

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Osmohale, inhalation powder, hard capsule

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 a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsule.

The powder is white or almost white.

The empty capsule is clear.

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 FEV₁ of 70% or more of the predicted value.

4.2 Posology and method of administration

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 forced expiratory volume in one second (FEV₁).

Prior to the challenge, spirometry should be performed and the reproducibility of the baseline FEV₁ 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 FEV₁ at least in duplicate to obtain two reproducible measurements. The highest reading becomes baseline FEV₁. The target FEV₁ is calculated by multiplying the baseline FEV₁ 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 FEV₁ from baseline (0 mg dose)

or

10% incremental fall in FEV₁ between doses

Examples of positive tests:

1. FEV₁ fall following dose step 2: 3%
FEV₁ fall following dose step 3: 8%
FEV₁ fall following dose step 4: 16%
- as the total fall is 16% ($\geq 15\%$), the test is positive.
2. FEV₁ fall following dose step 2: 3%
FEV₁ fall following dose step 3: 14%
- although the total fall is $< 15\%$, the incremental fall is 11% ($\geq 10\%$) and the test is positive.

Points to remember:

1. There should be minimal delay between FEV₁ measurement and the next dose so that the osmotic effect in the airway is cumulative.
2. At least 2 acceptable FEV₁ 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 dose are administered in multiples of 40 mg (i.e., 2 x 40 mg and 4 x 40 mg capsules, 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 beta₂ agonist to expedite recovery. Those with a negative challenge may also receive a standard dose of a beta₂ agonist to expedite recovery. Following administration of a beta₂ agonist, FEV₁ usually returns to baseline within 10-20 minutes. Patients should be monitored until their FEV₁ has returned to within 5% of baseline levels.

Children and adolescents (under 18 years of age)

The Osmohale test should not be used in patients below 6 years of age due to 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.

4.3 Contraindications

Known hypersensitivity to mannitol or to any of the capsule ingredients.

Osmohale should not be given to patients with severe airflow limitation (FEV₁ <50% predicted or <1.0l) 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 FEV₁ 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 FEV₁ 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 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.

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.

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 BETA₂ AGONISTS eg salbutamol, terbutaline
12 hours	INHALED CORTICOSTEROIDS e.g. beclomethasone dipropionate; budesonide; fluticasone propionate
12 hours	IPRATROPIUM BROMIDE
24 hours	LONG-ACTING BETA₂ AGONISTS e.g. salmeterol; formoterol

24 hours	INHALED CORTICOSTEROIDS PLUS LONG-ACTING BETA₂ AGONISTS eg fluticasone and salmeterol; budesonide and formoterol
24 hours	THEOPHYLLINE
72 hours	TIOTROPIUM BROMIDE
72 hours	ANTIHISTAMINES eg 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 Pregnancy and lactation

There are no data for D-mannitol on treatment of pregnant women. Animal studies do not indicate harmful effects on development of the embryo/foetus (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.

Since the overall systemic exposure for inhaled D-mannitol is assumed to be very low, no effects on breast-fed babies are expected. Osmohale may be used during breast-feeding.

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, however there are no known effects.

4.8 Undesirable effects

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

The safety population in the Osmohale pivotal study consisted of 627 subjects. Adverse events were monitored from the beginning of the challenge to a week following the challenge day. 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 (83%). In the remainder, it was frequent enough to cause some delay in continuation of the challenge (16%) 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.

The most frequent adverse events (occurring in at least 1% of patients receiving mannitol) reported in the pivotal study are listed below by organ class and absolute frequency:

Nervous system disorders:

Very common ($\geq 1/10$): Headache

Common ($\geq 1/100$ to $< 1/10$): Dizziness

Eye disorders:

Common ($\geq 1/100$ to $< 1/10$): Eye pruritus

Respiratory, thoracic and mediastinal disorders:

Common ($\geq 1/100$ to $< 1/10$): Pharyngolaryngeal pain, Cough*, Rhinorrhoea, Throat irritation, Aggravated asthma, Dyspnoea

Gastrointestinal disorders:

Common ($\geq 1/100$ to $< 1/10$): Nausea, Upper abdominal pain, Diarrhoea, Vomiting

Musculoskeletal and connective tissue disorders:

Common ($\geq 1/100$ to $< 1/10$): Back pain

Infections and infestations:

Common ($\geq 1/100$ to $< 1/10$): Nasopharyngitis, Upper respiratory tract infection

General disorders and administration site conditions:

Common ($\geq 1/100$ to $< 1/10$): Fatigue, Chest tightness

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

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 FEV₁ and inhaled a further dose (these studies used 20-25% as the target FEV₁ fall). The maximum fall measured was 50.2%. If excessive bronchoconstriction occurs, a beta₂ 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.

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 Trials:

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 FEV₁) in 211 adult subjects at a mean dose of 120.2 mg. The mean maximum FEV₁ fall (\pm SD) for the two challenges was comparable: 21.0% (\pm 5.7) for mannitol and 21.3% (\pm 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 beta₂ agonist. The mean % fall in FEV₁ for this group was 6.3% (\pm 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%.

5.2 Pharmacokinetic properties

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.

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 1.6g/kg, or in hamsters at 1.2g/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

There are no excipients in the powder.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

1 year

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 and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PA1382/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 12th October 2007

10 DATE OF REVISION OF THE TEXT