The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
6 June 2012

The draft opinion adopted by the Transparency Committee on 11 April 2012 was the subject of a hearing on 6 June 2012

METEOSPASMYL, soft capsules
B/20 (CIP code: 332 540-6)

Applicant: MAYOLY SPINDLER

INN alverine citrate, simeticone

ATC code (label): A03AX58 (alverine, combinations)

Marketing authorisation (procedure) and major amendment(s) 5 June 1990 (national procedure)

Reason for examination Re-assessment of actual benefit following the submission of new data pursuant to Article R163-12 of the Social Security Code.
01 Therapeutic indications (SPC)

“Symptomatic treatment of functional bowel disorders, particularly with bloating.”

02 Dosage

“For adults only.
1 capsule two to three times a day at the beginning of the meal.”

03 Comparator medicines

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
A03AX 58 : Alverine, combinations

Medicines in the same therapeutic category which are not strictly comparable

Antispasmodic agents belonging to the musculotropic class of drugs:
- DEBRIDAT (trimebutine maleate) and generic agents
- DICETEL (pinaverium bromide) and generic agents
- METEOXANE (simeticone / phloroglucinol hydrate)
- SPASFON (phloroglucinol trimethylphloroglucinol) and generic agents
- VISCERALGINE (tiemonium methylsulphate)
- Generic agents containing mebeverine

These medicines have low actual benefit, apart from the proprietary medicinal products containing mebeverine whose excipient contains peanut oil, for which the actual benefit is insufficient.

Medicines with a similar therapeutic aim

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

04 Prescription and/or usage data

04.1 Prescription data

According to IMS-EPPM data (year to date February 2012), 1,850,000 prescriptions were issued for METEOSPASMYL, soft capsules. The mean dose was 3.6 units a day and mean treatment duration was 30.4 days.
**Reminder of previous assessments by the Transparency Committee**

- **Opinion of 6 February 2008 (Listing renewal)**
  “Functional bowel disorders are transit disorders (diarrhoea, constipation or alternating symptoms) associated with abdominal pain and bloating (flatulence), with no organic cause. This disorder is a chronic disease that progresses in attacks. Functional bowel disorders are not serious and do not lead to marked deterioration in quality of life. These proprietary medicinal products are intended as symptomatic therapy. The efficacy/adverse effects ratio is low. These proprietary medicinal products are first-line therapies. There are treatment alternatives.

The actual benefit of these proprietary medicinal products remains low.”

- **Opinion of 5 May 2010 (Re-assessment of Actual Benefit)**
  "Functional bowel disorders are transit disorders (diarrhoea, constipation or alternating symptoms) associated with abdominal pain and bloating (flatulence), with no organic cause. This disorder is a chronic disease that progresses in attacks. Functional bowel disorders are not serious and do not lead to marked deterioration in quality of life. This proprietary medicinal product is intended as a symptomatic therapy. The efficacy/adverse effects ratio is modest. This proprietary medicinal product has a limited place in the strategy. There are treatment alternatives. The actual benefit of this proprietary medicinal product is provisionally classed as moderate pending the re-assessment of the class of antispasmodics”.

- **Opinion of 6 July 2011 (Re-assessment of Actual Benefit)**
  "Functional bowel disorders (FBD) are transit disorders (diarrhoea, constipation or alternating symptoms) associated with abdominal pain and bloating (flatulence). Diagnosis of FBD is above all a diagnosis of elimination, made after any underlying organic disorder has been eliminated. The main aim in the management of FBD is to restore normal bowel transit, mainly by applying lifestyle and dietary measures and reducing pain. These disorders progress by repeated attacks. Functional bowel disorders are not serious but may lead to marked deterioration in quality of life. These proprietary medicinal products are intended as symptomatic therapies. The efficacy/adverse effects ratio is weak. These proprietary medicinal products are first-line therapies, after compliance with lifestyle and dietary measures. There are treatment alternatives, i.e. the other antispasmodic agents, the actual benefit of which is low.

  Public health benefit: irritable bowel syndrome is a common disorder with a marked impact on quality of life, but it is not a serious disease. Its public health burden is low. Available data show that these proprietary medicinal products have a weak impact on symptom reduction; it cannot be concluded that they have any impact on improvement in quality of life. Although the availability of these proprietary medicinal products in the treatment arsenal may in theory allow patients to avoid the use of other more hazardous therapeutic groups (such as antidepressants), it is not possible to determine any public health benefit from these proprietary medicinal products.

The actual benefit of this proprietary medicinal product is low.”
06 Analysis of available data

06.1 Reminder of the clinical efficacy data

The clinical study data previously provided by the pharmaceutical company and considered by the Transparency Committee in its previous opinions consisted of:

Three studies versus DEBRIDAT, DUSPATALIN and DICETEL already considered in a previous opinion (TC opinion, 22 March 2000).

The Barhet et al. study showed that on day 56, “overall score” for pain was 6.3 +/- 3 in the METEOSPASMYL group and 9.3 +/- 3.6 in the DEBRIDAT group, p < 0.05.
On day 42, “overall score” for pain was 7.3 +/- 0.5 in the METEOSPASMYL group and 7.3 +/- 0.6 in the DUSPATALIN group with no significant difference.
On day 30, “overall score” for pain was 8 +/- 3.3 in the METEOSPASMYL group and 8.33 +/- 3.43 in the DICETEL group.

These data do not show any marked difference between METEOSPASMYL and the other three antispasmodic agents.

A randomised, controlled, double-blind, unpublished study comparing METEOSPASMYL with placebo performed in 252 patients who had had irritable bowel syndrome for at least three months. All the patients also received bran.
The main analysis could not demonstrate that METEOSPASMYL was superior to placebo using the primary efficacy endpoint “general digestive health” evaluated by the patient on a visual analogue scale (VAS).

A controlled, randomised, double-blind placebo-controlled study including 412 adult patients with irritable bowel syndrome. The aim of this study was to evaluate the efficacy and safety of METEOSPASMYL on abdominal pain in patients with irritable bowel syndrome diagnosed according to Rome III criteria.

At inclusion, there was no difference between the two treatment groups for demographic characteristics, abdominal pain/discomfort, gastrointestinal symptoms or anxiety (HAM-A) and depression (HAM-D) scores.

In particular, median pain severity score measured on a VAS was 71.0 mm [60; 92] in the METEOSPASMYL group and 73.5 mm [60; 96] in the placebo group.
On day 28 of the study, this score (primary efficacy endpoint) was 40.0 mm [0; 95] in the METEOSPASMYL group and 50.0 mm [0; 100] in the placebo group, i.e. a difference of 10 mm between the two groups (p = 0.0467) in favour of the METEOSPASMYL group after four weeks of treatment.
The effect size was low.

3 Kocian Study, 1998 unpublished
5 The Rome III criteria for diagnosing irritable bowel syndrome are: abdominal pain or discomfort present on at least 3 days a month over at least 3 months over the course of the last 6 months and associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, onset associated with a change in form [consistency] and appearance of stools.
06.2 New available clinical data on efficacy

The applicant provided new clinical data, i.e. the MASTER pragmatic study (FMT0901 protocol) which ended in December 2011.

**Aim:**
The main aim of this utility study of use was to compare the clinical benefit in a real-life setting of two strategies for managing irritable bowel syndrome.

**Study design:**
This was a French open, randomised study, conducted in general practice, in patients with irritable bowel syndrome defined according to Rome III criteria, which had been present for more than one year and less than ten years, who went to visit their doctor because of a moderate to severe painful attack requiring treatment. Two strategies for managing irritable bowel syndrome were compared. As it was the doctors who were randomised (cluster randomisation), the patients cannot be considered as independent from each other. In these conditions, the number of subjects needed should have been calculated to give a greater sample size.

The investigators were randomised into two groups:
- one used strategy A: one capsule of METEOSPASMYL three times a day before meals with a duration of administration as required with the aim of obtaining a benefit that the patient considered as optimal,
- the other used strategy B: the investigator's usual choice of treatment with the aim of obtaining clinical benefit.

**Inclusion/non-inclusion criteria:**
The outpatient adults included had irritable bowel syndrome and went to see their doctor for moderate to moderately severe symptoms (C.Y. FRANCIS score between 175 and 400). Any further investigations required, including colonoscopy in patients aged 50 years and over, were performed to eliminate any other cause that could explain the symptoms and if appropriate result in the non-inclusion of the patient. The main non-inclusion criteria were: treatment with METEOSPASMYL during the previous six months, previous gastrointestinal surgery within the previous eighteen months.

**Efficacy endpoints:**
The primary efficacy endpoint was percentage improvement (or worsening) on the specific IBSQoL scale between day 0 and 6 months. The IBSQoL scale is specific for patients with irritable bowel syndrome. It consists of 34 items exploring the impact of the disease on physical, emotional and social functions, sleep, sex life, etc. The responses to each of the 34 questions are scored out of 5 by the patient, added up and reported on a scale of 0 to 100.

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8 Impact of Irritable Bowel Syndrome on health-related Quality of Life
The secondary endpoints were:
- change in the various subscores on the specific IBSQoL quality of life scale
- change in the C.Y. FRANCIS symptomatic score
- change in the quality of life score on the non-specific SF36 scale (subscore analysis),
- mean frequency and severity of painful manifestations,
- symptoms of anxiety or depression: presence, frequency and outcome,
- impact of the disease on quality of sleep and outcome, etc.

Results:
A total of 88 doctors were included, who recruited 436 patients, i.e. 222 in group A and 214 in group B.
Patient characteristics were:
- Women: 73%
- Average age: 55.0 ± 15.3 years
- Average time since diagnosis: 6.5 ± 4.7 years

Results for the primary efficacy endpoint:
Improvement in overall IBSQoL score at six months (mean of differences) was 13.8 (+/- 17.09) for strategy A, and 8.4 (+/- 17.36) for strategy B (p = 0.0008).

Results for secondary endpoints:
- IBSQoL subscores
  Change in six of the nine subscores showed an improvement in favour of strategy A for the subscores Sleep (14.31 ± 20.76 versus 6.66 ± 21.90), Mental health (11.12 ± 21.23 versus 5.87 ± 21.02), Emotional health (17.56 ± 24.71 versus 12.93 ± 25.41), Feeding (14.15 ± 21.52 versus 6.74 ± 22.54), Social life (10.83 ± 25.38 versus 6.26 ± 22.74) and Vitality (16.14 ± 24.92 versus 10.70 ± 23.25); p < 0.05.

- Change in the FRANCIS symptomatic score
  There was a decrease in the score of -169.98 ± 105 in group A versus -110.7 ± 97.99 for group B. Responder rate (a responder patient’s score improved by at least 50%) based on this score was higher in the group receiving strategy A: 58.6% versus 35.9% for strategy B; p < 0.05.

- Change in the subscores of the SF36 quality of life questionnaire was in favour of strategy A for six out of the eight subscores, in particular for the subscores for Physical status (18±38.34 versus 13.21 ± 43.00) and Physical pain (15.97 ± 25.65 versus 13.14 ± 27.54); p < 0.05.

- Change in the severity of abdominal pain (between inclusion and the last assessment): there was an improvement for 76.1% of the patients in group A versus 59.2% in group B; p < 0.05.

- Change in the subscore Anxiety showed a reduction in average anxiety scores for group A of 2.44 versus 1.33 for group B; p < 0.05.

Overall for the global IBSQoL score, the primary efficacy endpoint of the study, there was a significant improvement in favour of strategy A (13.8 +/- 17.09 versus 8.4 +/- 17.36; p = 0.0008). However, the relative amount of effect observed was minimal on a clinical level (difference of 5 points between the two strategies compared on a scale of 100). Moreover, the magnitude of a clinically relevant size of effect had not been defined beforehand in the study protocol.
The study design and methodology do not provide a sufficient level of evidence in terms of the efficacy of METEOSPASMYL with regard to other antispasmodic proprietary medicinal products (all the antispasmodic agents were involved). The argument justifying the lack of blinding because of the pragmatic nature of the study remains debatable, in view of the possible existence of confounding factors not controlled for, such as the placebo effect, systematic measurement errors and the effect of concomitant treatments, which in particular exposed the results to follow up and assessment bias. Finally, in view of the performance of an intermediate analysis at the initiative of the pharmaceutical company and the multiplicity of statistical analyses performed, control of alpha risk inflation by the Peto and Haybittle method should have been anticipated in the analysis plan.

06.3 Newly-available safety data

- The pharmaceutical company has provided new safety data (PSUR covering the period 01 January 2008 to 31 December 2010 and its addendum for the period 01 January 2011 to 31 May 2011).

No changes have been made to the SPC concerning the categories “Undesirable effects”, “Special warnings and precautions for use” or “Contraindications” since the last assessment by the Committee.

A total of 21 cases considered to be severe (eight for which a causal relationship was judged to be possible and thirteen judged to be doubtful) were reported during this period (Table 1).

### Table 1: severe cases observed in the last PSUR

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders:</td>
<td></td>
</tr>
<tr>
<td>Swollen tongue</td>
<td>1</td>
</tr>
<tr>
<td>Hepatobiliary Disorders:</td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>3</td>
</tr>
<tr>
<td>Hepatic cytolysis</td>
<td>1</td>
</tr>
<tr>
<td>Investigations:</td>
<td></td>
</tr>
<tr>
<td>Hepatic enzymes increased</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue Disorders:</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1</td>
</tr>
<tr>
<td>Immune system Disorders:</td>
<td></td>
</tr>
<tr>
<td>Urticaria /vasovagal symptoms /hypotension</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system Disorders:</td>
<td></td>
</tr>
<tr>
<td>Syncope /overdose/prescribing error</td>
<td>1</td>
</tr>
<tr>
<td>Blood and lymphatic system Disorders:</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenic purpura</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue Disorders:</td>
<td></td>
</tr>
<tr>
<td>Erythematous rash</td>
<td>1</td>
</tr>
<tr>
<td>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome)</td>
<td>1</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>2</td>
</tr>
<tr>
<td>Generalised urticaria (hives)</td>
<td>1</td>
</tr>
<tr>
<td>Maculopapular exanthema</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus/jaundice/increased transaminases/hyperbilirubinaemia</td>
<td>2</td>
</tr>
<tr>
<td>Skin rash/pruritus/fever/eosinophilia</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>21</td>
</tr>
</tbody>
</table>

- In the MASTER study, 40.5% of the patients on strategy A (METEOSPASMYL) and 41% on strategy B (all other forms of treatment) experienced an adverse event. The main adverse events were nausea, diarrhoea, gastralgia and urticaria, which were not considered to be severe. There were 2.3% adverse effects with strategy A and none with strategy B.

- These data are unlikely to change the safety profile already established for this proprietary medicinal product.
Note that the main adverse effects are linked to the presence of alverine, as is mentioned in the SPC for the product:

- rare cases of urticaria, sometimes with laryngeal oedema, shock;
- rare case of liver disorders, regressing on withdrawal of treatment.

### 06.4 Conclusion

In the MASTER utility study the improvement in the overall IBSQoL score (primary efficacy endpoint) was greater in strategy A than in strategy B (13.8 +/- 17.09 versus 8.4 +/- 17.36; \( p = 0.0008 \)). However, the relative size of effect is minimal and of questionable clinical relevance (difference of five points between the two strategies compared on a scale of 100).

The results of the MASTER study have a low level of evidence, particularly because of the open nature of the study, its cluster randomisation design which was not taken into account either in the initial calculation of the number of subjects necessary nor in the statistical analysis initially performed. The argument justifying the lack of blinding because of the pragmatic nature of the study remains debatable, in view of the possible existence of uncontrolled confounding factors such as the placebo effect, systematic measurement errors, and the effect of concomitant treatments, which in particular expose the results to follow up and assessment bias. Finally, taking into account the performance of an intermediate analysis at the initiative of the pharmaceutical company and the multiplicity of statistical analyses performed, control of alpha risk inflation by the Peto and Haybittle method should have been included beforehand in the analysis plan.

The analysis of the data from the last PSUR reported 21 severe pharmacovigilance cases, the main adverse effects being linked to the presence of alverine, as mentioned in the current SPC.
Re-assessment of Actual Benefit

Functional bowel disorders (FBD) include transit disorders (diarrhoea, constipation or alternating symptoms), abdominal pain and bloating (flatulence). The diagnosis of FBD is made after any underlying organic disorder has been eliminated. The main aim of treatment for FBD is to restore normal bowel transit, mainly by applying lifestyle and dietary measures and reducing pain.

These disorders progress by repeated attacks. Functional bowel disorders are not serious but may lead to marked deterioration in quality of life. This proprietary medicinal product is intended as a symptomatic therapy.

In the light of the studies performed, the amount of effect from this drug is low and there are adverse effects more particularly linked to the presence of alverine. The efficacy/adverse effects ratio is therefore low.

This proprietary medicinal product is a first-line therapy, after compliance with lifestyle and dietary measures.

Public health benefit:
Irritable bowel syndrome is a common disorder with a marked impact on quality of life, but it is not a serious disease.
Its public health burden is low.
Available data show that these proprietary medicinal products have a low impact on symptom reduction; it cannot be concluded that they have any impact on improvement in quality of life.
Although the availability of these proprietary medicinal products in the treatment arsenal may in theory allow patients to avoid the use of other more hazardous therapeutic groups (such as antidepressants), it is not possible to establish any public health benefit from these proprietary medicinal products.

There are treatment alternatives, i.e. the other antispasmodic agents.

As a result, the transparency Committee considers that the actual benefit of METEOSPASMYL capsules remains low.

Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance in the indication and at the dosages given in the Marketing Authorisation.

- Packaging: Appropriate for the prescription conditions.
- Reimbursement rate: 15%

This opinion is available on the Haute Autorité de Santé website: [http://www.has-sante.fr](http://www.has-sante.fr)