ASMANEX* TWISTHALER* Dry Powder Inhaler
Brand of mometasone furoate
FOR ORAL INHALATION

DESCRIPTION: Each inhalation contains either 100 micrograms, 200 micrograms or 400 micrograms of mometasone furoate anhydrous. Inactive ingredients: Lactose (which contains trace amount of milk proteins).

ACTIONS: Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties.

It is likely that much of the mechanism for the anti-allergic and anti-inflammatory effects of mometasone furoate lies in its ability to inhibit the release of mediators of the inflammatory cascade. *In vitro*, mometasone furoate significantly inhibits the release of leukotrienes from leukocytes of allergic patients. In cell culture, mometasone furoate demonstrated high potency in inhibition of synthesis and release of IL-1, IL-5, IL-6, and TNFα; it is also a potent inhibitor of LT production and in addition it is an extremely potent inhibitor of the production of the TH_2 cytokines, IL-4 and IL-5, from human CD4+ T-cells.

Mometasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor, which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone.

Double-blind placebo-controlled trials of 12 weeks duration in patients ≥ 12 years of age have shown that treatment with ASMANEX* TWISTHALER* at delivered doses within the range of 200-800 micrograms per day resulted in improved lung function as measured by FEV_1 and peak expiratory flow, improved asthma symptom control, and decreased need for inhaled $beta_2$ agonist. Improved lung function was observed within 24 hours of the start of treatment in some

patients, although maximum benefit was not achieved before 1 to 2 weeks or longer. Improved lung function was maintained for the duration of treatment.

A 12-week, placebo-controlled trial of 296 patients 4- to 11- years of age with asthma of at least 6 months duration was conducted to demonstrate the efficacy of the ASMANEX* TWISTHALER* in the treatment of asthma. There was a significantly superior change in treatment response (mean % predicted FEV_1 change) in subjects treated with ASMANEX* TWISTHALER* 100 mcg once daily in the evening or ASMANEX* TWISTHALER* 100 mcg twice daily than in patients treated with placebo. In other measures of lung function (AM and PM PEF), both doses of ASMANEX* TWISTHALER* were significantly more efficacious than placebo for improving lung function at endpoint. Additionally, pediatric patients treated with ASMANEX* TWISTHALER* had less use of $beta_2$ agonist rescue medication compared to pediatric patients treated with placebo.
Clinical trials in healthy volunteers demonstrated a low rate of systemic bioavailability (<1%) and essentially complete first pass metabolism by the liver following oral inhalation of mometasone furoate.

INDICATIONS AND USAGE

Adults and adolescents 12 years and older ASMANEX* TWISTHALER* inhaler is indicated as prophylactic therapy in the management of all severities of asthmatic patients, including those who have been dependent upon either inhaled or systemically administered corticosteroids, and non-corticosteroid-dependent patients inadequately controlled on other drug regimens.

Pediatric patients ages 4 through 11 years: ASMANEX* TWISTHALER* is also indicated for the maintenance treatment of asthma as prophylactic therapy.

DOSAGE AND ADMINISTRATION

ASMANEX* TWISTHALER* should be administered by oral inhalation only. After each dose, patients should be advised to rinse their mouth with water and spit out the contents without swallowing.

ASMANEX* TWISTHALER* is intended for use in adults, adolescents and pediatrics 4 years of age and older.

Mild to moderate asthma (patients ≥ 12 years of age):
The recommended starting dose of ASMANEX* TWISTHALER* therapy for patients with mild to moderate asthma is 400 micrograms once daily. Data suggests that better asthma control is achieved if once daily dosing is administered in the evening. Some patients, such as those previously on high doses of inhaled corticosteroids, may be more adequately controlled on a dose of 400 micrograms daily given in 2 divided doses (200 micrograms BID).

A dose reduction to 200 micrograms once daily given in the evening may be an effective maintenance dose for some patients.

The dose should be individualised and titrated to the lowest dose at which effective control of asthma is maintained.

Severe asthma (patients ≥ 12 years of age):
For patients with severe asthma who may require oral corticosteroids, the recommended starting dose of ASMANEX* TWISTHALER* is 400 micrograms twice daily, which is the maximum recommended dose. Once reduction of oral steroid dose is complete (see below) or symptoms are controlled, titrate ASMANEX* TWISTHALER* to the lowest effective dose.

Inhaled mometasone furoate demonstrated improved lung function within 24 hours after the first dose. In some patients, however, maximum benefit may not be achieved before 1 to 2 weeks or longer.

Pediatric asthma patients (4 to 11 years of age):
The recommended dose is 100 micrograms once daily given in the evening.

The patient should be made aware of the prophylactic nature of this product and be instructed to use it regularly to maintain therapeutic benefit, even when no symptoms are present.

The patient needs to be instructed how to use the inhaler correctly.

Prior to removing the cap, be sure the dose counter and the pointer on the cap are aligned and the inhaler is held upright with the coloured* base at the bottom. The inhaler can be opened by removing the white cap while holding the coloured base, gripping the base and twisting the cap counterclockwise. Upon removal of the cap, the counter will register the number down by one count. Instruct the patient to place the inhaler in the mouth, closing the lips around the mouthpiece (do not cover the ventilation holes), and to breathe in rapidly and deeply. Then, the inhaler is removed from the mouth, and the breath is held for about 10 seconds, or as long as comfortable. The patient is not to breathe out through the inhaler. The inhaler must be kept clean and dry at all times. The outside of the mouthpiece can be cleaned with a dry cloth or tissue. The inhaler must not be cleaned with water. To close, replace the cap immediately after each inhalation while holding the unit upright, loading for next dose by rotating the cap clockwise while gently pressing down until a click sound is heard and the cap is fully closed. The arrow on the cap will be fully aligned with the counter window. Rinsing the mouth after inhalation is advised. This helps to reduce the risk of candidiasis.
* Grey for 100 micrograms, pink for 200 micrograms and maroon for 400 micrograms

The digital dose counter display will indicate the number of doses remaining. After dose 01, the counter will read 00 and the cap will lock, at which time the unit must be discarded.

Initially, in patients with severe asthma, ASMANEX* TWISTHALER* inhaler is for use concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately one week, gradual withdrawal of the systemic corticosteroid is initiated by reducing the daily or alternate daily dose. The next reduction is made after an interval of one to two weeks, depending on the response of the patient. Generally, these decrements are not to exceed 2.5 mg of prednisone daily or its equivalent. A slow rate of withdrawal is strongly recommended. During withdrawal of oral corticosteroids, patients must be carefully monitored for signs of unstable asthma, including objective measures of airway function, and for adrenal insufficiency (see PRECAUTIONS). During dose reduction, some patients may experience

symptoms of systemic corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients are to be encouraged to continue with ASMANEX* TWISTHALER* treatment, but must be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, increase the systemic corticosteroid doses temporarily and thereafter continue withdrawal more slowly. During periods of stress or severe asthma attack, these patients may require supplementary treatment with systemic corticosteroids.

DRUG INTERACTIONS

Co-administration with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, cobicistat-containing products) may lead to increased plasma concentrations of corticosteroids and potentially increase the risk for systemic corticosteroid side-effects. Consider the benefit of co-administration versus the potential risk of systemic corticosteroid effects, in which case patients should be monitored for systemic corticosteroid side-effects.

ADVERSE EFFECTS

Adults and adolescents (12 years of age and older): The most common (1-10%), treatment-related undesirable effects in placebo-controlled studies were oral candidiasis, pharyngitis, dysphonia and headache. Oral candidiasis was reported by 6% and 15% of the patients treated with the 200 microgram and 400 microgram twice daily dosing regimens, respectively, and by 2% in both of the once-daily regimens. The incidence in placebo-treated patients was 1%.

In comparison, among patients with severe asthma treated with oral corticosteroids who received ASMANEX* TWISTHALER* 400 micrograms BID for 12 weeks, oral candidiasis was reported by 20% of patients (versus. 9% with placebo), and dysphonia by 7% of patients (versus. 0% with placebo). These effects were considered treatment-related.

Treatment-related pharyngitis in the twice daily treatment regimens was reported by 4% (200 micrograms) and 8% (400 micrograms) of patients. On the once-daily regimen, the

incidence was 4% (200 micrograms) and 2% (400 micrograms) versus 2% of patients in the placebo group.

Related headache was reported by 3% to 4% of patients in active treatment groups and by 3% of placebo-treated patients. Dysphonia occurred in 1% to 3% of patients in the active treatment groups and in 1% of placebo treated patients.

There was no suggestion of an increased risk for undesirable effects in adolescents or patients 65 years of age or older.

Systemic effects of inhaled corticosteroids may occur, particularly when prescribed at high doses for prolonged periods.

Rare cases of glaucoma, increased intraocular pressure, cataracts and tachycardia have been reported.

Pediatric (4 to 11 years of age): ASMANEX* TWISTHALER* 100 mcg once daily was well tolerated in clinical trials conducted in children with asthma aged 4 to 11 years. The most common treatment related undesirable effects reported in one 12-week placebo-controlled pediatric study with ASMANEX* TWISTHALER* 100 micrograms taken once daily in the evening were headache (2% versus 0% placebo), pharyngitis (1% versus 1% placebo) and cough (1% versus 0% placebo).

Post marketing experience

The following additional adverse reactions have been reported in post-marketing use with ASMANEX* TWISTHALER*: hypersensitivity reactions (e.g., rash, pruritus, angioedema and anaphylactic reaction), asthma aggravation (e.g., cough, dyspnea, wheezing and bronchospasm), and vision blurred.

CONTRAINDICATIONS

Patients with known hypersensitivity to mometasone furoate or to milk proteins, which are contained in the excipient lactose.

PRECAUTIONS

Oropharyngeal Candidiasis

During clinical trials with ASMANEX* TWISTHALER*, oral candidiasis, which is associated with the use of this class of drugs, occurred in some patients. This infection may require treatment with appropriate antifungal therapy or discontinuance of ASMANEX* TWISTHALER* (see ADVERSE EFFECTS). After dosing with ASMANEX* TWISTHALER*, advise patients to rinse their mouth with water and spit out the contents without swallowing.

As with other glucocorticoid products, the potential for hypersensitivity reactions, including rashes, urticaria, pruritus and erythema, and edema of the eyes and face, lips, and throat should be considered.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with the ASMANEX* TWISTHALER* inhaler, immediate treatment with a fast-acting inhaled bronchodilator is recommended. Treatment with the ASMANEX* TWISTHALER* inhaler should be discontinued and alternative therapy instituted.

Systemic Effects of Corticosteroids

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, growth retardation in children and adolescents, decrease in bone mineral density, cataracts and glaucoma. Therefore, it is important that the dose of inhaled corticosteroids is titrated to the lowest dose at which effective control of asthma is maintained.

Visual disturbance may be reported with systemic and topical (including, intranasal, inhaled and intraocular) corticosteroid use. If a patient presents with symptoms such as blurred vision or

other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes of visual disturbances which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Transferring from Systemic Corticosteroid Therapy

Particular care is needed for patients who are transferred from systemically active corticosteroids to the ASMANEX* TWISTHALER* inhaler, because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypopituitary-adrenal (HPA) axis function.

During periods of stress, including trauma, surgery, or infection, or a severe asthma attack, patients transferred from systemic corticosteroids will require supplementary treatment with a short course of systemic corticosteroids, which is gradually tapered as symptoms subside. It is recommended that such patients carry a supply of oral corticosteroids and a warning card indicating their need and recommended dosage of systemic corticosteroids during stressful periods. Periodic testing of adrenocortical function, particularly measurement of early morning plasma cortisol levels, is recommended.

Transfer of patients from systemic corticosteroid therapy to ASMANEX* TWISTHALER* may unmask pre-existing allergic conditions previously suppressed by systemic corticosteroid therapy. If this occurs, symptomatic treatment is recommended.

Acute Asthma Episodes

ASMANEX* TWISTHALER* is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm. A short acting $beta_2$-agonist should be available at all times. Patients must be informed of the need to seek medical treatment immediately if their asthma deteriorates suddenly.

Asthma Exacerbations

Instruct patients to contact their physician immediately when asthmatic episodes are not responsive to bronchodilators during treatment with ASMANEX* TWISTHALER*. During such episodes, patients may require an upward titration of ASMANEX* TWISTHALER* inhaler to the maximum daily dose and/or systemic corticosteroid therapy.

The ASMANEX* TWISTHALER* inhaler will often permit control of asthma symptoms with less suppression of HPA axis function than therapeutically equivalent oral doses of prednisone. Although mometasone furoate has demonstrated low systemic bioavailability at the recommended dosage, it is absorbed into the circulation and can be systemically active at higher doses. Thus, to maintain its profile of limited potential for HPA axis suppression, recommended doses of ASMANEX* TWISTHALER* must not be exceeded, and must be titrated to the lowest effective dose for each individual patient. When prescribing ASMANEX* TWISTHALER* inhaler, physicians are advised to consider that sensitivity to cortisol production may vary from patient to patient.

No evidence supports that the administration of ASMANEX* TWISTHALER* in amounts greater than recommended doses increases efficacy.

Immunosuppression

Use ASMANEX* TWISTHALER* with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections or ocular herpes simplex.

Advise patients who are receiving corticosteroids or other immunosuppressant medicines of the risk of exposure to certain infections (e.g., chickenpox, measles) and of the importance of obtaining medical advice if such exposure occurs. This is of particular importance in children.

Adrenal Suppression

When using inhaled corticosteroids, the possibility for clinically significant adrenal suppression may occur, especially after treatment with higher than recommended doses. This must be

considered during periods of stress or elective surgery, when additional systemic corticosteroids may be needed. However, during clinical trials there was no evidence of clinically significant HPA axis suppression after prolonged treatment with ASMANEX* TWISTHALER* at doses ≤ 800 micrograms per day.

The patient should be advised against abrupt discontinuation of therapy with ASMANEX* TWISTHALER* inhaler.

Clinical Studies Experience

A 52-week, placebo-controlled, parallel-group study was conducted in 142 asthmatic children 4 to 9 years of age receiving ASMANEX* TWISTHALER* to determine the potential growth effects of ASMANEX* TWISTHALER* at 100 micrograms twice daily (100 mcg QD AM + 100 mcg QD PM) and 100 micrograms once daily administered in the morning (QD AM). ASMANEX* TWISTHALER* 100 micrograms twice daily demonstrated a marginal decrease in growth velocity when compared with placebo. At the total daily recommended dosage of 100 micrograms once daily (administered in the morning), ASMANEX* TWISTHALER* did not show a statistically significant effect on growth velocity when compared to placebo treated patients. The growth of children (4 to 11 years of age) receiving orally inhaled corticosteroids should be monitored routinely. The potential growth effects of prolonged treatment with orally inhaled corticosteroids should be weighed against the clinical benefits obtained and the availability of safe and effective non-corticosteroid treatment alternatives.

Safety and effectiveness in children less than 4 years of age have not been established.

Adverse events in the elderly population (≥ 65 years) were similar in type and incidence to those reported in younger patients.

USAGE DURING PREGNANCY AND LACTATION

There are no adequate and well controlled studies in pregnant women, and it is not known if mometasone furoate is excreted in human milk. As with other inhaled corticosteroid preparations, ASMANEX* TWISTHALER* must not be used during pregnancy or by nursing

mothers unless the potential benefit justifies the potential risk to the mother, foetus or infant. Infants born of mothers who received corticosteroids during pregnancy must be observed carefully for hypoadrenalism.

OVERDOSAGE

Because of the low systemic bioavailability of mometasone, overdose is unlikely to require any therapy other than observation, followed by initiation of the appropriate prescribed dosage. Inhalation or oral administration of excessive doses of corticosteroids may lead to suppression of HPA axis function.

HOW SUPPLIED

Each strength is available in two pack sizes.

ASMANEX* TWISTHALER* 100 mcg/inhalation is available in 7 doses/container or 30 doses/container with grey colored base. Each container delivers 7 or 30 metered doses containing 100 micrograms of mometasone furoate anhydrous per actuation.

ASMANEX* TWISTHALER* 200 mcg/inhalation – is available in 30 doses/container or 60 doses/container with pink colored base. Each container delivers 30 or 60 metered doses containing 200 micrograms of mometasone furoate anhydrous per actuation.

ASMANEX* TWISTHALER* 400 mcg/inhalation – is available in 30 doses/container or 60 doses/container with maroon colored base. Each container delivers 30 or 60 metered doses containing 400 micrograms of mometasone furoate anhydrous per actuation.
Shelf life information can be found on the immediate and outer labels of the product.
Not all presentations may be available locally.

STORAGE

Store in original foil package until opened. Store unopened package below 30°C. After opening the package, keep the inhaler in a dry place at a temperature below 25°C. Keep the inhaler

clean and dry at all times. Clean the outside of the mouthpiece with a dry cloth or tissue; avoid contact with water.

Discard the product within 12 weeks of removal from the foil wrapped package.

Do not use after the expiry date stated on the container.

Do not use if the metered counter is not working properly.

Keep out of reach and sight of children.

Further information can be obtained from the doctor or pharmacist.

Product Registrant:

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Date of revision: July 2022

* Registered Trademark

ORGANON

PATIENT INSTRUCTIONS FOR USE

Remove from foil pouch

HOW TO USE

1. **Open inhaler**

   To open the inhaler remove the cap as follows:

   Hold the inhaler upright with the coloured* base down as shown in (Figure 1).

   Grip the base and twist the cap counter-clockwise to remove it.

   As you remove the cap, the inhaler's counter will count down by one.

   The counter on the coloured* base and the pointer on the body above the counter should be in line with one another.

   Keep the inhaler upright once the cap is removed and prior to inhaling your dose.

2. Inhale dose

a) Bring the inhaler up to your mouth with the mouthpiece pointing toward you. Place the inhaler in mouth, close lips around the mouthpiece, then breathe in rapidly and deeply.

b) Remove the inhaler from mouth and hold breath for about 10 seconds, or for as long as is comfortable (Figure 2). Do not breathe out through the inhaler.

c) After dosing, rinse your mouth with water and spit out the contents without swallowing.

3. Close the inhaler

Replace the inhaler cap immediately after each inhalation.

The cap must be fully replaced and rotated to load the dose for the next inhalation.

This should be done by rotating the cap clockwise while gently pressing the cap down until a click sound is heard and the cap is fully closed (Figure 3). The arrow on the cap should be fully aligned with the counter window (Figure 4).

Repeat steps 1 – 3 as prescribed (see Figures 1 – 4).

FURTHER INFORMATION ABOUT THE INHALER

The inhaler delivers your medication as a very fine powder that you may not taste, smell or feel. By following the instructions in this leaflet, you can be confident you have received the correct dose.

STORING YOUR INHALER

Keep your inhaler clean and dry at all times. Do not wash the inhaler. Clean the outside of the mouthpiece with a dry cloth or tissue. Keep your inhaler in a dry place at a temperature below 25°C.

Keep your inhaler out of the reach of young children. Do not use after the date shown on the inhaler or beyond 12 weeks after removal from the foil pouch.

HOW TO KNOW WHEN YOUR INHALER IS EMPTY

The inhaler has a dose indicator window on the coloured* base. It is a digital display which displays the number of doses remaining. When the unit reads 01, this indicates the last remaining dose. After dose 01, the counter will read 00, and the cap will lock. The unit must then be discarded.

* Grey for 100 micrograms, pink for 200 micrograms, maroon for 400 micrograms

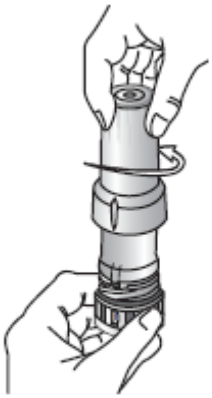

Figure 1
Cap removal

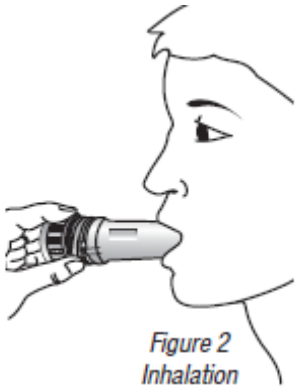

Figure 2
Inhalation

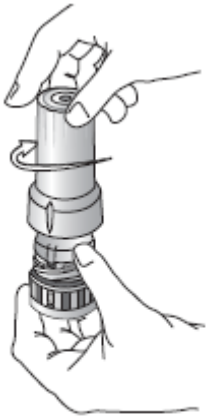

Figure 3
Closing the inhaler

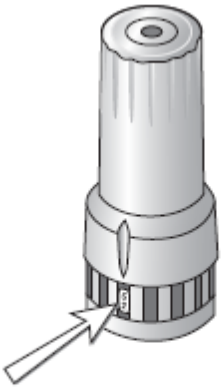

Figure 4
Closed Inhaler