SMECTA, powder for oral solution in sachets
30 sachets of 3.76 g (CIP: 34009 319 230-7 7)
60 sachets of 3.76 g (CIP: 34009 319 231-3 8)

Applicant: IPSEN PHARMA

INN | Diosmectite
---|---
ATC Code (2012) | A07BC05 (INTESTINAL ADSORBENT)
Reason for the review | Renewal of inclusion
List concerned | National Health Insurance (French Social Security Code L.162-17)

Indications concerned
• "Symptomatic treatment of acute diarrhoea in children and infants in addition to oral rehydration and in adults.
• Symptomatic treatment of chronic diarrhoea.
• Symptomatic treatment of pain associated with oesophageal-gastroduodenal and bowel disorders."
<table>
<thead>
<tr>
<th>Actual Benefit</th>
<th>The actual benefit (AB) of SMECTA is:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- moderate for acute diarrhoea in children and adults.</td>
</tr>
<tr>
<td></td>
<td>- low in the symptomatic treatment of pain associated with bowel disorders.</td>
</tr>
<tr>
<td></td>
<td>- insufficient in the symptomatic treatment of pain associated with oesophageal-gastroduodenal disorders.</td>
</tr>
</tbody>
</table>

The actual benefit of SMECTA was considered as insufficient for chronic diarrhoea (Opinion of 16 April 2008), which has not been re-assessed.
01 ADMINISTRATIVE AND REGULATORY INFORMATION

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Prescribing and dispensing conditions / special status</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATC Classification</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Alimentary tract and metabolism</td>
</tr>
<tr>
<td>A07</td>
<td>Antidiarrheals, intestinal antiinflammatory /antiinfective agents</td>
</tr>
<tr>
<td>A07B</td>
<td>Intestinal adsorbents</td>
</tr>
<tr>
<td>A07BC</td>
<td>Other intestinal adsorbents</td>
</tr>
<tr>
<td>A07BC05</td>
<td>Diosmectite</td>
</tr>
</tbody>
</table>

02 BACKGROUND

Review of the dossier for proprietary medicinal products included for a 5-year period starting on 31/12/2007 (Official Gazette of 23/12/2008).

On 16 April 2008, during the previous assessment for the renewal of its inclusion, the Committee estimated that the actual benefit of SMECTA was:
- moderate for acute diarrhoea in children and adults,
- low in the symptomatic treatment of pain associated with oesophageal-gastroduodenal and bowel disorders,
- insufficient in the treatment of chronic diarrhoea.

The therapeutic benefit of SMECTA and its therapeutic use should be re-assessed in the indications where the Committee estimated that the actual benefit was sufficient. To this end, the applicant was asked to provide all data, both initial and recent, in the indications concerned.

03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

03.1 Therapeutic indications

- "Symptomatic treatment of acute diarrhoea in children and infants in addition to oral rehydration and in adults."
- Symptomatic treatment of chronic diarrhoea.
- Symptomatic treatment of pain associated with oesophageal-gastroduodenal and bowel disorders."

03.2 Dosage

See SPC
04 ANALYSIS OF NEW AVAILABLE DATA

04.1 Efficacy

4.1.1 Acute diarrhoea in children

The impact of acute diarrhoea on general health is linked to loss of fluids and the significance of dehydration. The endpoint considered as being the most relevant by the French-speaking hepatogastroenterology and paediatric nutrition group (le groupe francophone d’hépatogastroentérologie et nutrition pédiatrique) for the assessment of medicinal products indicated for acute diarrhoea, is stool output, i.e. the weight or volume of stools reported over time. The frequency of stools and the duration of diarrhoea were not considered as being relevant. The group recommended the use of the total weight of stools passed over a 72 hour period following the treatment being taken and a reduction of 30% in stool rate for the product to be considered as being effective in the treatment of diarrhoea.

This is why only the three published studies based on stool output are described.

Pérou 1 Study (unpublished):
IPSEN, the applicant, carried out the Pérou study in 2002; it was a randomised, double-blind, placebo-controlled study of diosmectite. This study did not demonstrate a difference between the two groups regarding stool output (98.5 ± 78.0 g/kg with diosmectite versus 112.1 ± 91.8 g/kg with placebo, p = 0.32), with the difference in median duration of diarrhoea (secondary endpoint) of 43 hours (10; 289) vs. 72 hours (12; 287) being significant (p = 0.02).

Pérou 2 study and Malaisie Study (2009):
These two randomised, double-blind, placebo-controlled studies, published simultaneously, were carried out using the same study protocol. Their aim was to compare the efficacy of diosmectite versus placebo on stool output, in combination with oral rehydration with an oral rehydration solution (ORS).

The primary endpoint was the total weight of stools passed over the first 72 hours, expressed in g/kg of bodyweight measured at inclusion. Treatment was administered over a minimum duration of 3 days and up to recovery, not exceeding 7 days.

As a secondary endpoint, the duration of diarrhoea was measured: time elapsed between the 1st study treatment taken and recovery (defined as the passing of the first formed stool, followed by either a non-watery stool or the absence of a stool during the next 24 hours).

Results from the Pérou 2 Study
The study included 300 boys, with a mean weight of 9.35 ± 1.67 kg.
The total weight of stools over 72 hours (primary efficacy endpoint) was 102 ± 65.5 g/kg in the diosmectite group versus 118.8 ± 92.5 g/kg in the placebo group, which is a reduction of 14% (p = 0.0315). Although these results are statistically significant, showing a reduction in total weight of stools under 30%, they do not enable a satisfactory effect in the reduction of the risk of dehydration to be concluded.

Results from the Malaisie Study
The study included 302 boys, with a mean weight of 9.02 ± 2.05 kg.
The total weight of stools over 72 hours (primary efficacy endpoint) for the diosmectite group, 87.95 ± 81.18 g/kg of bodyweight, was different to that of the placebo group (90.73 ± 94.04 g/kg, p = 0.0071), which is a reduction of 3%. Although these results are statistically significant,

showing a reduction in total weight stools of under 30%, they do not enable a satisfactory effect in the reduction of the risk of dehydration to be concluded.

In conclusion, in two studies out of three, the total weight of stools over 72 hours was less high in the diosmectite group than in the placebo group. However, this difference is low and not clinically relevant, not enabling a possible reduction in the risk of dehydration to be demonstrated.

For information, the applicant has also presented one meta-analysis\textsuperscript{2} of nine placebo-controlled studies with the primary efficacy endpoint being the duration of diarrhoea. Results show an improvement in the duration of diarrhoea with diosmectite versus placebo of \(-22.7\) hours (95\% CI: \(-24.8; -20.6\)). However, this endpoint is not considered as relevant.

4.1.2 Acute diarrhoea in adults

No data was provided about stool output. However, there was data regarding the duration of diarrhoea:
- A randomised, double-blind study on 346 patients (Khediri\textsuperscript{3}) was carried out in Tunisia. This study showed a shorter duration of diarrhoea with diosmectite \((53.8\) hours \([3.7 – 167.3]\)) than with placebo \((69.0\) hours \([2.0 – 165.2]\)) \((p=0.029)\).
- Four open-label, randomised studies were provided, which compared diosmectite to loperamide. They are presented in the table below. These studies are old, carried out on small cohorts and there is little detail in the reports. The endpoints to measure efficacy used in these studies varied.

Table 1: Studies of diosmectite versus loperamide for acute diarrhoea in adults

<table>
<thead>
<tr>
<th>Author of the study (country)</th>
<th>Number of patients</th>
<th>Primary efficacy endpoint</th>
<th>Result</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Sola Pool\textsuperscript{4} 1987 (USA)</td>
<td>D: 39 L: 41</td>
<td>Reduction in mean number of stools between Day 0 and Day 2</td>
<td>D: -4 L: -3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Van Maercke\textsuperscript{5} 1987 (Belgium)</td>
<td>D: 51 L: 45</td>
<td>% score &lt; 5 at 48 hours (Score = number of stools/24 hours + 1 if stool normal or + 2 of stool soft or + 3 if watery stools)</td>
<td>D: 74.5% (38/51) L: 53.3% (24/45)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Dupont\textsuperscript{6} 1990 (Mexico)</td>
<td>D: 97 L: 78</td>
<td>Mean time to last unformed stool</td>
<td>Time D: 19.5 h; L: 14.2 h</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number of unformed stools in the first 12 hours of treatment</td>
<td>D: 1.5; L: 2.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Leber\textsuperscript{7} 1988 (Germany)</td>
<td>D: 33 L: 30</td>
<td>number of patients free from pain symptoms after 2 days</td>
<td>D: 82.5% (33/40) L: 70% (28/40)</td>
<td>NS</td>
</tr>
</tbody>
</table>

D: diosmectite L: loperamide

\textsuperscript{4} De Sola Pool N. Comparaison d’agents antidiarrhéiques systémiques et non systémiques dans le traitement de la diarrhée aiguë non spécifique de l’adulte. Today’s therapeutic trends 1987; 5:31-8
\textsuperscript{5} Van Maercke Y. Comparative clinical trial of Diasorb (local intestinal treatment with diosmectite) and loperamide in adults. Tijdschrift voor Gastro-enterologie, 1987, 17: 367-71
\textsuperscript{6} Dupont HK. A randomised, open-label comparison of non prescription loperamide and attapulgite in the symptomatic treatment of acute diarrhoea. Am. Med. 1990; 88 (suppl 6A): 20S-23S
In conclusion, for diarrhoea in adults,
- There is no study that has investigated the efficacy of SMECTA on stool output.
- One randomised, double-blind, placebo-controlled study showed that diosmectite had an effect on the duration of diarrhoea.
- Four open-label studies versus loperamide were carried out. Results do not demonstrate that diosmectite has an effect on the possible reduction of the risk of dehydration.

4.1.3 Oesophageal-gastro-duodenal and bowel pain

No data was provided about oesophageal-gastro-duodenal pain

The Taiwanese, randomised, double-blind placebo-controlled study by Chang\(^8\) evaluated the efficacy of diosmectite on diarrhea-predominant irritable bowel syndrome. The dosage was 3 sachets per day for 8 days. Loperamide could be used on request. The two primary efficacy endpoints were intensity of pain or discomfort on a VAS ranging from 0 to 100 and the overall evaluation of irritable bowel syndrome on a VAS ranging from 0 to 10.

Table 2: Intensity of pain / discomfort associated with irritable bowel syndrome

<table>
<thead>
<tr>
<th>VAS 0 to 100 (mean ± SD)</th>
<th>Diosmectite n=52</th>
<th>Placebo n=52</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>16.4 ± 7.2</td>
<td>17.2 ± 6.8</td>
<td>-</td>
</tr>
<tr>
<td>Change at Day 28</td>
<td>-6.7 ± 5.3</td>
<td>0.8 ± 5.0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Change at Day 56</td>
<td>-8.7 ± 5.8</td>
<td>-0.3 ± 5.5</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Table 3: Overall evaluation of irritable bowel syndrome

<table>
<thead>
<tr>
<th>VAS 0 to 10 (mean ± SD)</th>
<th>Diosmectite n=52</th>
<th>Placebo n=52</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.19 ± 0.49</td>
<td>4.25 ± 0.47</td>
<td>-</td>
</tr>
<tr>
<td>Change at Day 28</td>
<td>-1.92 ± 0.68</td>
<td>-1.13 ± 0.65</td>
<td>NS</td>
</tr>
<tr>
<td>Change at Day 56</td>
<td>-2.57 ± 0.69</td>
<td>-1.38 ± 0.67</td>
<td>0.02</td>
</tr>
</tbody>
</table>

In this study, the reduction in pain or discomfort between Day 56 and inclusion was more significant in the diosmectite group than in the placebo group. However, the difference between the two groups (8.4% at Day 58) below 10% is not clinically relevant. This difference is not found at Day 28.

The applicant also presented one prospective open-label\(^9\) study on functional chronic diarrhoea with the aim of comparing the effects of diosmectite and loperamide on various symptoms and their impact on quality of life for chronic diarrhoea. The results for the pain endpoint (secondary endpoint) evaluated using a score that includes both frequency and intensity and ranges from 1 to 16, are presented in the table below for indicative purposes only, however the methodological characteristics limit its benefit.

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\(^8\) Chang FY. Efficacy of dioctahedral smectite in treating patients of diarrhea-predominant irritable bowel syndrome. J Gastroenterol Hepatol 22: 2266-2272.

Table 4: Results for the Dumitrascu study on pain

<table>
<thead>
<tr>
<th>Pain score (mean ± SD)</th>
<th>Diosmectite (n = 41)</th>
<th>Loperamide (n = 43)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of treatment</td>
<td>9.3 ± 3.5</td>
<td>10.0 ± 4.2</td>
<td></td>
</tr>
<tr>
<td>End of treatment (2 weeks)</td>
<td>4.4 ± 2.2</td>
<td>6.7 ± 1.1</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

4.1.4 Conclusions for efficacy

For acute diarrhoea in children, two studies out of three showed a difference between diosmectite and placebo for the endpoint of stool output, which is not clinically relevant to draw conclusions on the effect of diosmectite on reducing the risk of dehydration.

For acute diarrhoea in adults, no data was provided on the effect of diosmectite on stool output, however one study showed that diosmectite had an effect on the duration of diarrhoea.

For oesophageal-gastroduodenal and bowel pain, only bowel pain was investigated in one study on irritable bowel syndrome and as a secondary endpoint in a quality of life study. In the first study, diosmectite was superior to placebo; however the difference was not clinically relevant. In the second study, the methodology was not appropriate to be able to draw any conclusions regarding the efficacy of diosmectite on pain.

04.2 Adverse Effects

- The applicant has provided new safety data (PSUR covering the period from 01 December 2007 to 30 November 2010) that did not show any new safety concerns.
- During recent studies, no new serious or adverse effects related to the product have been observed.
- There have been no amendments made to the SPC since the previous opinion.
- In summary, the known safety profile of this medicinal product has not changed.

04.3 Prescription data

According to IMS data (moving annual total, Autumn 2012), there have been 3.2 million prescriptions per year for SMECTA. In 73% of cases, the dose was 3 sachets per day and in 75% of cases the reason for the prescription was gastroenteritis or colitis, which is in accordance with the SPC.

04.4 Therapeutic use

Scientific data regarding methods of managing diarrhoea and oesophageal-gastroduodenal and bowel pain were also taken into consideration.10,11,12

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12 Managing acute gastroenteritis among child: oral rehydration, maintenance and nutritional therapy. King K, Glass R et al. MMWR Recommendations and Reports 2003; 52(RR16); 1-16
Diarrhoea is defined as the passing of overly frequent and abundant stools of an abnormal consistency and weighing more than 300 g per day. The term diarrhoea is used when at least three unformed stools are passed per day.

With acute diarrhoea, the cause is nearly always infection, and spontaneous resolution often occurs in less than 3 days. The aim of treating acute diarrhoea is to prevent dehydration or to provide appropriate rehydration to those who have become dehydrated, in particular at risk patients such as children and the elderly. Oral rehydration solutions contain electrolytes and glucose and form the basis of diarrhoea treatments. In cases of severe dehydration, intravenous rehydration is used. Maintaining food intake is essential, especially for infants and young children.

For children, diosmectite did not demonstrate its efficacy in reducing dehydration; it is not recommended by WHO for acute diarrhoea in children. It does however reduce the number of stools; therefore it is an adjuvant treatment in addition to oral rehydration in children.

For adults, mild forms of diarrhoea may be reduced and shortened by taking a motor or secretory anti-diarrhoeal agent (such as loperamide or racecadotril). Depending on the aetiology, rehydration may be combined with an anti-diarrhoeal agent that slows down digestive transit, in addition or not to an anti-infective agent, for certain cases of infectious diarrhoea caused by bacteria. The antibiotic selected will depend on the bacteria identified.

For bowel disorders, pain symptoms, in the absence of associated symptoms and signs of urgency, are treated if required. Diosmectite or antispasmodic agents may be prescribed in addition to hygiene and dietary measures when these are not adequately effective.

For pain associated with upper digestive tract pain (ulcer, GERD, dyspepsia), treatment should be appropriate for the condition and the intensity of the pain. Depending on the situation, alginates, antacids, anti-H2 and even PPIs can be used. Diosmectite is not intended for the treatment of these conditions.

05 TRANSPARENCY COMMITTEE CONCLUSIONS

05.1 Actual benefit

5.1.1 Acute diarrhoea in children and adults

- Acute diarrhoea is a common symptom. It can, especially in infants, children and the elderly, have severe consequences due to dehydration, and its complications can sometimes be fatal.
- SMECTA is an adjuvant treatment, to be used, in particular, in addition to rehydration therapy, which is an essential element in the treatment of acute diarrhoea in children.
- The efficacy/adverse effects ratio is moderate, however SMECTA does not reduce the risk of dehydration.
- There are alternative treatments and medicinal products available, which should be appropriate to the age of the patient: oral rehydration solutions, loperamide or racecadotril.

Consequently, the Committee considers that the actual benefit of SMECTA is moderate for acute diarrhoea in children and adults.
5.1.2 Bowel pain

- Pain associated with bowel disorders, even if they are not serious, vary in intensity and are sometimes difficult to treat.
- SMECTA is intended as a symptomatic treatment.
- The efficacy/adverse effects ratio for SMECTA is low.
- Anti-spasmodic agents are alternative treatments.

Consequently, the Committee considers that the actual benefit of SMECTA is low in the symptomatic treatment of pain associated with bowel disorders.

5.1.3 Oesophageal-gastroduodenal pain

- Pain associated with oesophageal-gastroduodenal disorders has different aetiologies and varying levels of severity depending on the aetiology: ulcer, gastritis, GERD pain, dyspepsia, etc.
- The efficacy/adverse effects ratio for SMECTA is low.
- There is no therapeutic use for SMECTA for this type of pain.
- There are treatment alternatives.

Consequently, the Committee considers that the actual benefit of SMECTA is insufficient in the symptomatic treatment of pain associated with oesophageal-gastroduodenal disorders.

05.2 Transparency Committee Recommendations

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance, only for the indications "acute diarrhoea in children and adults" and in the "symptomatic treatment of pain associated with bowel disorders."

The Commission gives a negative opinion to continue inclusion on the list of medicines refundable by National Health Insurance for the indication “symptomatic treatment of pain associated with oesophageal-gastroduodenal disorders”.

Furthermore, the Committee still does not recommend inclusion on the list of medicines refundable by National Health Insurance in chronic diarrhoea.

- **Proposed reimbursement rate:** 30%

- **Packaging**
  Appropriate for the prescription conditions.