Miflonide® Breezhaler®

Other drugs for obstructive airway diseases, inhalants: Glucocorticoids

DESCRIPTION AND COMPOSITION

Powder for inhalation in capsules to be used in combination with the Miflonide Breezhaler inhaler.

Each capsule contains the equivalent of either 200 micrograms or 400 micrograms of budesonide.

Pharmaceutical form(s)

Inhalation powder, hard capsules.

Excipients

Lactose monohydrate.

INDICATIONS

Bronchial asthma

Miflonide Breezhaler is indicated in asthmatic patients forlong-term anti-inflammatory control of persistent asthma including prophylaxis of acute exacerbations of asthma.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage

The dosage should be adjusted individually to the lowest dose required for maintenance therapy. Budesonide should be taken regularly every day. The dose should be re-titrated individually, when transferring a patient from one inhalation device to another.

The lowest dosage in a single capsule is 200 micrograms. If a single dose of less than 200 micrograms is required, this product cannot be used.

General target population

Adult patients

Treatment of adults with mild asthma may be initiated at the minimum effective dosage of 200 micrograms once daily. The usual maintenance dosage is 200 to 400 micrograms twice daily (equivalent to 400 to 800 micrograms daily).

The dosage may be increased up to 1,600 micrograms daily to be taken in 2 to 4 doses during asthma exacerbations, when switching from oral corticosteroid therapy to budesonide inhalation therapy, or when reducing the dose of oral corticosteroid therapy.

Special populations

Patients with renal impairment

There are no clinical studies in patients with renal impairment. On the basis of pharmacokinetic data with oral budesonide it is unlikely that systemic exposure will be altered to clinically significant levels in such patients (see section CLINICAL PHARMACOLOGY).

Patients with hepatic impairment

There are no clinical studies in patients with hepatic impairment. However, since budesonide is predominantly cleared by hepatic metabolism caution should be exercised when using Miflonide Breezhaler in patients with severe hepatic impairment. On the basis of pharmacokinetic data with oral budesonide, patients with mild to moderate hepatic impairment are unlikely to experience a clinically significant alteration in drug exposure (see section CLINICAL PHARMACOLOGY).

Pediatric patients (6 years of age and above)

Due to the absence of clinical experience in children under 6 years of age, Miflonide Breezhaler should not be used in this age group.

Treatment of children aged 6 years and older with mild asthma may be initiated at a dosage of 200 micrograms once daily. The usual maintenance dosage is 200 micrograms twice daily (equivalent to 400 micrograms daily). The maximum total daily dose is 800 micrograms. Miflonide Breezhaler should be used under the supervision of adults. The use of the Miflonide Breezhaler should depend on the ability of the child to use the inhaler correctly.

Geriatric patients (65 years of age and older)

There are no clinical studies in patients above 65 years of age.

Method of administration

Miflonide Breezhaler should only be used in conjunction with the Miflonide Breezhaler inhaler and is for oral inhalation only.

To ensure proper administration of the drug, a physician or another healthcare professional should:

- Instruct the patient on the proper use of the Miflonide Breezhaler inhaler in accordance with the user instructions to ensure that the drug reaches the target areas in the lungs
- Instruct the patient that the capsules are only for inhalation use with the Miflonide Breezhaler inhaler and must not be swallowed (see section WARNINGS AND PRECAUTIONS)

Detailed handling instructions are included in the INSTRUCTIONS FOR USE AND HANDLING under INFORMATION FOR PATIENTS section. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it.

In order to reduce the risk of a candida infection it is recommended to rinse the mouth out well with water and to subsequently spit out the rinsing water after each administration (see section

WARNINGS AND PRECAUTIONS and section ADVERSE DRUG REACTIONS). Rinsing the mouth may also help to prevent throat irritation and reduce the risk of systemic effects.

CONTRAINDICATIONS

- Known hypersensitivity to budesonide or any of the excipients of the medicinal product (see section DESCRIPTION AND COMPOSITION for excipients).
- Active pulmonary tuberculosis.

WARNINGS AND PRECAUTIONS

Prophylactic nature of therapy

Patients should be made aware of the prophylactic nature of therapy with inhaled budesonide, and that it must be taken regularly even when the patients are asymptomatic. Inhaled budesonide does not relieve acute bronchospasm, nor is it appropriate for the primary treatment of status asthmaticus or other acute asthmatic episodes.

Concomitant conditions

Special care is needed in patients with concomitant disorders such as quiescent pulmonary tuberculosis, or fungal and viral airway infections.

Caution is necessary when treating patients with concomitant pulmonary disorders such as bronchiectasis and pneumoconiosis due to the possibility of fungal infections.

Risk of pneumonia in COPD patients (unapproved indication)

An increase in the incidence of pneumonia, including pneumonia requiring hospitalization, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies. The clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products is inconclusive.

Physicians should be vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low BMI and severe condition COPD.

Asthma exacerbations

Acute exacerbations of asthma may need an increase in the dose of Miflonide Breezhaler or additional treatment with a short course of oral corticosteroids and/or an antibiotic if there is an infection.

Patients should always keep a short-acting inhaled bronchodilator available as rescue medication to alleviate acute asthma symptoms.

Patients should be advised to contact their doctor if their asthma deteriorates (increased frequency of short-acting inhaled bronchodilator treatment or persistent respiratory symptoms). The patient should be reassessed and the need for increased anti-inflammatory therapy, an increase in the dose of inhaled or oral corticosteroid, should be considered.

Paradoxical bronchospasm

In rare cases inhalation of Miflonide Breezhaler can cause bronchospasm after dosing. If paradoxical bronchospasm occurs, inhalation using Miflonide Breezhaler must be stopped immediately and, if necessary, be replaced with another treatment. Paradoxical bronchospasm responds to a fast-acting inhaled bronchodilator.

Systemic effects

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, hyperadrenocorticism/Cushing's syndrome, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, hypersensitivity reactions, and more rarely, a range of psychological or behavioral effects including psychomotor hyperactivity, sleep disorders, anxiety, depression, and aggression (particularly in children). Therefore, it is important that the dose of inhaled corticosteroid is titrated to the lowest effective dose in order to control asthma (see section ADVERSE DRUG REACTIONS).

Effect on growth

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids be monitored regularly. If growth retardation is noted, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest effective dose to control the symptoms of asthma. In addition, it should be considered whether to refer the patient to a pediatric respiratory specialist. The long-term effects of this reduction in growth associated with inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

Concomitant medications

Care should be taken during long-term co-administration of Miflonide Breezhaler and a potent CYP3A4 inhibitor, e.g. itraconazole, atazanavir, ketoconazole, ritonavir, nelfinavir, amiodarone, and clarithromycin (see section INTERACTIONS).

Patients starting treatment with steroids

A therapeutic effect is usually reached within 10 days. In patients with excessive mucus secretion in the bronchi, a short (about 2-week) additional oral corticosteroid regimen can be given initially.

Steroid-dependent patients

The patient should be in a relatively stable phase when switching therapy from oral steroids to inhaled budesonide. A high dose of budesonide is given in combination with the previously used oral steroid for about 10 days. The oral dose should then be gradually reduced (for example, by 2.5 mg prednisolone or equivalent each month) to the lowest possible level. Treatment with supplementary systemic steroids or Miflonide Breezhaler should not be stopped abruptly but should take place slowly.

Particular caution is required in the first few months after switching from systemic corticosteroids to budesonide, to ensure that the patient's adrenocortical reserve is capable of countering specific crisis situations, such as trauma, surgery, or severe infections. HPA (hypothalamic-pituitary-adrenal) axis function should be monitored regularly. Some patients need an extra supply of corticosteroids under these circumstances; they are advised to carry a warning card with them drawing attention to their potentially serious condition. Substitution of systemic corticosteroids with budesonide may reveal allergies previously suppressed by the systemic corticosteroids, such as allergic rhinitis or eczema and patients may suffer from lethargy, muscle or joint pain, and sometimes nausea and vomiting. Such allergies should be properly treated with locally applied antihistamines or corticosteroids.

Additional precautions

To prevent oral candidiasis, patients should be advised to rinse the mouth with water after each administration. If this condition develops, it will respond in most cases to topical anti-fungal therapy without having to discontinue treatment with Miflonide Breezhaler (see section DOSAGE AND ADMINISTRATION and section ADVERSE DRUG REACTIONS).

Dysphonia may occur but readily reverses after discontinuing treatment, reducing the dose, and/or resting the voice (see section ADVERSE DRUG REACTIONS).

Incorrect route of administration

There have been reports of patients who have mistakenly swallowed Miflonide Breezhaler capsules instead of placing the capsules in the inhalation device. The majority of these ingestions were not associated with side effects. Healthcare providers should instruct the patient on the correct use of Miflonide Breezhaler (see section DOSAGE AND ADMINISTRATION, subsection Method of administration). If a patient who is prescribed Miflonide Breezhaler does not experience improvement in breathing, the healthcare provider should ask how the patient is using Miflonide Breezhaler.

ADVERSE DRUG REACTIONS

Adverse drug reactions (Table 1) are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Table 1 Adverse drug reactions with budesonide

Endocrine disorders	
Rare:	Adrenal suppression, Cushing's syndrome, hyperadrenocorticism, reduction in growth velocity in children and adolescents
Eye disorders	
Rare:	Cataract, glaucoma
Immune system disorders	
Rare:	Hypersensitivity reactions, rash, urticaria, angioedema, pruritus
Musculoskeletal and connective tissue disorders	

	Rare:	Decrease in bone mineral density
Respiratory, thoracic and mediastinal disorders		
	Common	Cough
	Rare:	Paradoxical bronchospasm, oropharyngeal candidiasis, dysphonia, throat irritation

Adverse drug reactions from post-marketing experience (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with budesonide (Table 2). Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Immune system disorders
Contact dermatitis (a type IV [delayed] hypersensitivity reaction)
Psychiatric disorders
Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioral changes (predominantly in children)
Respiratory, thoracic and mediastinal disorders
Pneumonia*
Skin and subcutaneous tissue disorders
Skin bruises*

*ADRs reported in the published literature of long-term clinical trials in the COPD patients.

INTERACTIONS

Agents resulting in CYP34A inhibition

The main route of metabolism of budesonide is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). Co-administration of known CYP3A4 inhibitors (e.g. itraconazole, atazanavir, ketoconazole, ritonavir, nelfinavir, amiodarone, clarithromycin) are known to inhibit the metabolism of budesonide and hence increases systemic exposure. If these products are administered together, adrenocortical function should be monitored and the dose of budesonide adjusted according to the response (see section WARNINGS AND PRECAUTIONS and section CLINICAL PHARMACOLOGY).

Agents resulting in CYP3A4 induction

Co-administration of strong inducers of CYP3A4 (e.g. rifampicin) may increase the metabolism of budesonide and hence decrease systemic exposure (see section CLINICAL PHARMACOLOGY).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

There are no adequate and well-controlled studies using Miflonide in pregnant women. Results from a large prospective epidemiological study indicated that inhaled budesonide during pregnancy had no adverse effects on the health of the fetus / new born child.

Animal data

In rats administered with 0.25 microgram/kg inhaled budesonide, there were no teratogenic effects. Subcutaneously administered budesonide showed teratogenic effects at greater than or equal to 100 µg/kg/day in rats and greater than or equal to 5 µg/kg/day in rabbits with the maternal exposure margins approximately 2.4 and 0.24 times the maximum human inhaled dose of 400 microgram/day, respectively, based on body surface area. In rats administered budesonide subcutaneously in a pre- and postnatal developmental study, there were no effects on the pregnant rats or their offspring. As with other glucocorticoids, subcutaneously administered budesonide has been shown to be teratogenic and fetotoxic (decreased viability of pups) in rats. Fetotoxicity was also noted in rabbits (reduction in growth velocity and fetal death observed at maternally toxic dose levels).

Lactation

Inhaled budesonide is secreted in the breast milk. Plasma concentrations achieved in infants would be expected to reach around $1/600^{th}$ of the concentrations in maternal plasma (see Section CLINICAL PHARMACOLOGY). While these low amounts of budesonide suggest that Miflonide can be used during breast-feeding, the clinical impact on suckling infants during long-term treatment is unknown.

Females and males of reproductive potential

There is no special recommendation for women of child bearing potential.

Infertility

There are no data available on the use of budesonide and its effect on fertility in humans. In rats, subcutaneously administered budesonide did not have an adverse effect on fertility.

OVERDOSAGE

Acute: The acute toxicity of budesonide is low. Suppression of hypothalamic pituitary-adrenal (HPA) function is the main harmful effect resulting from inhalation of large amounts of the drug over a short period of time. No special emergency measures need to be taken. Treatment with Miflonide Breezhaler should be continued at the recommended dose to control asthma.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA) and Pharmacodynamics (PD)

Budesonide is a corticosteroid with marked topical action but practically no systemic action in humans. Like other inhaled glucocorticoids, budesonide exerts its pharmacologic effects by interacting with intracellular glucocorticoid receptors. The production of many different cytokines, chemokines, enzymes, and cell adhesion molecules is inhibited. When used as an inhalation powder in patients who benefit from corticosteroid therapy, it can generally bring asthma under control within 10 days of initiation of treatment. Regular use of budesonide

reduces chronic inflammation in asthmatic lungs. Budesonide thereby improves lung function and asthma symptoms, reduces bronchial hyper-reactivity and prevents asthma exacerbations.

Pharmacokinetics (PK)

Absorption

The amount of budesonide deposited in the lungs is rapidly and completely absorbed. Peak plasma concentrations are reached immediately after administration. After correction for the dose deposited in the oropharynx absolute bioavailability is 73%. Only 10 to 13% of the swallowed fraction of an inhaled dose is bioavailable due to significant pre-systemic metabolism in the liver. Systemic exposure of budesonide in the recommended dosing range of Miflonide can be expected to be dose-proportional as has been observed with other budesonide dry powder inhalers.

Distribution

The plasma protein binding of budesonide is 85 to 90% over the concentration range 1 to 100 nmol. Budesonide is widely distributed into tissues, with a volume of distribution of 183 to 301 liters at steady state. It also passes into the breast milk, with a milk to plasma concentration ratio of around 0.46. The estimated daily infant dose is 0.3 % of the daily maternal dose, and the estimated average plasma concentration in infants is $1/600^{th}$ of the maternal plasma concentration, even after assuming complete infant oral bioavailability has taken place.

Animal studies have shown high concentrations in spleen, lymph glands, thymus, adrenal cortex, reproductive organs, and bronchi. Budesonide crosses the placental barrier in mice.

Biotransformation/Metabolism

Budesonide is not metabolized in the lungs. After absorption it is broken down in the liver to yield a number of inactive metabolites, including 6-beta-hydroxybudesonide and 16-alpha-hydroxyprednisolone.

The main route of metabolism of budesonide is via CYP3A4 and may be affected by known inhibitors or inducers of this enzyme (see section INTERACTIONS).

Elimination

In human volunteers inhaling radiolabeled budesonide (via metered dose inhaler) approximately 32% of the discharged dose was recovered in the urine and 15% in the faeces. Following inhalation, 16-alpha-hydroxyprednisolone, but not budesonide was detected in the urine.

Budesonide shows high plasma clearance (84 L/h) following intravenous dosing. The elimination half-life was around 2.8 to 5 h.

Special populations

Geriatric patients

The pharmacokinetics of budesonide has not been studied in elderly patients. However, limited data in patients over 65 years of age suggest there is no significant difference in pharmacokinetics compared to younger adults after oral and intravenous administration.

Pediatric patients

The pharmacokinetics of budesonide has not been studied in the pediatric population. However, data with other inhalational budesonide products suggest that body weight normalized clearance in children above 3 years of age is around 50% higher than in adults.

Patients with hepatic impairment

The pharmacokinetics of inhaled budesonide has not been studied in patients with hepatic impairment. However, after oral administration, the systemic availability of budesonide was reported to be 2.5 times higher in patients with cirrhosis than in healthy controls. Mild hepatic impairment is reported to have little effect on systemic exposure of oral budesonide.

Patients with renal impairment

The pharmacokinetics of budesonide has not been studied in patients with renal impairment but no significant effect is anticipated. However, as metabolites of budesonide are excreted in the urine, an increased risk of adverse events due to accumulation of metabolites cannot be excluded in severe renal impairment.

CLINICAL STUDIES

Budesonide is an established product. No clinical trials have been conducted.

NON-CLINICAL SAFETY DATA

Repeated dose toxicity

Preclinical data from repeated dose toxicity studies revealed no specific hazard for humans at the intended therapeutic dose.

Mutagenicity and carcinogenicity

Budesonide was shown to have no mutagenic potential in a battery of in vitro and in vivo mutagenicity tests.

Orally administered budesonide was shown to increase the incidence of liver tumors in male rats starting at dose levels of 25 microgram /kg/day. These effects were also observed in a follow-up study including other steroids (prednisolone and triamcinolone acetonide) and are considered a class effect of corticosteroid administration.

Reproductive toxicity (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL)

INCOMPATIBILITIES

None.

STORAGE

See folding box.

Miflonide Breezhaler should not be used after the date marked “EXP” on the pack.

Miflonide must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

To ensure proper administration of the drug, the patient should be shown how to use the inhaler by a physician or another healthcare professional.

It is important for the patient to understand that the gelatin capsule may very occasionally break up and small pieces of gelatin may reach the mouth or throat after inhalation. The patient may be reassured that the gelatin will soften in the mouth and can be swallowed. The risk of the capsule breaking up is minimized by not piercing the capsule more than once.

The capsule should be removed from the blister pack only immediately before use.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

The inhaler provided with each new prescription should be used. Each inhaler should be disposed of after finishing the pack.

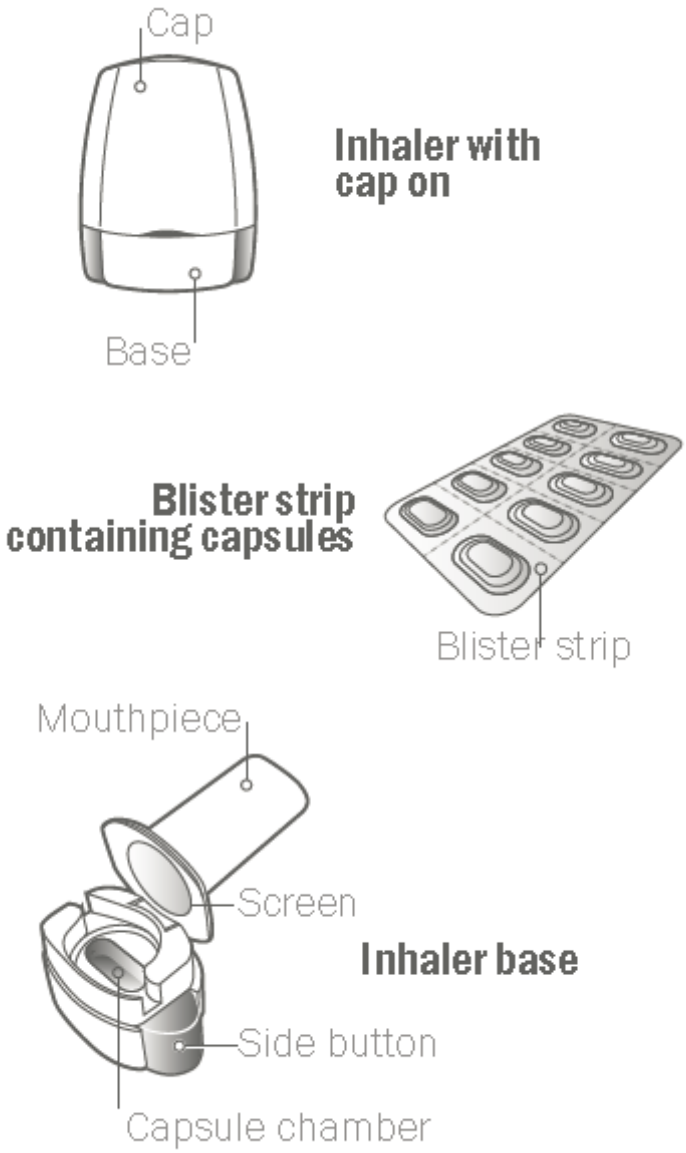
INFORMATION FOR PATIENTS

How to use the capsules with your Breezhaler inhaler

Follow the illustrated instructions to learn how to use Miflonide Breezhaler capsules with the Miflonide Breezhaler inhaler.

The powder in the capsules is to be used for inhalation only.

Your Miflonide Breezhaler pack:

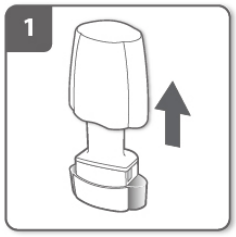


Each Miflonide Breezhaler pack contains:

- one Miflonide Breezhaler inhaler
- one or more blister strips containing Miflonide Breezhaler capsules to be used in the inhaler.

The Miflonide Breezhaler inhaler enables you to inhale the medicine contained in a Miflonide Breezhaler capsule.

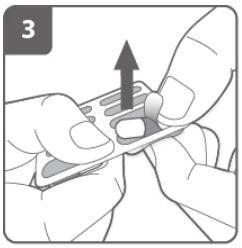
How to use your Miflonide Breezhaler inhaler



Pull off the cap

Open inhaler

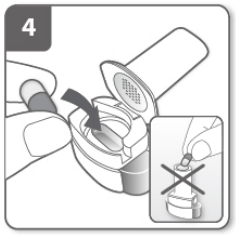
Hold the base of the inhaler firmly and tilt the mouthpiece. This opens the inhaler.



Prepare capsule

Immediately before use, with dry hands, remove one capsule from the blister.

Do not swallow the capsule.



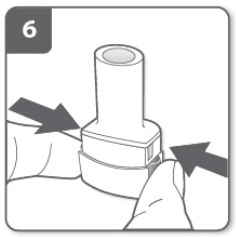
Insert capsule

Place the capsule into the capsule chamber.

Never place a capsule directly into the mouthpiece.

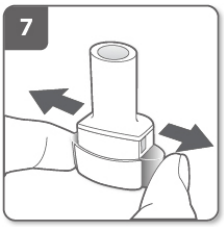
Close the inhaler:

Close the inhaler until you hear a “click”.

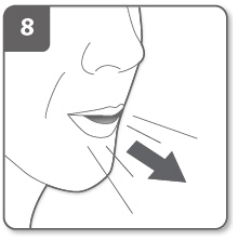


Pierce the capsule

- Hold the inhaler upright with the mouthpiece pointing up.
- Pierce the capsule by firmly pressing together both side buttons at the same time. **Do this only once.**
- You should hear a “click” as the capsule is being pierced.



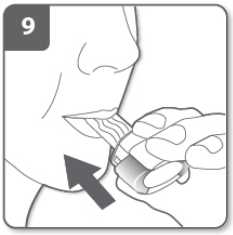
Release the side buttons fully



Breathe out

Before placing the mouthpiece in your mouth, breathe out fully.

Do not blow into the mouthpiece.



Inhale the medicine

To breathe the medicine deeply into your airways:

- Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons.
- Place the mouthpiece in your mouth and close your lips firmly around the mouthpiece.
- Breathe in rapidly but steadily and as deeply as you can.

Note:

As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. You may experience a sweet flavour as the medicine goes into your lungs.

Additional information

Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed or inhaled. The chances of the capsule shattering will be increased if the capsule is accidentally pierced more than once (step 6).

If you do not hear a whirring noise

The capsule may be stuck in the capsule chamber. If this happens:

- Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Do not press the side buttons.
- Close the inhaler and inhale the medicine again by repeating steps 8 and 9.

Hold breath

After you have inhaled the medicine:

- Hold your breath for at least 5-10 seconds or as long as you comfortably can while taking the inhaler out of your mouth.
- Then breathe out.
- Open the inhaler to see if any powder is left in the capsule.

If there is powder left in the capsule

- Close the inhaler.
- Repeat steps 8, 9, 10 and 11.

Most people are able to empty the capsule with one or two inhalations.

Additional info

If the capsule is empty, you have received enough of your medicine.

- Open the mouthpiece again and remove the empty capsule by tipping it out of the capsule chamber. Put the empty capsule in your household waste.

If your prescription requires you to take more than 1 capsule, repeat steps 3 – 12 as necessary.

After you have finished taking your medicine

- Close the inhaler and replace the cap.

Rinse your mouth well with water after using your medicine. Spit out the rinse water. This will reduce the risk of developing a fungal infection (thrush) in the mouth.

Do not store the capsules in the Miflonide Breezhaler inhaler.

How to clean your inhaler

Never wash your inhaler with water. If you want to clean your inhaler, wipe the mouthpiece inside and outside with a clean, dry, lint-free cloth to remove any powder residue. Keep the inhaler dry.

Remember

- Do not swallow Miflonide Breezhaler capsules.
- Only use the Miflonide Breezhaler inhaler contained in this pack.
- Capsules must always be stored in the blister pack, and only removed immediately before use.
- Never place a Miflonide Breezhaler capsule directly into the mouthpiece of the Miflonide Breezhaler inhaler.
- Do not press the side buttons more than once.
- Never blow into the mouthpiece of the Miflonide Breezhaler inhaler.
- Always release the side buttons before inhalation.
- Never wash the Miflonide Breezhaler inhaler with water. Keep it dry. See “How to clean your inhaler”.
- Never take the Miflonide Breezhaler inhaler apart.
- Always use the new Miflonide Breezhaler inhaler that comes with your new Miflonide Breezhaler medication pack. Dispose of each inhaler after finishing the pack.
- Do not store the capsules in the Miflonide Breezhaler inhaler.
- Always keep the Miflonide Breezhaler inhaler and Miflonide Breezhaler capsules in a dry place.

Manufacturer:

See folding box.

International Package Leaflet

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® = registered trademark

Novartis Pharma AG, Basel, Switzerland