SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Osmohale inhalation powder, hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 capsule contains 0 mg, 5 mg, 10 mg, 20 mg or 40 mg mannitol

The delivered dose from each of the 5, 10, 20 and 40 mg capsules is approximately 3.4, 7.7, 16.5 and 34.1 mg, respectively.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsules.

The powder is white or almost white.

The empty capsule is clear, printed with two white bands.

The capsule containing 5 mg is half white, half clear, marked 5 mg.

The capsule containing 10 mg is half yellow, half clear, marked 10 mg.

The capsule containing 20 mg is half pink, half clear, marked 20 mg.

Capsules containing 40 mg are half red, half clear, marked 40 mg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Osmohale is indicated for identifying bronchial hyperresponsiveness in subjects with a baseline forced expiratory volume in one second (FEV_1) of 70% or more of the predicted value.

4.2 Posology and method of administration

Posology

Adults
The capsules are supplied in kit form containing sufficient number of capsules to complete one maximum dose challenge, and an inhaler.

The airway response to Osmohale is measured using the FEV_1.

Paediatric population
The Osmohale test should not be used in children aged under 6 years because of their inability to provide reproducible spirometric measurements (see section 5.1).

There is limited information on the use of Osmohale in patients 6-18 years of age therefore Osmohale is not recommended in this population.

Method of administration
Prior to the challenge, spirometry should be performed and the reproducibility of the baseline FEV_1 established.

The patient should be seated comfortably and encouraged to maintain good posture to assist the effective delivery of Osmohale to the lungs. The test should proceed as follows:

1. Apply a nose clip. The patient should be directed to breathe through the mouth.
2. Insert the 0 mg capsule into the inhalation device. Puncture the capsule by depressing the buttons on the sides of the device carefully, and once only (a second puncture may shatter the capsules).
3. The patient should exhale completely, before inhaling from the device in a controlled rapid deep inhalation.
4. At the end of the deep inspiration, start a 60 second timer. The patient should hold his/her breath for 5 seconds and exhale through the mouth before removal of the nose clip.
5. At the end of the 60 seconds, measure the FEV_1 at least in duplicate to obtain two reproducible measurements. The highest reading becomes baseline FEV_1. The target FEV_1 is calculated by multiplying the baseline FEV_1 by 0.85.
6. Insert the 5 mg capsule into the inhalation device, and proceed as above.
7. Repeat steps 1 – 5 following the dose steps in the table below until the patient has a positive response or 635 mg have been administered.

DOSE STEPS FOR OSMOHALE CHALLENGE			
Dose #	**Dose mg**	**Cumulative Dose mg**	**Capsules per dose**
1	0	0	1
2	5	5	1
3	10	15	1
4	20	35	1
5	40	75	1
6	80	155	2 x 40 mg
7	160	315	4 x 40 mg
8	160	475	4 x 40 mg
9	160	635	4 x 40 mg

A positive response is achieved when the patient experiences either of the following:
15% fall in FEV_1 from baseline (0 mg dose)
or
10% incremental fall in FEV_1 between doses

Examples of positive tests:

1. FEV_1 fall following dose step 2: 3%
   FEV_1 fall following dose step 3: 8%
   FEV_1 fall following dose step 4: 16%
   - as the total fall is 16% (≥ 15%), the test is positive.

2. FEV_1 fall following dose step 2: 3%FEV_1 fall following dose step 3: 14%
   - although the total fall is < 15%, the incremental fall is 11% (≥ 10%) and the test is positive.

Points to remember:

1. There should be minimal delay between FEV_1 measurement and the next dose so that the osmotic effect in the airway is cumulative.

2. At least 2 acceptable FEV_1 measures should be obtained after each dose. More than 2 measurements may be required, for example in the case of variability between readings or improper manoeuvres during measurement (such as the occurrence of cough).

3. The 80 and 160 mg doses are administered in multiples of 40 mg capsules (i.e., 2 x 40 mg and 4 x 40 mg, respectively). There is no interval between administering multiple capsules for these doses. One capsule should be followed immediately by the next until the total dose has been inhaled.

4. After inhalation of each dose, the capsule should be checked to ensure it is empty. A second inhalation from the same capsule may be required if the dose has not been entirely dispersed from the capsule.

Most patients recover spontaneously after the challenge test, however those with a positive challenge or who experience aggravation of asthma should receive a standard dose of a $beta_2$ agonist to expedite recovery. Those with a negative challenge may also receive a standard dose of a $beta_2$ agonist to expedite recovery. Following administration of a $beta_2$ agonist, FEV_1 usually returns to baseline within 10 - 20 minutes. Patients should be monitored until their FEV_1 has returned to within 5% of baseline levels.

4.3 Contraindications

Hypersensitivity to mannitol or to any of the capsule ingredients.

Osmohale should not be given to patients with severe airflow limitation (FEV_1 < 50% predicted or< 1.0 l) or conditions that may be compromised by induced bronchospasm or repeated blowing manoeuvres. These include: aortic or cerebral aneurysm, uncontrolled hypertension, myocardial infarction or a cerebral vascular accident in the previous six months.

4.4 Special warnings and precautions for use

Osmohale is to be administered by inhalation only. Inhaled mannitol causes bronchoconstriction. The Osmohale inhalation test should only be conducted in suitable laboratories/clinics under the supervision of an experienced physician and by a physician or another health professional appropriately trained to perform bronchial provocation tests and to manage acute bronchospasm. The responsible physician, appropriately trained to treat acute bronchospasm, including appropriate use of resuscitation equipment, must be close enough to respond quickly to an emergency. A stethoscope, sphygmomanometer, and pulse oximeter should be available.

Patients should not be left unattended during the procedure once the administration of Osmohale has begun.

Medications to treat severe bronchospasm must be present in the testing area. They include adrenaline for subcutaneous injection, and salbutamol or other beta agonists in metered-dose inhalers. Oxygen must be available. A small-volume nebuliser should be readily available for the administration of bronchodilators.

General precautions when conducting spirometry and bronchial provocation testing should be observed, including using caution in patients with the

following: ventilatory impairment (baseline FEV_1 of less than 70% of predicted normal values or an absolute value of 1.5 l or less in adults), spirometry induced bronchoconstriction, haemoptysis of unknown origin, pneumothorax, recent abdominal or thoracic surgery, recent intraocular surgery, unstable angina, inability to perform spirometry of acceptable quality or upper or lower respiratory tract infection in the previous 2 weeks.

If a patient has spirometry induced asthma or the FEV_1 fall is greater than 10% at continued administration after the 0 mg capsule, a standard dose of bronchodilator should be given and the Osmohale challenge discontinued.

Exercise: Vigorous exercise should be fully avoided on the day of the test, as this may affect test results.

Smoking: Since smoking may affect test results it is recommended that patients refrain from smoking for at least 6 hours prior to testing.
The effects of repeat Osmohale testing within a short period of time have not been investigated therefore careful consideration should be given to repeat use of Osmohale.

Paediatric population
The Osmohale test should not be used in patients below 6 years of age due to their inability to provide reproducible spirometric measurements.

There is limited information on the use of Osmohale in patients 6-18 years of age therefore Osmohale is not recommended in this population.

4.5 Interaction with other medicinal products and other forms of interaction

Regular use of inhaled corticosteroids reduces the airway sensitivity to Osmohale and in many individuals, complete inhibition of the airway response occurs.

The following medicines should be withheld before conducting an Osmohale test as they may affect the results:
Recommended periods for withholding medicines before the Osmohale test are listed below.

Time to Withhold	**Medication**
6-8 hours	**INHALED NON-STEROIDAL ANTI-INFLAMMATORY AGENTS** e.g. sodium cromoglycate, nedocromil sodium
8 hours	**SHORT-ACTING BETA$_2$ AGONISTS** e.g. salbutamol, terbutaline
12 hours	**INHALED CORTICOSTEROIDS** e.g. beclomethasone dipropionate, budesonide, fluticasone propionate

12 hours	**IPRATROPIUM BROMIDE**
24 hours	**LONG-ACTING BETA$_2$ AGONISTS** e.g. salmeterol, formoterol
24 hours	**INHALED CORTICOSTEROIDS PLUS LONG-ACTING BETA$_2$ AGONISTS** e.g. fluticasone and salmeterol, budesonide and formoterol
24 hours	**THEOPHYLLINE**
72 hours	**TIOTROPIUM BROMIDE**
72 hours	**ANTIHISTAMINES** e.g. cetirizine, fexofenadine and loratadine
4 days	**LEUKOTRIENE-RECEPTOR ANTAGONISTS** e.g. montelukast sodium

Food: Ingestion of significant quantities of coffee, tea, cola drinks, chocolate or other food containing caffeine may decrease bronchial responsiveness and should be totally avoided on the day of the test.

4.6 Fertility, Pregnancy and lactation

Pregnancy
There are no data or limited amount of data (less than 300 pregnancy outcomes) from the use of D-mannitol in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
The effects of a possible hyperresponsiveness reaction on the mother and/or the foetus is unknown and therefore Osmohale should not be given to pregnant women.

Breastfeeding
No effects on the breast-fed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to inhaled D-mannitol is negligible. Osmohale may be used during breast-feeding.

Fertility
For mannitol no clinical data on fertility are available. Animal reproduction studies have not been carried out with inhaled mannitol. However, studies with orally administered mannitol indicate no fertility effects (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Osmohale has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
A positive result with Osmohale may produce symptoms of bronchospasm such as chest tightness, cough or wheezing.

The safety population consisted of 1,046 subjects including patients with asthma, symptoms suggestive of asthma, and healthy individuals from 6 to 83 years of age who participated in the two clinical trials. The racial distribution of subjects was 84% Caucasian, 5% Asian, 4% Black, and 7% Other. In study DPM-A-301, adverse events were monitored from the beginning of the challenge to a week following the challenge day. In study DPM-A-305, adverse reactions were reported at the time of the testing procedure and for one day thereafter. No serious adverse reactions were reported following bronchial challenge testing with Osmohale in either trial. Due to the short half-life of mannitol, the causal link would be expected to diminish over this period of time. No serious adverse events were reported during the study. Most adverse events were reported to be mild and transient.

Most patients experienced cough during the challenge; however, it was only occasional in the majority of these patients (87%). In the remainder, it was frequent enough to cause some delay in continuation of the challenge (13%) or discontinuation (1%). Pharyngolaryngeal pain was also a commonly reported adverse event; its occurrence may be reduced if the mouth is rinsed after the test. Five adult subjects (0.6%) discontinued from the studies within a day following administration of Osmohale because of cough, decreased lung function, feeling jittery, sore throat, and throat irritation. One subject (0.4%) discontinued from the studies within a day following administration of Osmohale because of retching.
Tabulated list of adverse reactions
The adverse reactions reported in the two studies are listed below by organ class and absolute frequency:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)

Infections and infestations:
Common: Nasopharyngitis

Nervous system disorders:
Common: Headache
Uncommon: Dizziness

Eye disorders:
Uncommon: Eye irritation

Vascular disorders:
Uncommon: Flushing, Peripheral coldness

Respiratory, thoracic and mediastinal disorders:

Common: Cough*, Dyspnoea, Pharyngolaryngeal pain, Rhinorrhoea, Throat irritation, Aggravated Asthma
Uncommon: Hoarseness, Epistaxis, Oxygen saturation decreased

Gastrointestinal disorders:
Common: Nausea, Vomiting
Uncommon: Upper abdominal pain, Diarrhoea, Mouth ulceration

Skin and subcutaneous tissue disorders:
Uncommon: Pruritus, Hyperhidrosis

Musculoskeletal and connective tissue disorders:
Uncommon: Musculoskeletal pain

General disorders:
Common: Chest tightness
Uncommon: Fatigue, Feeling jittery, Thirst

* Cough was only defined as an adverse event during the challenge test if it led to discontinuation of the challenge.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

Susceptible persons may suffer a hyperresponsiveness reaction from an overdose. The reaction can be treated with a bronchodilator. There is some experience with Osmohale in clinical studies where patients experienced a 15% fall in FEV_1 and inhaled a further dose (these studies used 20-25% as the target FEV_1 fall). The maximum fall measured was 50.2%. If excessive bronchoconstriction occurs, a $beta_2$ agonist should be given, and oxygen if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Diagnostic Agents, ATC code: V04CX
Osmohale is an indirect bronchial provocation test used to measure bronchial hyperresponsiveness.

Mechanism of action and pharmacodynamic effects

Published data indicate that inhaled mannitol increases the osmolarity in the airways which results in a release of different bronchoconstriction mediators from inflammatory cells within the airways. The mediators then act via specific receptors to cause contraction of the bronchial smooth muscle and the airways to narrow.

Clinical efficacy and safety

DPM-A-301

The ability of the Osmohale test to identify bronchial hyperresponsiveness was investigated in a clinical study that enrolled 646 subjects (aged 6 to 83 years) of whom 466 adult subjects (aged 18 years and over) completed the trial. Subjects underwent two challenge tests: one with mannitol and one with hypertonic saline at two separate visits.

Following completion of the study, a respiratory physician assessed the data and categorised the subjects as being clinically asthmatic or non-asthmatic on the basis of their medical history, history of respiratory symptoms, medications and the results of the hypertonic saline challenge. In adults, compared to this clinical diagnosis, the mannitol challenge had a sensitivity of 55%, and a specificity of 98%. The positive predictive value was 99% and the negative predictive value was 34%.

The mannitol challenge test was positive (15% fall in FEV_1) in 211 adult subjects at a mean dose of 120.2 mg. The mean maximum FEV_1 fall (± SD) for the two challenges was comparable: 21.0% (± 5.7) for mannitol and 21.3% (± 5.9) for hypertonic saline.

For the 169 adult subjects classified as asthmatic by the respiratory physician, but negative to mannitol, 84% were taking either inhaled corticosteroids alone or in combination with a long acting $beta_2$ agonist. The mean % fall in FEV_1 for this group was 6.3% (± 3.7). It is important to consider current glucocorticosteroid therapy when interpreting indirect challenge test results. In 195 adults not taking inhaled corticosteroids, compared to the clinical diagnosis, the mannitol challenge had a sensitivity of 65% and a specificity of 98%. The positive predictive value was 97% and the negative predictive value was 68%.

DPM- A-305

In the second clinical study, Osmohale was compared with a methacholine bronchial challenge test in detecting bronchial hyperresponsiveness in subjects with symptoms suggestive of asthma but without a definite diagnosis of asthma. The 509 subjects aged 6 to 50 years were screened for enrolment with 419 and 420 subjects receiving at least one dose of Osmohale or methacholine, respectively. The maximum cumulative dose of Osmohale was 635 mg.

During the course of the study subjects underwent three types of bronchial challenge tests, exercise, Osmohale, and methacholine. A positive exercise test was defined as a decrease in $FEV_1 \geq 10\%$, a positive bronchial challenge test

with Osmohale was defined by either a decrease in FEV_1 by ≥ 15% from baseline or a between-dose reduction in FEV_1 ≥ 10%, and a positive methacholine response was defined as a decrease in FEV_1 ≥ 20% after breathing methacholine at a concentration less than or equal to 16 mg/ml. When compared to the surrogate standards of truth of positive exercise testing and a physicians diagnosis, the mannitol and methacholine challenge tests were diagnostically (90% CI within 80-125%) and statistically equivalent using test sensitivity and specificity as the primary efficacy endpoint.

Comparisons of the sensitivity and specificity for the Osmohale test and methacholine in Study DPM-A-305

	Treatment	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**
Positive Exercise Challenge			
	Osmohale	59 (51, 66)	65 (59, 71)
	Methacholine	56 (48, 63)	69 (64, 75)
Physicians Diagnosis			
	Osmohale	56 (49, 62)	73 (66, 80)
	Methacholine	51 (45, 57)	75 (66 ,80)

5.2 Pharmacokinetic properties

Absorption and distribution
There are no pharmacokinetic data available for dry powder mannitol following inhaled administration although limited animal data on mannitol solution indicates an absorption half-life of approximately 12-60 minutes. Following absorption, the pharmacokinetic profile of inhaled mannitol can be expected to follow that of intravenously administered mannitol.

Biotransformation and elimination
When administered intravenously, mannitol is eliminated largely unchanged by glomerular filtration and 80% of the dose is excreted in the urine within 3 hours. The elimination half-life in adults is approximately 1-2 hours. In the presence of renal failure, the half-life is extended, however this is not expected to be of clinical significance.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on short- and long-term oral repeat dose toxicity, genotoxicity and local tolerance studies. Animal reproduction studies have not been carried out with inhaled mannitol. However, studies conducted with orally administered mannitol indicated no teratogenic effects in mice or rats, at doses of up to 1.6 g/kg, or in hamsters at 1.2 g/kg.

In addition, safety of the inhalation route was demonstrated by a single dose and a two week repeat dose toxicity study in rats that revealed no toxicologically significant findings.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Capsules are packed in Aluminium/Aluminium blisters.
1 diagnostic kit consists of:

- 1 empty capsule
- 1 capsule containing 5 mg mannitol
- 1 capsule containing 10 mg mannitol
- 1 capsule containing 20 mg mannitol
- 15 capsules containing 40 mg mannitol
- 1 inhaler made of styrene plastics

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Pharmaxis Europe Limited
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PL 50608/0001

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