SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

BECLOREST 50 pressurised inhalation solution

BECLOREST 100 pressurised inhalation solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains 50 micrograms of micronized beclometasone dipropionate.

Each metered dose contains 100 micrograms of micronized beclometasone dipropionate.

Contains the propellant HFA-134a.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation solution.

A clear solution in a pressurised aluminium canister fitted with a metering valve and an actuator.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BECLOREST is indicated for the prophylactic treatment of bronchospasm in the following groups of patients with asthma:

- Patients who are expected to be on long-term steroid maintenance therapy.
- Asthmatic patients poorly controlled by bronchodilators. In these patients BECLOREST may facilitate asthma control and may reduce the need for bronchodilators.
- Patients who are inadequately controlled by sodium cromoglycate in addition to bronchodilators.4.2 Posology and method of administration
- Patients with severe asthma who are dependent on systemic corticosteroids or those patients who are receiving intermittent courses of oral steroids.
- Inhaled beclometasone dipropionate is particularly important for managing asthma in children as effective control can be achieved without growth retardation commonly associated with systemic steroids.

Posology

Do not exceed the recommended dose.

The initial dose of BECLOREST should be appropriate to the severity of the asthma.

The dose is then adjusted until control is achieved or reduced to the minimum effective dose according to the individual patient's response.

Adults:

The usual dose is 200 µg twice daily.

In more severe cases the dosage may be started at or increased to 600 – 800 µg per day and subsequently reduced when the patient's asthma has been stabilised.

The total daily dose may be administered as two, three or four divided doses.

In patients with severe asthma, or those showing only partial response to standard inhalation doses, high dose inhalation therapy may be considered, and dosage of up to 1 mg daily (1 000 µg) in divided doses, may be used.

Maximum daily dose: 1 000 µg (1 mg) daily.

Children:

50 – 100 µg should be given two, three of four times daily according to the age and response.

Alternatively, 100 µg or 200 µg twice daily may be administered.

Maximum daily dose: 500 µg daily.

Method of administration

BECLOREST is for oral inhalation use only.

An appropriate spacer device should be used in patients who struggle to coordinate aerosol actuation with inspiration of breath.

4.3 Contraindications

- Hypersensitivity to beclomethasone dipropionate or to any of the excipients listed in section 6.1.
- Acute status asthmaticus.
- Safety of BECLOREST in pregnancy has not been established.

4.4 Special warnings and precautions for use

Patients should be instructed on the proper use of the inhaler to ensure that the medicine reaches the target areas within the lungs. Patients should also be informed that BECLOREST should be used on a regular basis, even when they are asymptomatic.

BECLOREST does not provide relief of acute asthma symptoms, which require a short-acting inhaled bronchodilator. Patients should have relief medication available.

Severe asthma requires regular medical assessment, including lung-function testing, as there is a risk of severe attacks and even death. Patients should be instructed to seek medical attention if short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are required as this may indicate deterioration of asthma control. If this occurs, patients should be assessed and the need for increased anti-inflammatory therapy considered (e.g., Higher doses of inhaled corticosteroid or a course of oral corticosteroid).

Severe exacerbations of asthma must be treated in the usual way, i.e., by increasing the dose of inhaled BECLOREST (see section 4.2), giving a systemic steroid if necessary, and/or an appropriate antibiotic if there is an infection, together with β-agonist therapy.

Treatment with BECLOREST should not be stopped abruptly.

Systemic effects of inhaled corticosteroids may occur, particularly when prescribed at high doses 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, cataract, and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression, or aggression (particularly in children) (see section 4.8). It is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroids, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should also be given to referring the patient to a paediatric respiratory specialist.

Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression.

Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The transfer to BECLOREST of patients who have been treated with systemic steroids for long periods of time or at high doses needs special care, since recovery from possible adrenocortical suppression may take considerable time. Reduction of the dose of systemic steroid can be commenced approximately one week after initiating treatment with BECLOREST. The size of the reduction should correspond to the maintenance dose of systemic steroid. For patients receiving maintenance doses of 10 mg daily or less of prednisolone (or equivalent) reductions in dose of not more than 1 mg are suitable. For higher maintenance doses, larger reductions in dose may be appropriate. These oral dosage reductions should be introduced at not less than weekly intervals.

Adrenocortical function should be monitored regularly as the dose of systemic steroid is gradually reduced.

Some patients feel unwell during withdrawal of systemic steroids despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with inhaled BECLOREST and to continue withdrawal of systemic steroid unless there are objective signs of adrenal insufficiency.

Patients weaned off oral steroids whose adrenocortical function is impaired should carry a steroid warning card indicating that they may need supplementary systemic steroids during periods of stress, e.g., worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by the systemic medicine. These allergies should be symptomatically treated with antihistamine and/or topical preparations, including topical steroids.

Special care is necessary in patients with active or quiescent pulmonary tuberculosis using inhaled corticosteroids.

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 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.

Patients should be advised that this product contains small amounts of ethanol (approximately 4,32 mg per actuation). At the normal doses, the amounts of ethanol are negligible and do not pose a risk to patients (see section 4.5, Interaction with other medicines and other forms of interaction).

4.5 Interaction with other medicines and other forms of interaction

BECLOREST contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

Beclometasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however, the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g., ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of BECLOREST in pregnancy has not been established (see section 4.3).

It should not be used in pregnancy.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate and intra-uterine growth retardation. There may, therefore, be a risk of such effects in the human foetus. It should be noted, however, that the foetal changes in animals occur after relatively high systemic exposure. BECLOREST is delivered directly to the lungs by the inhaled route and so avoids the high level of exposure that occurs when corticosteroids are given by systemic routes.

There is no experience with or evidence of safety of propellant HFA-134a in human pregnancy.

Breastfeeding

No specific studies examining the transfer of BECLOREST into the milk of lactating animals have been performed. It is reasonable to assume that BECLOREST is secreted in milk, but at the dosages used for direct inhalation there is low potential for significant levels in breast milk.

There is no experience with or evidence of safety of propellant HFA-134a during lactation.

Fertility

Studies of the effect of HFA-134a on reproductive function and embryofoetal development in animals have revealed no clinically relevant adverse effects.

4.7 Effects on ability to drive and use machines

Patients experiencing blurred vision should not drive or operate machines (see section 4.8).

4.8 Undesirable effects

Tabulated summary of adverse reactions

System Organ Class	Frequency	Description
Infections and infestations	*Frequent*	Oral candidiasis (of the mouth and throat)
Immune system disorders	*Less frequent*	Hypersensitivity reaction with the following manifestations: rash, urticaria, pruritus, erythema, oedema of the eyes, face, lips, and throat
Endocrine disorders **Psychiatric disorders (see section 4.4 Special warnings and precautions for use)** **Nervous system disorders**	*Less frequent*	Adrenal suppression*, growth retardation* (in children and adolescents), bone density decreased*
	Frequency unknown	Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural disorders (predominantly in children)
	Frequency unknown	Headache
Eye disorders **Respiratory, thoracic, and**	*Less frequent*	Cataract*, glaucoma*, blurred vision (see also section 4.4 and 4.7)

System Organ Class	Frequency	Description
mediastinal disorders	*Frequent*	Hoarseness, throat irritation
	Less frequent	Paradoxial bronchospasm, wheezing, dyspnoea, cough
Gastrointestinal disorders	*Frequency unknown*	Nausea

* Systemic reactions are a possible response to inhaled corticosteroids, especially when a high dose is prescribed for a prolonged time (see section 4.4 Special warnings and precautions for use).

Description of selected adverse reactions

Paradoxical bronchospasm may occur with an immediate increase in wheezing, shortness of breath and cough after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. BECLOREST should be discontinued immediately, the patient assessed and, if necessary, alternative therapy instituted.

Candidiasis of the mouth and throat occurs in some patients, the incidence increasing with doses greater than 400 micrograms BECLOREST per day. Patients with high blood levels of Candida precipitins, indicating a previous infection, are most likely to develop this complication. Patients may find it helpful to rinse their mouth thoroughly with water after inhalation. Symptomatic oral candidiasis can be treated with topical antifungal therapy while continuing with BECLOREST.

Hoarseness or throat irritation may occur in some patients. These patients should be advised to rinse the mouth out with water immediately after inhalation. Use of a spacer device may be considered.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

The only harmful effect that follows inhalation of large amounts of the drug over a short time-period is suppression of hypothalamic-pituitary-adrenal (HPA) function. No special emergency action need to be taken. Treatment should be continued at the recommended dose. HPA function recovers in a day or two. In the event of excessive intake of beclomethasone for a long period of time a degree of adrenal suppression could occur in addition to suppression of HPA function. The patient should be treated as steroid dependent and transferred to a suitable maintenance dose of systemic steroids.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.5.1. Corticosteroids and analogues

Pharmacotherapeutic group: Glucocorticoid

ATC Code: R03B A01

Mechanism of action

Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is extensively hydrolysed via esterase enzymes to the active metabolite beclometasone-17-monopropionate (B-17-MP), which has potent topical anti-inflammatory activity..

5.2 Pharmacokinetic properties

Absorption

Systemic absorption of unchanged beclometasone dipropionate (BDP) occurs through the lungs. There is negligible oral absorption of the swallowed dose of unchanged BDP. Prior to absorption there is extensive conversion of BDP to its active metabolite B-17-MP. The systemic absorption of B-17-MP arises from both lung deposition (36 %) and oral absorption of the swallowed dose (26 %). The absolute bioavailability following inhalation is approximately 2 % and 62 % of the nominal dose for unchanged BDP and B-17-MP, respectively. BDP is absorbed rapidly with peak plasma concentrations observed (t_{max}) at 0,3 hours. B-17-MP appears more slowly with a t_{max} of 1 hour. There is an approximately linear increase in systemic exposure with increasing inhaled dose. When administered orally the bioavailability of BDP is negligible but pre-systemic conversion to B-17-MP results in 41 % of the dose being absorbed as B-17-MP.

Distribution

The tissue distribution at steady-state for BDP is moderate (20 L) but more extensive for B-17-MP (424 L). Plasma protein binding is moderately high (87 %).

Biotransformation

BDP is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite (B-17-MP). Minor inactive metabolites, beclometasone-21-monopropionate (B-21-MP) and beclometasone (BOH), are also formed but these contribute little to the systemic exposure.

Elimination

The elimination of BDP and B-17-MP are characterised by high plasma clearance (150 L/hour and 120 L/hour) with corresponding terminal elimination half-lives of 0,5 hours and 2,7 hours. Following oral administration of tritiated BDP, approximately 60 % of the dose was excreted in the faeces within 96 hours mainly as free and

conjugated polar metabolites. Approximately 12 % of the dose was excreted as free and conjugated polar metabolites in the urine. The renal clearance of BDP and its metabolites is negligible.

5.3 Preclinical safety data

Preclinical safety studies indicate that beclometasone dipropionate shows negligible systemic toxicity when administered by inhalation.

The non-CFC propellant HFA-134a has been shown to have no toxic effect at very high vapour concentrations, far more than those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of up to two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

HFA-134a, Ethanol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze.

Protect from direct sunlight or heat.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50 °C. Do not pierce the canister.

6.5 Nature and contents of container

BECLOREST 50 is supplied in an aluminium canister fitted with a metering valve, pink plastic actuator, and brown dust cap, packed inside a cardboard carton containing a leaflet.

Each inhaler delivers 200 actuations.

BECLOREST 100 is supplied in an aluminium canister fitted with a metering valve, beige plastic actuator and brown dust cap, packed inside a cardboard carton containing a leaflet.

Each inhaler delivers 200 actuations.

6.6 Special precautions for disposal and other handling

Not applicable.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8 REGISTRATION NUMBER

BECLOREST 50: 50/21.5.1/0185

BECLOREST 100: 50/21.5.1/0186

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 April 2021

10 DATE OF REVISION OF THE TEXT

14 May 2021