Public Assessment Report

Decentralised Procedure

Espumisan 100mg/ml oral drops, emulsion

UK/H/1398/001/DC
UK licence no: PL 15548/0001

BERLIN-CHEMIE AG (MENARINI GROUP)
LAY SUMMARY

On 11th June 2010, the MHRA granted BERLIN-CHEMIE AG (MENARINI GROUP) a Marketing Authorisation (licence) for the medicinal product Espumisan 100 mg/ml oral drops, emulsion. This is a general sales licence medicine (GSL) for:
- treating the symptoms of gas-related gastro-intestinal complaints, for example build up of gas in the intestines (meteorism), flatulence or when there is an increase in intestinal gas after operations;
- preparing diagnostic procedures in the abdominal region (e.g. X-ray and sonography, endoscopic examinations, as an adjunct to contrast media suspensions)

The product contains the active substance simeticone to treat the symptoms of flatulence (wind and trapped wind) and is suitable for all age-groups. It works by disintegrating gas bubbles embedded in the food mass and in the mucus of the digestive tract. The gases released in the process can then be taken up by the intestinal wall, as well as removed by intestinal movement.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Espumisan 100 mg/ml oral drops, emulsion outweigh the risks; hence a Marketing Authorisation has been granted.
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   2 Quality aspects
   3 Non-clinical aspects
   4 Clinical aspects
   5 Overall conclusions
Module 6 Steps taken after initial procedure
# Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Espumisan 100 mg/ml oral drops, emulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Article 10a, Well-established use application</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Simeticone</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Oral drops, emulsion</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>1% w/v</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>BERLIN-CHEMIE AG (MENARINI GROUP) Glienicker Weg 125, 12489 Berlin, Germany</td>
</tr>
<tr>
<td><strong>Reference Member State</strong></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Concerned Member States</strong></td>
<td>Bulgaria, Czech Republic, Estonia, Finland, Hungary, Latvia, Poland, Romania, Slovenia and the Slovak Republic</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1398/001/DC</td>
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<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 18th May 2010</td>
</tr>
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</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Espumisan 100 mg/ml oral drops, emulsion
100 mg/ml
Oral drops, emulsion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance: simeticone

1 ml contains 100 mg simeticone.

Excipient: sorbitol (E420), 199 mg/ml

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Oral drops, emulsion
Milky-white, slightly viscous emulsion

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- For the symptomatic treatment of gas-related gastrointestinal complaints such as meteorism or increased gas formation after operations
- As a diagnostic aid in the abdominal region (e.g. to reduce gas shadows in X-rays, sonography; endoscopic examinations; as an adjunct to contrast media suspensions)

4.2 Posology and method of administration
Dosing can take place with a dropper insert or a measuring cap with ml graduation.
25 drops are equivalent to 1 ml (or 100 mg simeticone).

In gas-related gastrointestinal complaints

<table>
<thead>
<tr>
<th>Age-group</th>
<th>Dosage in drops</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>5 -10 drops each to every bottle feed or before every breast-feed*</td>
</tr>
<tr>
<td>1 - 6 years</td>
<td>10 drops 3 - 5 times daily</td>
</tr>
<tr>
<td>6 - 14 years</td>
<td>10 to 20 drops 3 - 5 times daily</td>
</tr>
<tr>
<td>Adolescents and adults</td>
<td>20 drops 3 - 5 times daily</td>
</tr>
</tbody>
</table>

* 5 -10 drops each are put into the bottle feed or administered to the infant with a small spoon immediately before breast-feeding.

It is also possible to take Espumisan 100 mg/ml oral drops, emulsion after operations.

For the preparation of imaging examinations

<table>
<thead>
<tr>
<th>Dosage in ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml 3 times on the day before the examination after meals and 1 ml on the morning of the examination</td>
</tr>
</tbody>
</table>

As an adjunct to contrast media suspensions

<table>
<thead>
<tr>
<th>Dosage in ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml to 4 ml to 1 litre of contrast meal for double-contrast imaging</td>
</tr>
</tbody>
</table>
For the preparation of gastroduodenoscopy

<table>
<thead>
<tr>
<th>Dosage in ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml to 3 ml before endoscopy</td>
</tr>
<tr>
<td>If necessary, a few more ml of</td>
</tr>
<tr>
<td>the emulsion can be put through</td>
</tr>
<tr>
<td>the instrument canal of the</td>
</tr>
<tr>
<td>endoscope during the examination</td>
</tr>
<tr>
<td>to eliminate interfering</td>
</tr>
<tr>
<td>foam bubbles.</td>
</tr>
</tbody>
</table>

Method and duration of administration

Shake well before use!

In order to achieve dosage-compatible dropping, the bottle must be held vertically with the dropper insert facing downwards.

As a measuring device, a measuring cap with millilitre graduation is attached to the screw-cap of the 30-ml and 50-ml dropper bottles. If necessary (for example with doses of 25 drops and more), it can be pulled off and used instead of the dropper insert to measure off the dose.

Note: Due to the danger of swallowing, the measuring cup should be kept away from children.

In gas-related gastrointestinal complaints
Espumisan 100 mg/ml oral drops, emulsion is taken with or after meals, also before going to bed if necessary.

The duration of therapeutic use is in line with the course of the complaints.

If required, Espumisan 100 mg/ml oral drops, emulsion can also be taken over a long period of time.

For the preparation for imaging examinations
The recommended dose of Espumisan 100 mg/ml oral drops, emulsion is taken on the day before the examination and on the morning of the examination.

Note:
In newly occurring and/or persistent complaints, they should be clinically investigated.

4.3 Contraindications
Espumisan 100 mg/ml oral drops, emulsion should not be used in patients with hypersensitivity to the active substance simeticone or one of the other ingredients.

4.4 Special warnings and precautions for use
Espumisan 100 mg/ml oral drops, emulsion contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
None known to date

4.6 Pregnancy and lactation
For Espumisan 100 mg/ml oral drops, emulsion, no clinical data on exposed pregnancies are available. Caution should be exercised when prescribing to pregnant women.

4.7 Effects on ability to drive and use machines
No special precautions

4.8 Undesirable effects
Undesirable effects in association with the use of Espumisan 100 mg/ml oral drops, emulsion have not been observed to date.

4.9 Overdose
Intoxications following use of simeticone have not become known to date.
Simeticone is not absorbed and not changed chemically or enzymatically during gastrointestinal passage. Intoxication is therefore practically ruled out. Even large quantities of Espumisan 100 mg/ml oral drops, emulsion are tolerated without symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Gastrointestinal agent, polysiloxane, defoaming agent

ATC code: A03AX13, OTHER DRUGS FOR FUNCTIONAL BOWEL DISORDERS, Silicones

Espumisan 100 mg/ml oral drops, emulsion contains as the active substance simeticone, a stable, surface-active polydimethylsiloxane. It alters the surface tension of the gas bubbles embedded in the bolus and in the mucus of the digestive tract, which thus disintegrate.

The gases released in the process can then be absorbed by the intestinal wall, as well as eliminated through intestinal peristalsis.

Simeticone has a physical action and is not involved in chemical or enzymatic reactions.

5.2 Pharmacokinetic properties
Simeticone is not absorbed following oral administration and is excreted unchanged after passage through the gastrointestinal tract.

5.3 Preclinical safety data
Simeticone behaves in a chemically inert manner and is not absorbed from the intestinal lumen. Systemic toxic effects are therefore not expected.

There are no non-clinical data on Espumisan 100 mg/ml oral drops, emulsion. Preclinical data on simeticone reveal no specific hazard for humans based on limited studies of repeated-dose toxicity, carcinogenic potential and reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Macrogol stearate
Glycerol monostearate 40-55
Sorbic acid
Sodium hydroxide (for pH adjustment)
Acesulfame potassium
Sodium chloride
Sorbitol liquid (non-crystallising) (E 420)
Carbomer
Sodium citrate
Banana flavour
Purified water

6.2 Incompatibilities
Not applicable

6.3 Shelf life
The shelf life is 36 months

After the first opening, Espumisan 100 mg/ml oral drops, emulsion is stable for 3 more months. The medicinal product should not be used after the expiry date.

6.4 Special precautions for storage
This medical product does not require any special storage conditions.

6.5 Nature and contents of container
Labelled 30-ml or 50-ml amber-glass bottle with dropper insert, screw-cap and attached measuring cap

Not all pack sizes may be marketed.
6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
BERLIN-CHEMIE AG (MENARINI GROUP)
Glienicker Weg 125
12489 Berlin, Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 15548/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Espumisan 100 mg/ml oral drops, emulsion

100 mg/ml, oral drops, emulsion
Active substance: simeticone

Read all of this leaflet carefully because it contains important information for you.
This medicine is available without prescription. However, you still need to use Espumisan comfort carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if the symptoms worsen or do not improve.
- If you notice a side effect, please tell your doctor or pharmacist.

In this leaflet:

1. What Espumisan 100 mg/ml oral drops, emulsion is and what it is used for
2. Before you use Espumisan 100 mg/ml oral drops, emulsion
3. How to use Espumisan 100 mg/ml oral drops, emulsion
4. Possible side effects
5. How to store Espumisan 100 mg/ml oral drops, emulsion
6. Further information

1. What Espumisan 100 mg/ml oral drops, emulsion is and what it is used for

Espumisan 100 mg/ml oral drops, emulsion treats the symptoms of flatulence (wind and trapped wind) and is suitable for all age-groups. It works by disintegrating gas bubbles embedded in the food mass and in the mucus of the digestive tract. The gases released in the process can then be taken up by the intestinal wall, as well as removed by intestinal movement.

Uses

Espumisan 100 mg/ml oral drops, emulsion is used:
- for treating the symptoms of gas-related gastro-intestinal complaints, for example build up of gas in the intestines (meteorism), flatulence or when there is an increase in intestinal gas after operations;
- for preparing diagnostic procedures in the abdominal region (e.g. X-ray and sonography, endoscopic examinations, as an adjunct to contrast media suspensions).
2. **Before you use Espumisan 100 mg/ml oral drops, emulsion**

   **Do not use Espumisan 100 mg/ml oral drops, emulsion:**
   - If you are allergic (hypersensitive) to the active substance simeticone or any of the other ingredients of Espumisan 100 mg/ml oral drops, emulsion. Please keep in mind when administering Espumisan 100 mg/ml oral drops, emulsion to others that this may also apply to them.

   **Take special care with Espumisan 100 mg/ml oral drops, emulsion**

   In both new and/or persistent stomach complaints you should visit a doctor. They will investigate whether there is an underlying disease that requires other treatment.

   Particularly if used in infants and children, the doctor should be consulted.

   **Taking other medicines**

   Interactions with other medicines are not known.

   **Taking Espumisan 100 mg/ml oral drops, emulsion with food and drink**

   No special features are to be noted.

   **Pregnancy and breast-feeding**

   Ask your doctor or pharmacist for advice before taking any medicine. Since no clinical data on exposed pregnancies are available, the use of Espumisan 100 mg/ml oral drops, emulsion during pregnancy and breast-feeding is not recommended.

   **Driving and using machines**

   No special precautions are required.

   **Important information about some of the ingredients of Espumisan 100 mg/ml oral drops, emulsion**

   This medicinal product contains sorbitol. If you have been told by your doctor that an intolerance to some sugars exists, contact your doctor before using this medicinal product.

3. **How to use Espumisan 100 mg/ml oral drops, emulsion**

   Always use Espumisan 100 mg/ml oral drops, emulsion exactly according to the instructions in this package leaflet. You should check with your doctor or pharmacist if you are not sure.
There are two ways to measure a dose of Espumisan 100 mg/ml oral drops, emulsion:
Depending on how high the dose is, dosing can take place with:
- a dropper insert,
- a measuring cap with millilitre (ml) graduation.
More detailed instructions on using the measuring devices can be found after the dose tables.

Dosage

Dose Espumisan 100 mg/ml oral drops, emulsion according to the intensity of the complaints.

The usual dose is:

For treating the symptoms of gas-related gastro-intestinal complaints

<table>
<thead>
<tr>
<th>Age-group</th>
<th>Dosage in drops (dropper insert)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>5-10 drops each are put into the bottle feed or administered to the infant with a small spoon immediately before every breast-feeding</td>
</tr>
<tr>
<td>1 - 6 years</td>
<td>10 drops 3 to 5 times daily</td>
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<tr>
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<td>Adolescents and adults</td>
<td>20 drops 3 to 5 times daily</td>
</tr>
</tbody>
</table>

It is also possible to take Espumisan 100 mg/ml oral drops, emulsion after operations.

Espumisan 100 mg/ml oral drops, emulsion is taken with or after meals, also before going to bed if necessary.

Espumisan 100 mg/ml oral drops, emulsion should be taken for as long as the complaints persist. Espumisan 100 mg/ml oral drops, emulsion is suitable to be taken over a long period of time only upon medical advice. Please also read Section 2 “Take special care”.

For preparing diagnostic procedures

<table>
<thead>
<tr>
<th>Dosage in ml (measuring cap)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml 3 times daily after meals on the day before the examination and 1 ml on the morning of the examination</td>
</tr>
</tbody>
</table>

As an adjunct to contrast media suspensions

<table>
<thead>
<tr>
<th>Dosage in ml (measuring cap)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 4 ml to 1 litre of contrast meal for</td>
</tr>
</tbody>
</table>
For preparing inspections of the stomach and small intestine (endoscopy)

<table>
<thead>
<tr>
<th>Dosage in ml (measuring cap)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 3 ml before endoscopy</td>
</tr>
</tbody>
</table>

If necessary, a few more ml of the emulsion can be put through the instrument canal of the endoscope during the examination to eliminate interfering foam bubbles.

**Method of use**

Shake well before use!

**Using the dropper insert (10 - 25 drops):**
The bottle must be held vertically with the dropper insert facing downwards.
25 drops are equivalent to 1 ml of the emulsion (equivalent to 100 mg simeticone).

**Using the measuring cap:**
As a measuring device, a measuring cap with ml graduation is attached to the screw-cap of the 30-ml and 50-ml dropper bottles. If necessary (for example with doses of 25 drops and more), it can be pulled off and used instead of the dropper insert to measure off the dose.

Note: Due to the danger of swallowing, the measuring cap should be kept away from children.

If you use more *Espumisan 100 mg/ml oral drops, emulsion* than you should

Taking too much *Espumisan 100 mg/ml oral drops, emulsion* is unlikely to cause any ill effect. Even large quantities of *Espumisan 100 mg/ml oral drops, emulsion* are tolerated without causing problems. The active substance of *Espumisan 100 mg/ml oral drops, emulsion*, simeticone, makes foam in the gastro-intestinal canal disintegrate in a purely physical way. Simeticone is not absorbed and not changed chemically or enzymatically during passage through the intestines.
If you forget to use *Espumisan 100 mg/ml oral drops, emulsion*

You can make up for the dose at any time.

If you stop using *Espumisan 100 mg/ml oral drops, emulsion*

There may be a recurrence of the complaints.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

To date, *Espumisan 100 mg/ml oral drops, emulsion* has not been associated with any side effects.

If you notice any side effects, please tell your doctor or pharmacist.

5. How to store *Espumisan 100 mg/ml oral drops, emulsion*

No special storage conditions are required for this medicine.

Keep out of the reach and sight of children.

Do not use *Espumisan 100 mg/ml oral drops, emulsion* after the expiry date which is stated on the outer carton and label after “EXP”. The expiry date refers to the last day of that month.

*Espumisan 100 mg/ml oral drops, emulsion* can be used for up to 3 months after first opening.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What *Espumisan 100 mg/ml oral drops, emulsion* contains

The active substance is simeticone.

1 ml of oral emulsion contains 100 mg simeticone.

The other ingredients are:
Macrogol stearate, glycerol monostearate 40-55, sorbic acid, sodium hydroxide for pH adjustment; acesulfame potassium, sodium chloride, liquid sorbitol (non-crystallising) (E 420), carboxomer, sodium citrate, banana flavour, purified water

What *Espumisan 100 mg/ml oral drops, emulsion* looks like and contents of the pack

*Espumisan 100 mg/ml oral drops, emulsion* is a milky-white, slightly viscous emulsion in a labelled 30-ml or 50-ml amber glass bottle with dropper insert, screw-cap and attached measuring cap.

Not all pack sizes may be marketed.
Marketing Authorisation Holder and Manufacturer

BERLIN-CHEMIE AG
(Menarini Group)
Gienticker Weg 125
12489 Berlin, Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

United Kingdom (RMS) Espumisan 100 mg/ml oral drops, emulsion
Bulgaria Еспумисан комфорт 100 mg/ml перорални капки, емулсия
Czech Republic Espumisan kapky 100 mg/ml
Estonia Espumisan 100 mg/ml
Finland Espumisan 100 mg/ml tipat, emulsiio
Hungary Espumisan 100 mg/ml belsőleges emulzió
Latvia Espumisan 100 mg/ml emulsija iekšējai ietišanai
Poland Espumisan 100 mg/ml
Romania Espumisan 100 mg/ml, picături orale, emulsio
Slovenia Espumisan 100 mg/ml, perorálne kapličky, emulzija
Slovak Republic Espumisan confort 100 mg/ml perorálnie emulzné kvapky

This leaflet was last approved in
Module 4
Labelling

PARTICULARS TO APPEAR ON THE <OUTER PACKAGING>

FOLDING BOX

1. NAME OF THE MEDICINAL PRODUCT

Espumisan 100 mg/ml oral drops, emulsion [to be adapted nationally]
100 mg/ml, oral drops, emulsion

Simeticone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of oral drops, emulsion (= 25 drops) contains:
Simeticone 100 mg

3. LIST OF EXCIPIENTS

Contains sorbitol (E 420).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

[to be adapted nationally]

30 ml of oral drops, emulsion; packaging includes a measuring cap. [as sample package for physicians]
30 ml of oral drops, emulsion; packaging includes a measuring cap. [as original package]
50 ml of oral drops, emulsion; packaging includes a measuring cap. [as original package]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

– not applicable –
<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
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</thead>
<tbody>
<tr>
<td>EXP: [in terms as nationally required]</td>
</tr>
<tr>
<td>Shelf life after first opening: 3 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>– not applicable –</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>[to be completed nationally if required]</td>
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</table>

<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>BERLIN-CHEMIE AG (MENARINI GROUP)</td>
</tr>
<tr>
<td>Glienicker Weg 125</td>
</tr>
<tr>
<td>12489 Berlin, Germany</td>
</tr>
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</table>

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<thead>
<tr>
<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
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<tbody>
<tr>
<td>[to be completed nationally]</td>
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</table>

<table>
<thead>
<tr>
<th>13. BATCH NUMBER</th>
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</thead>
<tbody>
<tr>
<td>Batch: [in terms as nationally required]</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicinal product not subject to medical prescription</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>15. INSTRUCTIONS ON USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>[to be completed nationally]</td>
</tr>
<tr>
<td>For flatulence and meteorism</td>
</tr>
<tr>
<td>Diagnostic aid</td>
</tr>
<tr>
<td>Shake well before use.</td>
</tr>
<tr>
<td>To drop, please hold the bottle upside down.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>16. INFORMATION IN BRAILLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>espumisan 100 [to be adapted nationally]</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE <IMMEDIATE PACKAGING> LABEL

1. NAME OF THE MEDICINAL PRODUCT

Espumisan 100 mg/ml oral drops, emulsion  [to be adapted nationally]
100 mg/ml, oral drops, emulsion
Simeticone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of oral drops, emulsion (= 25 drops) contains:
Simeticone 100 mg

3. LIST OF EXCIPIENTS

Contains sorbitol (E 420).
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

[to be adapted nationally]

30 ml of oral drops, emulsion  [as sample package for physicians]
30 ml of oral drops, emulsion  [as original package]
50 ml of oral drops, emulsion  [as original package]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

– not applicable –

8. EXPIRY DATE

EXP: [in terms as nationally required]
Shelf life after first opening: 3 months
9. SPECIAL STORAGE CONDITIONS

– not applicable –

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[to be completed nationally, if required]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BERLIN-CHEMIE AG (MENARINI GROUP)
Glienicker Weg 125
12489 Berlin, Germany

12. MARKETING AUTHORISATION NUMBER(S)

[to be completed nationally]

13. BATCH NUMBER

Batch: [in terms as nationally required]

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription

15. INSTRUCTIONS ON USE

[to be completed nationally]

For flatulence and meteorism
Diagnostic aid

Shake well before use.
To drop, please hold the bottle upside down.
Read the package leaflet before use.

16. INFORMATION IN BRAILLE

espumisan 100  [to be adapted nationally]
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
On 11th June 2010, the MHRA granted BERLIN-CHEMIE AG (MENARINI GROUP) a Marketing Authorisation (licence) for the medicinal product Espumisan 100mg/ml oral drops, emulsion. This is a general sales licence medicine (GSL):
- for the symptomatic treatment of gas-related gastrointestinal complaints such as meteorism or increased gas formation after operations
- As a diagnostic aid in the abdominal region (e.g. to reduce gas shadows in X-rays, sonography; endoscopic examinations; as an adjunct to contrast media suspensions).

This application was submitted under the decentralised procedure (DCP), with the UK as reference member state (RMS), and Bulgaria, Czech Republic, Estonia, Finland, Hungary, Latvia, Poland, Romania, Slovenia and the Slovak Republic as concerned member states (CMS). It was submitted under Article 10a of Directive 2001/83 EC, a well-established use application.

The product contains the active ingredient simeticone. Simeticone is a defoaming agent used in the treatment of disorders or disadvantages due to excess gas in the gastrointestinal tract. As the drug has been in clinical use for more than 30 years, its clinical use has been established. Simeticone allows mucus-surrounded gas bubbles to coalesce and be expelled. It is physiologically inert and does not appear to be absorbed from the gastrointestinal tract or to interfere with gastric secretion or absorption of nutrients. After oral administration the drug is excreted unchanged in the faeces.

No new preclinical or clinical studies were conducted, which is acceptable given the nature of the application.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture of this product. Evidence of compliance with GMP has been provided for the named manufacturing sites.

The decentralised procedure was completed at Day 210 (18th May 2010), with the reference member state and all concerned member states agreeing that the licence was approvable. The national phase of the decentralised procedure was completed in the UK on 11th June 2010.
### II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th><strong>Name of the product in the Reference Member State</strong></th>
<th>Espumisan 100 mg/ml oral drops, emulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name(s) of the active substance(s) (INN)</strong></td>
<td>Simeticone</td>
</tr>
<tr>
<td><strong>Pharmacotherapeutic classification (ATC code)</strong></td>
<td>Silicones – other drugs for functional bowel disorders, Silicones (A03AX13)</td>
</tr>
<tr>
<td><strong>Pharmaceutical form and strength(s)</strong></td>
<td>100mg/1ml oral drops, emulsion</td>
</tr>
<tr>
<td><strong>Reference numbers for the Decentralised Procedure</strong></td>
<td>UK/H/1398/001/DC</td>
</tr>
<tr>
<td><strong>Reference Member State</strong></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Member States concerned</strong></td>
<td>Bulgaria, Czech Republic, Estonia, Finland, Hungary, Latvia, Poland, Romania, Slovenia and the Slovak Republic</td>
</tr>
<tr>
<td><strong>Marketing Authorisation Number(s)</strong></td>
<td>PL 15548/0001</td>
</tr>
<tr>
<td><strong>Name and address of the authorisation holder</strong></td>
<td>BERLIN-CHEMIE AG (MENARINI GROUP), Glienicker Weg 125, 12489 Berlin, Germany</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Simeticone
Chemical Name: Mixture of polydimethylsiloxane (PDMS) fluid and silica
PDMS (α-ω-bis-trimethylsiloxy polydimethylsiloxane)
Fumed silica: SiO2

Molecular Formula: $(\text{CH}_3)_2\text{Si}(\text{O-Si(\text{CH}_3)_2)_n=O-Si(\text{CH}_3)_3, SiO}_2$

Structure:

\[
\begin{array}{c}
\text{H}_3\text{C} \quad \text{CH}_3 \\
\text{H}_3\text{C} \quad \text{Si} \\
\text{Si} \\
\text{O} \\
\text{Si} \\
\text{Si} \\
\text{H}_3\text{C} \quad \text{CH}_3 \\
\end{array}
\]

Appearance: viscous translucent light grey liquid, practically insoluble in water,
very slightly soluble to practically insoluble in ethanol, practically insoluble in methanol, partly miscible with ethyl acetate, with methylene chloride, with methyl ethyl ketone and with toluene

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance simeticone. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Appropriate proof-of-structure data has been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

Batch analysis data are provided that comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all components of the container-closure system. The primary packaging has been shown to comply with European regulations concerning materials in contact with food.

A suitable retest period has been stated, based on stability studies performed on batches of the active substance stored in the proposed container-closure system, under conditions in compliance with current guidelines.

P Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients macrogol stearate, glycerol monostearate, sorbic acid, sodium hydroxide, acesulfame potassium, sodium chloride, carabomer, sodium citrate, banana flavour, purified water. With the exception of banana flavour, all excipients used comply with their respective European Pharmacopoeia monographs. Banana flavour complies with a suitable in-house specification. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin.
**Pharmaceutical Development**  
The applicant has provided a suitable product development rationale and data.

**Manufacture**  
A satisfactory batch formula has been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and has shown satisfactory results.

**Control of Drug Product**  
The finished product specification proposed is acceptable and provides an assurance of the quality of the finished product. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specification.

Satisfactory data on the characterisation of impurities have been provided.

**Reference Standards or Materials**  
Certificates of analysis for all reference standards used have been provided and are satisfactory.

**Container Closure System**  
The finished product is packaged in amber-coloured glass bottles, with a dropper insert, screw cap and a measuring cap.

The marketing authorisation holder has committed to submitting any mock-ups to the regulatory authorities for approval before marketing any pack size.

**Stability of the Drug Product**  
Stability data provided to support a shelf-life of 36 months for the unopened package, with no specific storage conditions. After opening, the emulsion is stable for a further 3 months.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**  
The SPC, PIL and labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Conclusion**  
It is recommended that a marketing authorisation is granted for this application.

**III.2 PRE-CLINICAL ASPECTS**  
No new pre-clinical studies have been submitted with this application and none are required. A suitable pre-clinical expert report has been written by an appropriately qualified person, based on literature references.

An environmental risk assessment has been submitted with this application. It shows that it is unlikely that this product will pose a risk to the environment.
III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

Pharmacodynamics
No new pharmacodynamic data have been provided and none are required for an application of this type.

Pharmacokinetics
No new pharmacokinetic data have been provided and none are required for an application of this type. Furthermore, the product is physiologically inert and does not appear to be absorbed from the gastrointestinal tract or to interfere with gastric secretion or absorption of nutrients. After oral administration, the drug is excreted unchanged in the faeces. Therefore, there is no information with respect to any clinically relevant pharmacokinetic data.

EFFICACY
No new efficacy data have been provided and none are required for an application of this type.

SAFETY
No new data are submitted with this application and none are required for an application of this type.

EXPERT REPORT
A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical practitioner.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
This is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is satisfactory and consistent with the SPC.

LABELLING
These are satisfactory.

CONCLUSION
There are no clinical objections to the grant of marketing authorisation for this application.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Espumisan 100mg/ml oral drops, emulsion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
No new clinical data have been submitted with this application and none are required. Simethicone is currently marketed in several countries for numerous preparations and pharmaceutical forms (emulsion, capsules, drops, and tablets). It has been available for more than 50 years and has been used clinically for more than 30 years. The following indications are generally accepted:
- For the symptomatic treatment of gas-related gastrointestinal complaints such as meteorism or increased gas formation after operations
- As a diagnostic aid in the abdominal region (e.g. to reduce gas shadows in X-rays, sonography; endoscopic examinations; as an adjunct to contrast media suspensions)

The SPC, PIL and labelling are satisfactory and typical for a product of this nature.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with simeticone is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
# Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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