

Package Leaflet: Information for the user

Osmohale inhalation powder, hard capsule Mannitol

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

1. What Osmohale is and what it is used for
2. Before you take Osmohale
3. How to take Osmohale
4. Possible side effects
5. How to store Osmohale
6. Further information

1. What Osmohale is and what it is used for

Osmohale is a **test** to see if you have airways sensitivity or not.

Osmohale contains the active ingredient mannitol.

Airways sensitivity may be caused by inflammation of the airways, making it difficult to breathe sometimes. People with airways sensitivity are often very susceptible to factors in the environment such as exercise, dust, smoke and other irritants.

Your doctor or another specifically trained healthcare professional will ask you to breathe in Osmohale, using a small inhaler.

- For people who **do** have **airways sensitivity**, their airways will become narrower and so they may find it harder to breathe.
- People who **do not** have **airways sensitivity** will not experience their airways becoming narrower when breathing in Osmohale. They will still be able to breathe normally.

As part of the test, you will be asked to blow into a tube that will measure the effect of Osmohale on your lungs.

This medicine is only used to see whether you have airways sensitivity.

2. Before you take Osmohale

Do not take Osmohale

- if you are **allergic** (hypersensitive) to mannitol or any of the other ingredients;
- if your **lung capacity** is **severely reduced** (this will be measured prior to the test);
- if you now have or used to have a swollen or weakened blood vessel around the heart or brain (**aneurysm**);
- if you have **high blood pressure** which is not controlled by medicine;

- if you have had a **heart attack** in the last 6 months;
- if you have had a **stroke** in the last 6 months.

Take special care with Osmohale

Tell your doctor

- if your **lung capacity** is **reduced** (this will be measured prior to the test);
- if you have previously experienced **difficulty in breathing**, or have **wheezed** or **coughed** during a spirometry test (blowing into a measuring instrument);
- if you are **coughing up blood**;
- if you have air in the pleural space between the chest wall and the lungs, causing chest pain and shortness of breath (**pneumothorax**);
- if you have recently had **stomach, chest or eye surgery**;
- if you experience chest pain (**angina pectoris**);
- if you have **problems performing the spirometry test** (the person doing the test will tell you);
- if you have had an **infection** of the **airways** in the last 2 weeks.

If you experience breathlessness, wheezing and/or cough during the spirometry test, you may be given a medicine to keep your air passages open and the test will be stopped.

Do not take vigorous exercise on the day of the test, especially before the test is done as this may affect the test results.

Do not smoke for at least 6 hours before the test as this may affect the test results.

Do not take Osmohale on your own. Osmohale is only to be given in a suitable laboratory or clinic by trained professionals familiar with the use of similar tests and their possible effects, under the supervision of an experienced doctor.

Children under the age of 6 should not be given Osmohale or perform the test.

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including those obtained without a prescription.

If you are taking medicines to treat asthma or allergies, you may need to stop taking these before the test. These medicines may affect your body's response to Osmohale. Your doctor will tell you which medicine(s) to stop and for how long (usually between 6 hours and 4 days before the test).

Taking Osmohale with food and drink

Do not drink coffee, tea or cola, eat chocolate or any other foods containing caffeine on the day of the test.

Pregnancy and breast-feeding

Do not take the Osmohale test if you are pregnant.

You can take Osmohale while breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

No effects have been observed.

3. How to take Osmohale

Adults

You will be given Osmohale via an inhaler by a doctor or another specially trained healthcare professional who will be with you throughout the test. You will not be left on your own.

You must not put Osmohale capsules in your mouth or swallow them.

Performing the test

1. You will be asked to sit comfortably on a chair.
2. Initially you will be asked to blow forcefully into a tube (spirometry test).
3. A nose clip will then be put on your nose so you will only be able to breathe in and out of your mouth.
4. After breathing out fully, you will be asked to deeply breathe in the Osmohale medicine using a special inhaler.
5. You will then hold your breath for five seconds before breathing out.
6. The nose clip will be removed and you will be asked to breathe normally.
7. Next you will be asked to blow forcefully into the tube again. This test measures the effect of Osmohale on your lungs.
8. Steps 3-7 may be repeated up to 9 times with more and more Osmohale depending on the effect on your lungs (as measured in step 7), until the test is finished.
9. Once the test has finished you may be given a medicine to help you breathe.

If you are unsure about any part of the test, or have questions about the medicine, please talk to the doctor or another specially trained healthcare professional performing the test.

Children and adolescents

Children under the age of 6 should not be given Osmohale or perform the test.

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

If you take more Osmohale than you should

If you think you may have been given too much medicine, tell the doctor or healthcare professional performing the test straight away. You may feel that you cannot breathe, become wheezy or cough if you have taken too much Osmohale. The doctor may give you oxygen and medicines to help you breathe.

4. Possible side effects

Like all medicines, Osmohale can cause side effects, although not everybody gets them.

Very common (likely to affect more than 1 in 10 people):

- Headache

Common (likely to affect less than 1 in 10 but more than 1 in 100 people):

- Nausea (feeling sick)
- upper stomach pains
- diarrhoea
- vomiting
- dizziness
- tiredness
- itchy eyes
- runny nose
- cold or flu
- sore or irritated throat
- discomfort when swallowing

- chest tightness
- back pain
- breathlessness
- cough or wheezing

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Osmohale

- Keep out of the reach and sight of children.
- Do not use Osmohale after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.
- Do not store above 25°C.

6. Further information

What Osmohale contains

The active substance is mannitol.

The mannitol powder is contained within capsules which are utilised for inhalation. A capsule contains 0 mg, 5 mg, 10 mg, 20 mg or 40 mg mannitol.

What Osmohale looks like and contents of the pack

The powder is white to off-white.

The empty capsule is clear.

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

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

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

The 40 mg capsules are half red, half clear, marked 40 mg.

The capsules are supplied in blister packs. One diagnostic kit, packed in a box, consists of:

- 1 empty capsule
- 1 x 5 mg capsule
- 1 x 10 mg capsule
- 1 x 20 mg capsule
- 15 x 40 mg capsules
- 1 inhaler

Marketing Authorisation Holder

Pharmaxis Pharmaceuticals Limited
 Basepoint Business & Innovation Centre
 110 Butterfield, Great Marlings
 Luton
 Bedfordshire LU2 8DL
 United Kingdom

Manufacturer responsible for batch release

IPC-Services A/S
 Tranegaardsvej 20
 DK-2900 Hellerup
 Denmark

If you have any questions about this medicinal product, please contact the Marketing Authorisation Holder.
Tel: +44(0) 1582 434 240
Fax: +44(0) 1582 434 250

This leaflet was last revised on 28-08-2007

INFORMATION FOR MEDICAL OR HEALTHCARE PROFESSIONALS

The following information is intended for medical or healthcare professionals only:

Contraindications

Known 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.

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, and caution should be exercised 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 following the 0 mg capsule is greater than 10%, 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.

Inhaler instructions

These instructions show you how to use the inhaler device.

1. **Remove Cap:** Using both hands, hold the inhaler upright and remove the cap.



2. **Open:** Hold the base of the inhaler firmly with one hand and open the device by rotating the mouthpiece in the direction of the arrow as shown.



3. **Load:** Make sure your hands are dry, remove a capsule from the Osmohale™ pack and place into the inhaler as illustrated. It does not matter which way the capsule is placed in the chamber.



4. **Close:** Keeping the device in an upright position, twist the mouthpiece into the closed position until you hear it 'click'.



5. **Pierce Capsule:** Hold the inhaler upright and fully depress both piercing buttons on the sides of the device at the same time.

Do this once only, since piercing the capsule more than once may cause it to split/fragment. The piercing action makes holes in the capsule and allows the powder in the capsule to be released during inhalation.



6. **Prepare for Inhalation:** Tilt the inhaler so that the mouthpiece faces slightly downward at a 45 degree angle as shown on the picture below, until the capsule drops forward into the spinning chamber. Keep the device tilted in this way and instruct the patient to breathe out completely (away from the inhaler).



7. **Inhale:** The patient should tilt their head back slightly, and keeping the inhaler at a 45 degree angle, raise the device to their mouth and ensure they close their lips tightly around the mouthpiece. Encourage the patient to take a controlled rapid and deep inspiration to fill the lungs. The patient should then hold their breath for five seconds.



Note: During a successful inhalation you should hear a 'rattling' sound as the capsule spins in the inhaler.

8. **Exhale:** Remove the inhaler from the patient's mouth, allow them to exhale and resume normal breathing.



9. **Check:** The Osmohale™ capsule must spin in the inhaler in order to empty. A second inhalation (using the same capsule) may be required immediately if the capsule is not empty following inhalation. Check the capsule following each inhalation.



Please Note:

The inhaler device is designed for SINGLE USE ONLY (one device per challenge) and should not be cleaned during the challenge. Discard the inhaler following each Osmohale™ challenge. The inhaler must not be sterilised or re-used as this may compromise the integrity of subsequent test results.

PLEASE REFER TO THE FULL SUMMARY OF PRODUCT CHARACTERISTICS BEFORE PERFORMING THIS CHALLENGE TEST.

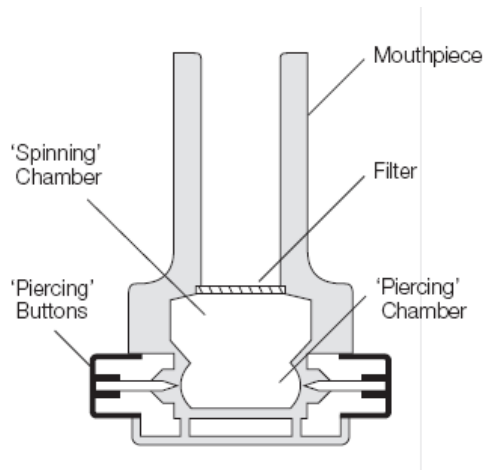
Further information can be obtained by contacting:

The Marketing Authorisation Holder: **Pharmaxis Pharmaceuticals Limited**
Basepoint Business & Innovation Centre, 110 Butterfield, Great Marlings, Luton
Bedfordshire LU2 8DL, United Kingdom

{Logo}

Osmohale™ Challenge Instructions

Osmohale™ Challenge Inhaler device



Challenge Outcomes

Positive Osmohale™ Challenge result

A positive Osmohale™ response may be achieved in 2 ways:
≥ 15% fall in FEV₁ from baseline (using the post 0mg FEV₁ as comparator)
≥ 10% incremental fall in FEV₁ (between consecutive Osmohale™ doses)

Negative Osmohale™ Challenge Result

An Osmohale™ challenge is considered to be negative when a cumulative dose of 635mg of

Osmohale™ has been administered and the patient's FEV₁ has not fallen by ≥ 15% from baseline.

Equipment

Osmohale™ Kit (containing Osmohale™ capsules, inhaler device and instruction leaflet)

Spirometer & mouthpiece

Nose clip

Timer (which can be set to 60 seconds)

Calculator

Bronchodilator (eg salbutamol)

Oxygen and other relevant emergency equipment should be readily available as per standard Bronchial Provocation Testing protocols.

Important Points to Note

a. The inhaler device is for SINGLE USE ONLY (one device per challenge) and should not be cleaned during the challenge. Discard the inhaler following each Osmohale™ challenge. The inhaler must not be sterilised or re-used as this may compromise the integrity of subsequent test results.

b. When the patients are exhaling during the Osmohale™ challenge, ensure they do so AWAY from the inhaler to minimise humidity within the device.

c. When piercing the capsule, do so once only (by depressing both buttons simultaneously and fully) as re-piercing may cause the capsule to split/fragment.

d. Using rubber gloves when administering the test and handling Osmohale™ capsules may increase static and inhibit capsule movement within the inhalation device.

e. If you suspect that static is an issue or notice that the sound of the capsule 'rattling' cannot be heard during inhalation of Osmohale™, firmly tap the base of the inhaler with one hand whilst holding the inhaler with the other (mouthpiece facing downwards at a 45° angle). This should ensure that the capsule has been 'dislodged' from the piercing chamber into the spinning chamber.



f. Inhalation of Osmohale™ may cause cough and/or a dry throat. This is a routine adverse effect of bronchial challenge testing. You can offer the patient a glass of water at challenge completion.

g. This challenge test is time critical and requires an osmotic gradient to be

established and maintained. Prolonged time intervals between doses may affect the validity of results and should be avoided.

Procedure Guidelines

STEP 1: Make sure the patient has withheld the following medications (See table below).

Recommended Medication Withholding Times

Failure to withhold medications may affect the results of the Osmohale™ challenge. Recommended periods for withholding medications are generally based on their duration of action.

| Time to Withhold | Medication |
|------------------|---|
| 6 – 8 hours | INHALED NON-STEROIDAL ANTI-INFLAMMATORY AGENTS <i>eg sodium cromoglycate, nedocromil sodium</i> |
| 8 hours | SHORT-ACTING BETA2 AGONISTS <i>eg salbutamol, terbutaline</i> |
| 12 hours | INHALED CORTICOSTEROIDS <i>eg beclomethasone; budesonide; fluticasone</i> |
| 12 hours | IPRATROPIUM BROMIDE |
| 24 hours | INHALED CORTICOSTEROIDS PLUS LONG-ACTING BETA2 AGONISTS <i>eg fluticasone and salmeterol; budesonide and formoterol</i> |
| 24 hours | LONG-ACTING BETA2 AGONISTS <i>eg salmeterol; formoterol</i> |
| 24 hours | THEOPHYLLINE |
| 72 hours | TIOTROPIUM BROMIDE |
| 72 hours | ANTIHISTAMINES <i>eg cetirizine, fexofenadine, loratadine</i> |
| 4 days | LEUKOTRIENE-RECEPTOR ANTAGONISTS <i>eg montelukast</i> |

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

Other factors that may affect results: Smoking and vigorous exercise should not be undertaken on the day of the test as this may affect test results.

STEP 2: The patient should be seated for the test. Explain the procedure; include what is required for an FVC manoeuvre and FEV₁ measurement and the type of inspiratory flow required for the inhaler. Demonstrate as required.

STEP 3: Enter the patient's details in the spirometer (age, height, race, date of birth, gender etc).

STEP 4: Determine the pre-challenge FEV₁. Ask the patient to perform an FVC manoeuvre according to the ATS/ERS guidelines, perform three acceptable manoeuvres of which two are reproduced. Use the highest value as pre-challenge FEV₁. The patient's FEV₁ should be ≥ 70% of the predicted value. Caution should be used in patients with an FEV₁ of less than 70% of the predicted value.

STEP 5: Calculate the baseline FEV₁ (0mg)

- Remove the **0mg Osmohale™** capsule from the blister, twist open the inhaler (as per the arrow on the device), place the capsule inside and close the device.
- Pierce the capsule once only by depressing the coloured buttons on either side of the inhaler.
- Ask the patient to put on the nose clip, and breathe through their mouth.
- Tilt the inhaler at a 45° angle (mouthpiece down). Check the capsule has moved from the piercing chamber into the spinning chamber closest to the mouthpiece. You can often hear the capsule fall forward or see the capsule through the vents on each side of the device. Give the inhaler to the patient ensuring that they keep the inhaler at the same angle.
- Ensure the patient is sitting up straight. Ask the patient to exhale (away from the

inhaler), seal their lips around the inhaler mouthpiece and take a controlled rapid and deep inspiration until their lungs are full. During successful inhalation you should hear a 'rattling' sound as the capsule spins within the device.

f. At the end of the patient's inhalation, start a 60 second timer, and ask the patient to hold their breath for 5 seconds. When 5 seconds has passed, instruct the patient to exhale through their mouth (away from the inhaler), remove the noseclip and breathe normally.

g. When the timer beeps after 60 seconds, immediately instruct the patient to perform two acceptable FEV₁ measurements. These measurements must be within 0.15l (150ml) variability. If there is greater than 0.15l variability between readings instruct the patient to perform another FEV₁. **Record the highest FEV₁ reading as the baseline FEV₁.** *If the highest FEV₁ is $\geq 10\%$ lower than the pre-challenge FEV₁ do not continue with the test.*

h. Calculate the target FEV₁

A positive Osmohale™ challenge result is achieved when the patient's FEV₁ falls $\geq 15\%$ from their baseline FEV₁. To calculate the target FEV₁, multiply the baseline FEV₁ (the highest reading obtained at 0mg) obtained above by 0.85. Record this value.

STEP 6: 5mg capsule

a. Insert 5mg capsule into the inhaler and pierce as in Step 5.

b. Repeat as in steps 5c – f above.

c. Following inhalation remove the capsule from the inhaler and check to ensure it has been emptied completely, if not, a 2nd inhalation will be required immediately.

d. Load the 10mg capsule in readiness for the next dose.

e. At 60 seconds following inhalation, immediately measure the patient's FEV₁ twice (*acceptability criteria must be met*). Use the highest of these two values to calculate the change in FEV₁.

f. Compare the FEV₁ value at this dose to the target FEV₁. If the FEV₁ value is equal to or below the target value, or there has been an incremental fall of $\geq 10\%$ from the previous dose, the challenge is positive and complete. If not, immediately proceed to next dose step.

STEP 7: 10mg, 20mg, 40mg capsules

Administer the 10mg, 20mg and 40mg doses following the directions given above (in step 6) for the 5mg dose.

STEP 8: 80mg dose (2 x 40mg capsules)

a. Insert and pierce the first of the 40mg capsules that comprise the 80mg dose.

b. The patient should inhale the dose in the same manner as previous doses, hold their breath for 5 seconds and exhale.

c. Remove the first 40mg capsule from device and check to ensure it has been emptied completely, if not, a 2nd inhalation will be required immediately. Do this following the administration of every capsule.

d. Following inhalation, load the second 40mg capsule and offer to the patient immediately following exhalation.

e. Instruct the patient to inhale the 2nd capsule immediately to ensure that the osmotic effect of Osmohale™ is cumulative.

f. Activate timer at the end of the 2nd capsule inhalation.

g. Instruct the patient to hold their breath for 5 seconds before exhaling.

h. At 60 seconds following inhalation of the 2nd capsule, immediately measure the patient's FEV₁ twice (*acceptability criteria must be met*). Use the higher of these two values to calculate the change in FEV₁.

i. Compare the FEV₁ value at this dose to the target FEV₁. If the FEV₁ value is equal to or below the target value, or there has been an incremental fall of $\geq 10\%$, the challenge is positive and complete. If not, immediately proceed to next dose step.

STEP 9: 1st of 160mg dose (4 x 40mg capsules)

- a. Insert and pierce the 1st of the 40mg capsules that comprise the 160mg dose.
- b. The patient should inhale the dose in same manner as previous doses, hold their breath for 5 seconds and exhale.
- c. Remove capsule from device and check to ensure it has been emptied completely, if not, a 2nd inhalation will be required immediately. Do this following the administration of every capsule.
- d. Following inhalation, load the 2nd 40mg capsule and offer to the patient immediately following exhalation.
- e. The patient should inhale contents of the 2nd capsule, hold their breath for 5 seconds and exhale.
- f. Following inhalation, load the 3rd 40mg capsule and offer to the patient immediately following exhalation.
- g. The patient should inhale the contents of the 3rd capsule, hold their breath for 5 seconds and exhale.
- h. Immediately following inhalation, load the 4th 40mg capsule and offer to the patient immediately following exhalation.
- i. Instruct the patient to inhale the 4th capsule immediately to ensure that the osmotic effect of Osmohale™ is cumulative.
- j. Activate timer at the end of the 4th capsule inhalation.
- k. Instruct the patient to hold their breath for 5 seconds, before exhaling.
- l. At 60 seconds following inhalation of the 4th capsule, immediately measure the patient's FEV₁ twice (*acceptability criteria must be met*). Use the higher of these two values to calculate the change in FEV₁.
- m. Compare the FEV₁ value at this dose to the target FEV₁. If the FEV₁ value is equal to or below the target value, or there has been an incremental fall of $\geq 10\%$ from the previous dose the challenge is positive and complete. If not, immediately proceed to next dose step.

STEP 10: 2nd x 160mg dose (4 x 40mg capsules)

Administer the 2nd 160mg dose following the directions given above in step 9.

STEP 11: 3rd x 160mg dose (4 x 40mg capsules)

Administer the 3rd 160mg dose following the directions given above in step 9.
At the completion of this dose, 635mg has been administered. Providing a positive response has not been met, the challenge should be considered negative and complete.

STEP 12: Following completion of the challenge with a positive result you should administer a bronchodilator and monitor the patient for 15 minutes to ensure their FEV₁ has returned to within 5% of pre-challenge level. (In the case of a negative result you may or may not wish to give a bronchodilator).