



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 April 2011

DICETEL 50 mg, film-coated tablet
B/20 (CIP code: 327 238-3)

DICETEL 100 mg, film-coated tablet
B/30 (CIP code: 338 762-0)

Applicant: ABBOTT PRODUCTS SAS

pinaverium (bromide)

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

List II

Dates of Marketing Authorisation:

DICETEL 50 mg, film-coated tablet - 22/08/1990

DICETEL 100 mg, film-coated tablet - 11/04/1995

Latest revision of Marketing Authorisation: 22/07/2010

Reason for request: Re-assessment of actual benefit in line with article R. 163-21 of the French Social Security Code, for the indication "functional bowel disorders".

The indications "symptomatic treatment of pain connected with functional disorders of the biliary tract and preparation for barium enema" are 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

Pinaverium bromide

1.2. Indications

" - 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. "

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
A03AX04	Pinaverium

2.2. Medicines in the same therapeutic category

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 10 March 2010 (renewal of inclusion)

In the indication "FBD", the TC concluded:

"Functional bowel disorders"

The Transparency Committee considers that the actual benefit provided by these proprietary medicinal products remains low for functional bowel disorders (FBDs)".

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 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. For pinaverium, a modest benefit over placebo was observed for abdominal pain (RR=1.57 [1.08; 2.26]) and for overall improvement in symptoms (RR=2.16 [1.54; 3.02]).

The results of these meta-analyses were difficult to interpret (the trials are old, the methodology is questionable, they are small and the length of follow-up is generally too short). It is also highly likely that there is publication bias.

4. UPDATE ON DATA MADE AVAILABLE SINCE PREVIOUS OPINION

4.1. Efficacy

No new data have been submitted since the last TC opinion.

New scientific data about functional bowel disorders and their management have been taken into consideration.³ The American College of Gastroenterology (ACG) Task Force has published a systematic review of the management of FBDs,⁴ in which it is noted that antispasmodics (hyoscine, cimetropium, pinaverium and peppermint) can provide short-term relief for the abdominal pains and discomfort of FBDs. There are no long-term efficacy data.

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 NICE Feb. 2008. Irritable bowel syndrome in adults: Diagnosis and management of irritable bowel syndrome in primary care. Clinical practice guideline.

⁴ Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, Talley NJ, Quigley EM. An evidence-based position statement on the management of irritable bowel syndrome. American College of Gastroenterology Task Force on Irritable Bowel Syndrome. *Am J Gastroenterol.* 2009;104 Suppl 1:S1-35.

4.2. Adverse effects

No new tolerance data that would warrant a change to the tolerance profile have been submitted by the applicant.

A search of the National Pharmacovigilance Database⁵ reveals seven cases of oesophageal ulceration, oesophagitis and/or mouth or tongue ulceration in which DICETEL was recorded as a possible cause. In addition, an article about the risk of oesophageal lesions associated with pinaverium bromide has recently been published.⁶ This article describes a case of oesophageal ulceration in a female patient aged 40 receiving pinaverium as an antispasmodic for bowel disease.

In section 4.2 of the Summary of Product Characteristics for DICETEL, it is noted that the tablets must not be crunched or sucked, and that they should be swallowed with a glass of water during a meal, and not while lying down or just before going to bed. The observations above show that these recommendations are not always followed in practice. Nevertheless, the risk of oesophageal lesions cannot be ruled out even when the product is taken in adherence to the recommended method of administration.

The Pharmacovigilance Unit at AFSSAPS has therefore sent a letter to the applicant, asking that they submit a request to modify the product information. This request is currently being examined.

The SPC states that "the following have been observed:

- Immune system conditions: possibility of hypersensitivity reactions such as urticaria, pruritus, angioedema.
- Gastrointestinal conditions: in rare cases, minor digestive disorders.
- Conditions of the skin and its appendages: isolated cases of adverse effects involving the skin, some of which were allergic. "

5. DRUG USAGE DATA

According to data from IMS (CMA February 2011), DICETEL was prescribed 248,000 times, the main indications being as follows: diarrhoea, abdominal and pelvic pain, other bowel diseases. The mean dosage was 2.6 tablets per day.

	Annual prescriptions
Diarrhoea	133,000
Abdominal pain	121,000
Other intestinal diseases	229,000
Functional intestinal disorders, not otherwise stated	224,000

⁵ AFSSAPS. Circular form, January 2011

⁶ Ahid S et al. Pinaverium bromide-induced esophageal ulcerations. Therapie 2008 Jan-Feb; 63(1): 67-8

6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of actual benefit

Functional bowel disorders (FBDs) are disorders of digestive system (diarrhoea, constipation or both) associated with abdominal pain and bloating (meteorism). Diagnosis of FBD is primarily a diagnosis of exclusion that 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 treatment alternatives, in the form of 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 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)⁸ 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.⁷ There have been successive consensus decisions about the diagnostic criteria for FBDs (the current criteria being Rome III⁸).

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).

⁷ Ducrotté P. Irritable bowel syndrome: dietary and pharmacological therapeutic options. *Gastroenterol clin biol.* 2009;33: suppl 1:s68-78.

⁸ Drossman DA, guest editor. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006;130:1377-90

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.^{9,10}
- 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.¹¹

6.3. Target population

Irritable bowel syndrome or 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%.¹²

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,¹³ 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,¹⁴ 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 criteria¹⁵. 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 6 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 DICETEL in this indication is estimated at between 2 and 4 million people.

⁹ Mertz H-R. Irritable bowel syndrome. *N Engl J Med* 2003; 349: 2136 -2146.

¹⁰ Spiller RC. Treatment of irritable bowel syndrome. *Curr treat options gastroenterol.* 2003; 6: 329-337.

¹¹ 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.

¹² Dapoigny M. Irritable bowel syndrome: epidemiology/economic burden. *Gastroenterol Clin Biol* 2009; 33 (suppl.1): 3-8.

¹³ Dapoigny M. Irritable bowel syndrome in France: a common, debilitating, costly disorder. *European Journal Gastroenterology Hepatology* 2004, 16:995-1001.

¹⁴ 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.

¹⁵ Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; 130:1480-1491.

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, digestive disorders and bowel discomfort connected with functional bowel disorders" and at the dosage in the Marketing Authorisation.

Summary of AB in other indications: the Committee notes that in its most recent assessment, it considered that the actual clinical benefit provided by DICETEL was insufficient for:

- Symptomatic treatment of pain connected with functional disorders of the biliary tract;
- Preparation for barium enema.

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	ACTUAL BENEFIT	DATE OF OPINION (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
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

<p>SPASFON</p>	<p>Phloroglucinol Trimethylphloroglucinol</p>	<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>	<p>low</p>	<p>22 June 2011</p>
<p>VISCERALGINE</p>	<p>Tiemonium (methylsulfate)</p>	<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>	<p>low</p>	<p>6 April 2011</p>

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			Insufficient*	6 April 2011
MEBEVERINE HYDROCHLORIDE MYLAN			Insufficient*	6 April 2011
MEBEVERINE BIOGARAN			Insufficient*	6 April 2011
MEBEVERINE EG	mebeverine (hydrochloride)	- Symptomatic treatment of intestinal pain and discomfort connected with functional disorders of the digestive tract	Insufficient*	6 April 2011
MEVERINE QUALIMED		- <i>Symptomatic treatment of intestinal pain and discomfort connected with functional disorders of the biliary tract</i>	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.