharmacological therapeutic options. *Gastroenterol clin biol.* 2009;33: suppl 1:s68-78.

⁵ Drossman DA, guest editor. The functional gastrointestinal disorders and the Rome iii process. *Gastroenterology* 2006;130:1377-90

⁶ Mertz H-R. Irritable bowel syndrome. *N Engl J Med* 2003; 349: 2136-2146

⁷ Spiller RC. Treatment of irritable bowel syndrome. *Curr treat options gastroenterol.* 2003; 6: 329-337.

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.⁸

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%.⁹

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,¹⁰ 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,¹¹ 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 that assess the prevalence of irritable bowel syndrome using the currently applicable Rome III criteria.¹² The prevalence of irritable bowel syndrome according to the Rome III should be higher than that identified using the Rome II 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,⁹ 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 DEBRIDAT 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 and on the list of medicines approved for hospital use and various public services for the indication "Symptomatic treatment:

- of pain connected with functional disorders of the digestive tract;
- of pain, digestive disorders and intestinal discomfort connected with functional bowel disorders" and at the dosage levels given in the Marketing Authorisation.

The transparency Committee would like to remind that in its most recent assessment it considered that the actual benefit provided by DEBRIDAT was insufficient for the indication "functional biliary tract disorders".

6.4.1 Packaging: Appropriate for the prescription conditions

6.4.2 Reimbursement rate: 15 %

⁸ 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.

⁹ Dapoigny M. Irritable bowel syndrome: epidemiology/economic burden. *Gastroenterol Clin Biol* 2009; 33 (suppl.1): 3-8.

¹⁰ Dapoigny M. Irritable bowel syndrome in France: a common, debilitating, costly disorder. *European Journal Gastroenterology Hepatology* 2004, 16:995-1001.

¹¹ 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

¹² Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; 130:1480-1491.

**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	ACTUAL BENEFIT	OPINION DATE (FBD)
DEBRIDAT	Trimebutine (maleate)	<p>Symptomatic treatment:</p> <ul style="list-style-type: none"> - of pain connected with functional disorders of the digestive tract; - of pain, digestive disorders and intestinal discomfort connected with functional bowel disorders. <hr/> <p><i>- of pain connected with functional disorders of the biliary tract;</i></p>	low	6 April 2011
DICETEL	Pinaverium bromide	<ul style="list-style-type: none"> - Symptomatic treatment of pain, digestive disorders and intestinal discomfort connected with functional bowel disorders. <hr/> <p><i>- Symptomatic treatment of pain connected with functional disorders of the biliary tract;</i></p> <p><i>- Preparation for barium enema</i></p>	low	6 April 2011
METEOSPASYL	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	<p>Symptomatic treatment of pain connected with functional disorders of the digestive tract.</p> <hr/> <p><i>Symptomatic treatment of pain connected with functional disorders of the biliary tract.</i></p> <p><i>Treatment of acute pain and spasm in the urinary tract: renal colic.</i></p> <p><i>Symptomatic treatment of painful spasms in gynaecology.</i></p> <p><i>Adjuvant treatment for contractions during pregnancy, in combination with rest (indication does not apply to solution for injection)</i></p>	low	22 June 2011
VISCERALGINE	Tiemonium (methylsulfate)	<p>Symptomatic treatment of acute pain connected with functional disorders of the digestive tract.</p> <hr/> <p><i>Symptomatic treatment of acute pain connected with functional disorders of the biliary tract.</i></p> <p><i>Symptomatic treatment of pain and spasm in the urinary tract.</i></p> <p><i>Symptomatic treatment of acute pain in gynaecology.</i></p>	low	6 April 2011

GENERIC GROUP "MEBEVERINE" 100 MG - 200 MG ORIGINATOR PRODUCT DUSPATALIN *				
PROPRIETARY MEDICINAL PRODUCT	INN	INDICATIONS	ACTUAL BENEFIT	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 - <i>Symptomatic treatment of intestinal pain and discomfort connected with functional disorders of the biliary tract</i>	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 - <i>Symptomatic treatment of intestinal pain and discomfort connected with functional disorders of the biliary tract</i>	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 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 products should not be recommended for reimbursement.