PROFESSIONAL INFORMATION

SCHEDULING STATUS

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1. NAME OF THE MEDICINE

PRESSIDO 200 (Metered dose inhaler)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation delivers 200 µg budesonide.

Sugar free

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Metered dose inhaler

PRESSIDO 200 (Metered dose inhaler) is a pressurised metered dose inhaler containing suspension aerosol filled in aluminum canister fitted with suitable metered valve. There should be no sign of physical damage or leakage.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRESSIDO 200 is indicated for the prophylaxis of the symptoms of asthma.

4.2 Posology and method of administration

Shake before use.

Adults and children over 12 years of age:

Initial dose: 400 µg daily in divided doses.

In patients whose asthma is not responding to low dose **PRESSIDO 200** therapy, or when the patient's asthma can no longer be controlled by the maximum maintenance dose of bronchodilators, the daily

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dosage may be increased up to 1600 µg. In controlled patients, twice daily administration may be adequate.

THE MAINTENANCE DOSE SHOULD BE INDIVIDUALISED AND SHOULD BE THE LOWEST POSSIBLE DOSAGE.

Patients on concomitant therapy with inhaled bronchodilators should use the bronchodilators several minutes before the inhalation of **PRESSIDO 200** to minimise possible local side-effects, such as cough.

The use of a spacer device is recommended when the daily dose exceeds 400 µg in adults and for all doses in children over 12 years of age. This will improve lung deposition and will reduce the systemic absorption of budesonide.

Rinse the mouth after each dosage administration. Treatment with inhaled steroids should not be stopped abruptly.

4.3 Contraindications

PRESSIDO 200 is contraindicated in:

- Patients with hypersensitivity to budesonide, or any of the components of **PRESSIDO 200,** listed in section 6.1.
- Patients with active or quiescent pulmonary tuberculosis or with other untreated airway infections of bacterial, fungal or viral origin.

4.4 Special warnings and precautions for use

Patients should be carefully instructed in the correct use of the inhaler, making sure that the inhaler in activation is synchronised with inspiration. Patients should also be made aware of the prophylactic nature of **PRESSIDO 200** therapy, and that it should be taken even when they are asymptomatic.

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Adrenal suppression may occur.

Bacterial and fungal (including Candida) infections of the mouth and throat may occur.

Patients with high blood levels of Candida precipitants, indicating a previous infection, are most likely to develop this complication. Some patients may find it helpful to rinse their mouth thoroughly with water after inhalation. The water should not be swallowed.

Paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. If this occurs, treatment with inhaled budesonide should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

PRESSIDO 200 is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required.

If patients find short-acting bronchodilator treatment ineffective or they need more inhalations than usual, medical attention must be sought. In this situation consideration should be given to the need for or an increase in their regular therapy, e.g. higher doses of inhaled **PRESSIDO 200** or the addition of a long acting beta agonist, or for a course of oral glucocorticosteroid.

Systemic effects may occur with any inhaled corticosteroids including **PRESSIDO 200**, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

Reduced liver function affects the elimination of corticosteroids causing lower elimination rate and higher systemic exposure. Be aware of possible systemic side effects.

<u>Pneumonia in patients with Chronic Obstructive Pulmonary Disease (COPD)</u>

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids including **PRESSIDO 200**. There is

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some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

Visual disturbance

Visual disturbance may be reported with systemic and topical 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 as soon as possible of possible causes 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.

Paediatric population

Influence on growth

It is recommended that the height of children receiving prolonged treatment with **PRESSIDO 200** is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. The benefit of the corticosteroid therapy and the possible risk of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

Transfer of patients, dependent upon oral steroids, to treatment with **PRESSIDO 200** demands special care, and is preferably done when the patient is in a relatively stable phase. **PRESSIDO 200** should be given in combination with the previously used oral steroid dose for about ten days. After this period of time, reduction of the oral corticosteroid can be started with a dose reduction corresponding to about 1 mg prednisolone per day per week. Some patients may experience uneasiness during the withdrawal period, due to decreased steroid effect. Acute exacerbations, accompanied by increased mucus viscosity and mucus plugging may require complementary treatment with an oral corticosteroid. It is important to monitor intercurrent infections and treat them appropriately.

Appropriate measures should be taken to protect the patient against stress situations, e.g. severe infections, surgery. Treatment with inhaled steroids should not be stopped abruptly.

Some patients may experience uneasiness during the withdrawal period due to a decreased steroid effect. The medical practitioner may have to explain the reason for **PRESSIDO 200** treatment in order

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to encourage the patient to continue. The length of time needed for the body to regain its natural production of corticosteroid in sufficient amounts is often extensive. Thus, during physically stressful situations such as severe infections, trauma and surgical operations, it will be necessary to give the patient an additional oral steroid dose. Acute exacerbations, accompanied by increased mucus viscosity and mucus plugging may require complementary treatment with an oral corticosteroid.

4.5 Interaction with other medicines and other forms of interaction

The metabolism of budesonide as contained in **PRESSIDO 200** is primarily mediated by CYP3A4. Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products, are expected to increase the risk of systemic side effects.

The combination of **PRESSIDO 200** with potent CYP3A inhibitors should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects. If **PRESSIDO 200** is co-administered with anti-fungals (such as itraconazole and ketoconazole), the period between treatments should be as long as possible. A reduction of the **PRESSIDO 200** dose could be considered.

Limited data about this interaction for high-dose inhaled **PRESSIDO 200** indicate that marked increases in plasma levels (on average four-fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 µg).

Raised plasma concentrations of and enhanced effects of corticosteroids have been observed in women also treated with oestrogens and contraceptive steroids, but no effect has been observed with budesonide and concomitant intake of low dose combination oral contraceptives.

Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

4.7 Effects on ability to drive and use machines

PRESSIDO 200 may cause blurred vision. If symptoms are severe, the patient should not drive or operate machinery.

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4.8 Undesirable effects

The following adverse reactions have been reported in association with **PRESSIDO 200**.

System organ class	Frequency	Undesirable effect
Infections and infestations	Frequent	Oropharyngeal candidiasis Pneumonia (in COPD patients)
Immune system disorders	Less frequent	Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and anaphylactic reaction
Endocrine/ metabolic disorders	Less frequent	Signs and symptoms of systemic corticosteroid effects including Adrenal suppression Growth retardation
Psychiatric disorders	Frequent	Psychotic behaviour - this may include nervousness, restlessness and depression
	Less frequent	Anxiety Psychomotor hyperactivity Sleep disorders Aggression Behavioural changes (predominantly in children)
Nervous system disorders	Less frequent	Tremor** Headache
Eye disorders	Less frequent	Cataract formation after prolonged use Vision, blurred
	Frequency unknown	Glaucoma

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Ear and labyrinth disorders	Frequent	Dysphonia, *Candida albicans* infections of the mouth and throat, dryness of mouth and throat, bad taste.
Respiratory disorders	Frequent	Local irritation and paradoxical bronchoconstriction. Pulmonary infiltrates with eosinophilia may occur Cough Hoarseness
Gastrointestinal disorders	Less frequent	Nausea and diarrhoea
Skin and subcutaneous tissue disorders	Frequent	Skin thinning and purpura. Other skin reactions may include urticaria, rashes and dermatitis
	Less frequent	Bruising
Musculoskeletal and connective tissue disorders	Less frequent	Muscle spasm
General disorders	Less frequent	Tiredness and thirst

* Rare in children

** based on the frequency reported in clinical trials

Occasionally, signs or symptoms of systemic glucocorticosteroid-side effects may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous corticosteroid exposure and individual sensitivity.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting

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Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Treatment with **PRESSIDO 200** should be continued at the recommended dose to control the asthma and appropriate measures taken to protect the patient against stress situations. Treatment is symptomatic and supportive.

Acute overdosage with **PRESSIDO 200**, even in excessive doses, is not expected to be a clinical problem. The only harmful effect that follows inhalation of large amounts of the medicine over a short period is suppression of hypothalamic pituitary-adrenal (HPA) function.

5. PHARMACOLOGICAL PROPERTIES

Category and Class:

A 21.5.1 Corticosteroids and analogues

ATC code: R03BA02

5.1 Pharmacodynamic properties

Mechanism of action

Budesonide is a non-halogenated corticosteroid, which, when inhaled, has a local anti-inflammatory action in the lungs.

5.2 Pharmacokinetic properties

Absorption

The maximal plasma concentration after inhalation of 1 milligram budesonide is about 3.5 nmol/L and is reached after about 20 minutes.

Distribution

Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85 - 90 %.

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Biotransformation

Budesonide undergoes an extensive degree (approximately 90 %) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1 % of that of budesonide. The metabolism of Budesonide is primarily mediated by CYP3A, a subfamily of cytochrome p450.

Excretion

The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has high systemic clearance (approximately 1.2 L/min) in healthy adults, and the terminal half-life of budesonide after iv dosing averages 2 - 3 hours.

Linearity:

The kinetics of budesonide are dose-proportional at clinically relevant doses. In a study, 100 mg ketoconazole taken twice daily, increased plasma levels of concomitantly administered oral budesonide (single dose of 10 mg) on average, by 7.8-fold. Information about this interaction is lacking for inhaled budesonide, but marked increases in plasma levels could be expected.

Paediatric safety data

Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic children. Per kg body weight children have a clearance which is approximately 50 % greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults. In asthmatic children treated with **PRESSIDO 200** (800 µg single dose), plasma concentration reached C_{max} (4.85 nmol/L) at 13.8 minutes after inhalation, and then decreased rapidly; AUC was 10.3 nmol·h/L. The value for AUC is generally comparable to that observed in adults at the same dose, however, the C_{max} value tends to be higher in children. Lung deposition in children (31 % of the nominal dose) is similar to that measured in healthy adults (34 % of nominal dose).

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5.3 Preclinical safety data

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1,1,1,2 Tetrafluoroethane (Propellant HFA 134a)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the date of manufacture.

6.4 Special precautions for storage

Store at or below 30 °C.

Avoid storage in direct sunlight or heat. The canister should not be punctured, broken or burnt even if it is apparently empty.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

A 19 ml aluminium canister fitted with metered dispensing 50 µl nitrile valve crimped in place and a polypropylene actuator attached (brown colored cap and white colour body), placed in a outer carton.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

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Macleods Pharmaceuticals SA (Pty) Ltd

Office Block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

54/21.5.1/0611.610

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 October 2023

10. DATE OF REVISION OF THE TEXT

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