

The legally binding text is the original French version

TRANSPARENCY COMMITTEEOPINION22 June 2011**SPASFON, film-coated tablets****B/30 (CIP code: 309 860-8)****SPASFON, suppositories****B/10 (CIP code: 309 861-4)****SPASFON, solution for injection in ampoules****B/6 (CIP code: 309 858-3)****SPASFON LYOC 80 mg, oral lyophilisate****B/10 (CIP code: 318 630-1)****Applicant: CEPHALON FRANCE**

Phloroglucinol / trimethylphloroglucinol

ATC code: A03AX12 (OTHER DRUGS FOR FUNCTIONAL BOWEL DISORDERS)

Date of Marketing Authorisation:

SPASFON, film-coated tablets:

Initial Marketing Authorisation 9 July 1974, confirmed 1 December 1993, last amended 14 August 2007

SPASFON, suppositories:

Initial Marketing Authorisation 2 July 1973, confirmed 1 December 1993, last amended 29 October 1999

SPASFON, solution for injection in ampoules

Initial Marketing Authorisation 6 February 1974, confirmed 1 December 1993, last amended 16 January 2001

SPASFON LYOC

Initial Marketing Authorisation 12 May 1975, confirmed 12 February 1992, last amended 16 January 2006

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

The indications "*Symptomatic treatment of pain related to functional disorders of the biliary tract, treatment of spasm and acute pain of the urinary tract: renal colic, symptomatic treatment of painful spasm in gynaecology*" are not covered by the re-assessment of actual benefit in this Opinion.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Phloroglucinol / trimethylphloroglucinol

1.2. Indications

Tablets and suppositories:

"Symptomatic treatment of pain related to functional disorders of the gastrointestinal tract and biliary tract.

Treatment of spasm and acute pain of the urinary tract: renal colic.

Symptomatic treatment of painful spasm in gynaecology.

Adjuvant therapy for contractions during pregnancy, in combination with rest."

Solution for injection:

"Symptomatic treatment of pain related to functional disorders of the gastrointestinal tract and biliary tract.

Treatment of spasm and acute pain of the urinary tract: renal colic.

Symptomatic treatment of painful spasm in gynaecology."

1.3. Dosage

See SPC

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

A	Alimentary tract and metabolism
A03	drugs for functional gastrointestinal disorders
A03A	drugs for functional bowel disorders
A03AX	other drugs for functional bowel disorders
A03AX12	phloroglucinol

2.2. Medicines in the same therapeutic category

Antispasmodics in the category of musculotropic agents are listed in Appendix 1 (reminder of actual benefit of these medicines).

2.3. Medicines with a similar therapeutic aim

Other medicines used in functional bowel disorders, and in particular, non-opioid analgesics.

3. REMINDER OF THE TRANSPARENCY COMMITTEE'S OPINION

Opinion of 6 February 2008 (renewal of listing):

In the indication "Symptomatic treatment of pain related to functional disorders of the gastrointestinal tract", the actual benefit of this proprietary medicinal product was classed as moderate.

This Opinion was based on clinical study no. 1100: this was a randomised double-blind placebo-controlled phase IV study to assess the efficacy of SPASFON against abdominal pain in patients with functional bowel disorders, according to the Rome II criteria.¹

An episode of pain was defined by a baseline visual analogue scale (VAS) score between 40 and 80 mm.²

Pain was assessed at baseline (day 0) and on day 7 by the patient using the VAS in the presence of the investigator.

The primary efficacy endpoint was a comparison of change in intensity of pain in the previous 24 hours between day 0 and day 7.

The ITT analysis included 300 patients (149 in the placebo group and 151 in the SPASFON group).

Mean patient age was 47 years in both groups. Mean duration of symptoms was 3.6±2.4 years and placebo group and 4±3.1 years in the SPASFON group.

At baseline (day 0), mean score was 62.0±9.0 in the SPASFON group and 61.8±8.5 in the placebo group (p=0.918).

On day 7, mean VAS score was 25.9±20 in the SPASFON group and 33.8±23.2 in the placebo group (p=0,004).

The amount of observed effect on mean score was $\Delta=7.8$, 95% CI [2.9 ; 12.7] in favour of the SPASFON group on a VAS from 0 to 100 mm.

For the primary outcome measure, the mean relative reduction had been larger in the SPASFON group than in the placebo group (57.8% ±31.7 versus 46.3% ±34.7, p=0.003).

In conclusion, the Opinion stated "The results of this SPASFON study using a recent method for measuring bowel function disorders demonstrated statistically and clinically significant efficacy in the symptomatic treatment of abdominal pain related to bowel function disorders compared with placebo. However, long-term benefit has not been demonstrated."

¹ According to the Rome II criteria, functional bowel disorders are defined as at least 12 weeks in the preceding 12 months of abdominal discomfort or pain, associated with transit disorders in acute episodes of pain (on two occasions, at least two days during the week preceding recruitment).

² The visual analogue scale measured 100 mm. The left-hand end 0 represented 'no pain' and the right-hand end 100 represented 'extreme pain'.

4. UPDATE ON THE DATA MADE AVAILABLE SINCE THE PREVIOUS OPINION

4.1. Efficacy

No new data have become available since the previous Opinion. The applicant has not submitted any further studies of efficacy. No data have become available from comparison with an active comparator, i.e. other antispasmodics.

4.2. Adverse effects

The facts identified since the last assessment are the introduction of the following text into the SPC for SPASFON (oral and rectal forms), in the section "Adverse effects": "Cutaneous, mucosal and allergic manifestations such as rash, rarely urticaria, very occasionally angioedema, hypotension, anaphylactic shock."

This means that the tolerance data for SPASFON have been somewhat modified. The most recent PSUR reported 1 840 736 852 days of treatment. As there has been a single case of pancreatitis, this adverse effect has been the subject of closer monitoring in the next PSUR.

5. DRUG USAGE DATA

According to IMS data, the moving annual total to February 2010 for the SPASFON range of proprietary medicinal products is 5725 million prescriptions.

Prescriptions for the SPASFON range were distributed as shown below:

Infectious bowel disease	38.1%
Gastrointestinal symptoms	18.0%
Other bowel disease	9.1%
Other urinary tract disease, and urinary tract stones	9.3%
Genital tract disease	11.6%

The mean dosage was 4.2 dosage units daily and mean treatment duration was 12.6 days.

6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of actual benefit

Functional bowel disorders (FBDs) cover transit disorders (diarrhoea, constipation, or both) combined with abdominal pain and bloating (meteorism). The diagnosis of FBD is mainly a diagnosis of exclusion, made after any underlying organic disorders have been excluded.

The main aim of treatment for FBD is to restore regular bowel transit, mainly by applying lifestyle and dietary measures and reducing pain.

These disorders occur in episodes and repeatedly. Functional bowel disorders are not serious but they may lead to deterioration in quality of life.

These proprietary medicinal products are intended as symptomatic therapy.

The efficacy/tolerance ratio is low.

These proprietary medicinal products are first-line therapies, after compliance with lifestyle and dietary measures.

There are treatment alternatives, i.e. other antispasmodics, for which the actual benefit is low.

Public health benefit: irritable bowel syndrome is a common disorder, which has a marked impact on quality of life, but is otherwise not serious. The public health burden which it represents is minor.

The available data show that these proprietary medicinal products have a low impact on reducing symptoms, and it is not possible to conclude that they have any impact on improving quality of life.

Although the availability of these proprietary medicinal products as part of the range of treatment options may theoretically allow patients to avoid using other more hazardous categories of drugs (such as antidepressants), it is not possible to establish any public health benefit for these proprietary medicinal products.

The actual benefit provided by these proprietary medicinal products is low.

6.2. Therapeutic use

Functional bowel disorders (FBDs) are defined according to current international criteria (Rome III)¹¹ as symptoms that have been present for more than six months and which occur on at least three days a month on three-monthly assessment. The main complaint for which patients go to see their doctor is abdominal pain which is generally relieved by defecation. The next most common complaint is transit disorder.³ FBDs have been the subject of successive consensus on their diagnostic criteria (currently Rome III⁴).

The diagnosis of FBD is first and foremost a diagnosis of exclusion, made after underlying organic disorders (mainly Crohn's disease or colorectal cancer) have been excluded.

The primary aim of treatment for FBD is to restore normal gastrointestinal transit and to alleviate pain.

The aim of the treatment strategy is to relieve the predominant symptom (constipation, diarrhoea or pain).

First of all, treatment of FBD consists of lifestyle and dietary measures:

- avoid foods likely to exacerbate symptoms,
- take regular physical exercise,

³ Ducrotté P. Irritable bowel syndrome: dietary and pharmacological therapeutic options. *Gastroenterol clin biol.* 2009; 33: suppl 1: s68-78.

⁴ Drossman DA, guest editor. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006; 130: 1377-90

- in the event of constipation, increase the proportion of fibre in the diet.^{5,6}
- in the event of diarrhoea, reduce the proportion of fibre, indigestible carbohydrates, fruit and caffeine.

The results of these measures are often suboptimal and could be increased by patient education.

If these measures are found to be insufficient, antispasmodics may be prescribed.

Antispasmodics appear to be the first-line therapy in primary care, particularly when abdominal pain and bloating are the predominant symptoms.⁷

6.3. Target population

Irritable bowel syndrome (or functional bowel disease) is the most common cause of functional bowel disorders.

The prevalence of irritable bowel syndrome is closely linked to country and the diagnostic criteria used in studies, and varies in practice from 1% to 20%.⁸

In France, two studies have measured the prevalence of irritable bowel syndrome:

- in one study based on a survey conducted by self-administered questionnaire in 20 000 subjects,⁹ the prevalence of irritable bowel syndrome defined according to Rome II criteria was 4.7% [4.36%-5.04%];
- in a study based on a telephone survey of 8 221 subjects,¹⁰ 23% of people questioned said that they had had abdominal pain during the last 12 months. The estimated prevalence of irritable bowel syndrome was 12% according to the Manning criteria (with no reference to symptom duration, and 2.5% including the concept of duration), 2.1% according to Rome I and 1% according to Rome II criteria.

It was not possible to find any epidemiological studies assessing the prevalence of irritable bowel syndrome according to the current criteria (Rome III).¹¹ The prevalence of irritable bowel syndrome according to the Rome III criteria should be higher than that found for the Rome II criteria, as the Rome III criteria are less restrictive in terms of duration of active symptoms (symptoms had to have been present for at least six months for the Rome III criteria compared with one year for the Rome II criteria).

According to Dapoigny⁸, the currently estimated prevalence of irritable bowel syndrome within the general adult population is about 8%.

Considering that the prevalence of irritable bowel syndrome is between 4 and 8% in the general adult population in France, the estimated target population for SPASFON in this indication is between two and four 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 in the indication "Symptomatic treatment of pain related to functional disorders of the gastrointestinal tract" and at the dosages given in the Marketing Authorisation.

⁵ Mertz H-R. Irritable bowel syndrome. *N Engl J Med* 2003; 349: 2136 –2146.

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

⁷ 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.

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

⁹ Dapoigny M. Irritable bowel syndrome in France: a common, debilitating, costly disorder. *European Journal Gastroenterology Hepatology* 2004; 16: 995-1001.

¹⁰ 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.

¹¹ Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; 130: 1480-1491.

The Transparency Committee states that at the time of the last assessment, it considered that the actual benefit of SPASFON was insufficient in:

- symptomatic treatment of pain related to functional disorders of the biliary tract and low in:

- treatment of spasm and acute pain of the urinary tract: renal colic.;
- symptomatic treatment of painful spasm in gynaecology.;
- adjuvant therapy for contractions during pregnancy, in combination with rest.

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	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

<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	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.