

## AEROCORT Inhaler (Beclomethasone dipropionate + Levosalbutamol)

### Composition

Each actuation delivers:

Beclomethasone Dipropionate IP..... 50 mcg

Levosalbutamol Sulphate IP equivalent to levosalbutamol.....50 mcg

Suspended in propellant HFA-134a..... q.s.

### Dosage Form

Inhalation aerosol

### Description

AEROCORT Inhaler is a combination of beclomethasone dipropionate and levosalbutamol, which have different modes of action and show additive effects. Levosalbutamol is the active (R)-enantiomer of the racemate, salbutamol. It is a single-isomer,  $\beta_2$ -agonist that differs from racemic salbutamol by the elimination of (S)-salbutamol, which is inactive. Levosalbutamol has a highly selective action on the receptors in bronchial muscle, resulting in bronchodilation. Beclomethasone dipropionate is a synthetic glucocorticoid with a potent anti-inflammatory activity and weak mineralocorticoid activity. This combination of levosalbutamol and beclomethasone dipropionate is specially provided for those patients who require regular doses of both drugs for treatment of their obstructive airways disease.

### Pharmacology

#### ► Pharmacodynamics

#### *Levosalbutamol*

Activation of  $\beta_2$ -adrenergic receptors on airway smooth muscle leads to the activation of adenylate cyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP is associated with the activation of protein kinase A, which in turn, inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation.

Levosalbutamol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Increased cyclic AMP concentrations are also associated with the inhibition of the release of mediators from mast cells in the airways. Levosalbutamol acts as a functional antagonist that relaxes the airway irrespective of the spasmogen involved, thereby protecting against all bronchoconstrictor challenges. While it is recognized that  $\beta_2$ -adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are  $\beta$ -receptors in the human heart, 10-50% of which are  $\beta_2$ -adrenergic receptors. The precise function of these receptors has not been established. However, all  $\beta$ -adrenergic agonist drugs can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic (ECG) changes.

### *Beclomethasone Dipropionate*

The precise mechanisms of glucocorticoid action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Glucocorticoids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of glucocorticoids may contribute to their efficacy in asthma.

Airway inflammation is known to be an important component in the pathogenesis of asthma. Inflammation occurs in both large and small airways. Corticosteroids have multiple anti-inflammatory effects, inhibiting both inflammatory cells (e.g.: mast cells, eosinophils, basophils, lymphocytes, macrophages and neutrophils) and release of inflammatory mediators (e.g.: histamine, eicosanoids, leukotrienes and cytokines). These anti-inflammatory actions of corticosteroids such as beclomethasone dipropionate contribute to their efficacy in asthma.

Beclomethasone dipropionate is a prodrug that is rapidly activated by the hydrolysis to the active monoester, 17 monopropionate (17- BMP). Beclomethasone 17 monopropionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, 1.5 times that of budesonide and 25 times that of beclomethasone dipropionate. The clinical significance of these findings is unknown.

Studies in patients with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with beclomethasone.

#### ► Pharmacokinetics

### *Levosalbutamol*

A population pharmacokinetics (PPK) model was developed using plasma concentrations of (R)-salbutamol obtained from 632 asthmatic patients, aged 4 to 81 years, in three large trials. The PPK model-derived pharmacokinetic parameters for (R)-salbutamol in pediatric and adolescent/adult patients receiving a 90 mcg dose of inhaled levosalbutamol or a 180 mcg dose of inhaled racemic salbutamol are presented in table 1.

These pharmacokinetic data indicate that mean exposure to (R)-salbutamol was 13–16% less in adult and 30–32% less in pediatric patients given inhaled levosalbutamol as compared to those given a comparable dose of racemic salbutamol. When compared to adult patients, pediatric patients given 90 mcg of levosalbutamol had a 17% lower mean exposure to (R)-salbutamol.

### *Metabolism and Elimination*

Information available in published literature suggests that the primary enzyme responsible for the metabolism of salbutamol enantiomers in humans is sulphotransferase 1A3 (SULT1A3). When racemic salbutamol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration time curves (AUC) between the (R) - and (S)-salbutamol enantiomers, with (S)-salbutamol concentrations being consistently higher. However, after either inhalation or oral administration without charcoal pre-treatment, the differences were 8 to 24-fold, suggesting that (R)-salbutamol is preferentially metabolized in the gastrointestinal tract, presumably by SULT1A3.

Table 1: Mean Model-Predicted (R)-Salbutamol Pharmacokinetic Parameters

		Treatment	
Study Population	Parameters	Levosalbutamol	Racemic Salbutamol

Adolescent/Adult Patients (≥ 12 years)	C <sub>max</sub> (pg/mL)	199	238
	t <sub>max</sub> (hr)	0.54	0.53
	AUC <sub>(0-6)</sub> (pg·hr/mL)	695	798
Paediatric Patients (4-11 years old)	C <sub>max</sub> (pg/mL)	163	238
	t <sub>max</sub> (hr)	0.76	0.78
	AUC <sub>(0-6)</sub> (pg·hr/mL)	579	828

The primary route of elimination of salbutamol enantiomers is through renal excretion (80–100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic salbutamol, between 25–46% of the (R)-salbutamol fraction of the dose was excreted as unchanged (R)-salbutamol in the urine.

#### *Special Populations*

##### *Hepatic Impairment*

The effect of hepatic impairment on the pharmacokinetics of levosalbutamol has not been evaluated.

##### *Renal Impairment*

The effect of renal impairment on the pharmacokinetics of racemic salbutamol was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67% decline in racemic salbutamol clearance. Caution should be used when administering high doses of levosalbutamol to patients with renal impairment.

#### *Beclomethasone Dipropionate*

##### *Absorption*

When administered via inhalation (via metered dose inhaler), systemic absorption of unchanged beclomethasone dipropionate (BDP) occurs through the lungs with negligible oral absorption of the swallowed dose. There is extensive conversion of BDP to its active metabolite B-17-MP within the lung prior to absorption. The systemic absorption of B-17-MP arises from both lung deposition and oral absorption of the swallowed dose. The absolute bioavailability following inhalation is approximately 60% of the nominal dose for B-17-MP. BDP is absorbed rapidly with peak plasma concentrations first being observed (t<sub>max</sub>) at 0.3h. B-17-MP appears more slowly with a t<sub>max</sub> of 1 h. 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 approximately 40% of the dose being absorbed as B-17-MP.

##### *Distribution*

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

##### *Metabolism*

It is cleared very rapidly from the systemic circulation, owing to extensive first-pass metabolism. The main product of metabolism is the active metabolite (B-17-MP). Minor inactive metabolites, beclomethasone-21-monopropionate (B-2-MP) and beclomethasone (BOH) are also formed, but these contribute little to systemic exposure.

##### *Elimination*

The elimination of beclomethasone dipropionate and B-17-MP are characterized by high plasma clearance (150 and 120 L/h), with corresponding terminal elimination half-lives of 0.5 hours and 2.7 hours. Following oral administration of titrated beclomethasone dipropionate, approximately 60% of the dose was excreted in the feces 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.

## Indications

AEROCORT Inhaler is indicated in the treatment of asthma, once the need for inhaled corticosteroid and bronchodilator therapy has been established.

## Dosage And Administration

Adults and Adolescents (12 years and above):

Two inhalations, three or four times daily, titrated to the lowest effective dose.

AEROCORT Inhaler may be used with a Zerostat VT Spacer device by patients who find it difficult to synchronize aerosol actuation with inspiration of breath.

## Contraindications

Hypersensitivity to any of the components of the formulation. Reactions with levosalbutamol have included urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

Beclomethasone is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Special care is necessary with the use of beclomethasone dipropionate in patients with active or quiescent pulmonary tuberculosis.

## Warnings And Precautions

AEROCORT Inhaler is not for use in acute attacks, but for routine long-term management; so, some patients will require a separate levosalbutamol inhaler for relief of acute bronchospasm. For those patients who are steroid-dependent, it is advisable to commence therapy with beclomethasone dipropionate as a separate inhaler. Patients who have been weaned in the previous few months from long-term systemic corticosteroids need special consideration until the hypothalamic-pituitary- adrenal system has recovered sufficiently to enable the patient to cope with emergencies such as trauma, surgery or infections. These patients should also be given a supply of oral steroids to use in an emergency when their airways obstruction worsens.

### ► Levosalbutamol

#### *Paradoxical Bronchospasm*

Levosalbutamol can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, levosalbutamol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new dosage.

#### *Deterioration of Asthma*

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of levosalbutamol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

#### *Use of Anti-Inflammatory Agents*

The use of a beta-adrenergic agonist alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

#### *Cardiovascular Effects*

Levosalbutamol, like other beta-adrenergic agonists can produce clinically significant cardiovascular effects in some patients, as measured by heart rate, blood pressure, and symptoms. Although such effects are uncommon after administration of levosalbutamol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, levosalbutamol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

#### *Do Not Exceed Recommended Dose*

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

#### *Immediate Hypersensitivity Reactions*

Immediate hypersensitivity reactions may occur after administration of racemic salbutamol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving levosalbutamol

#### *Coexisting Conditions*

Levosalbutamol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator. Large doses of intravenous racemic salbutamol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

#### *Hypokalemia*

As with other beta-adrenergic agonist medications, levosalbutamol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

### ▶ Beclomethasone Dipropionate

#### *Local Effects*

Localized infections with *Candida albicans* have occurred in the mouth and pharynx in some patients receiving beclomethasone dipropionate. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with beclomethasone dipropionate therapy, but at times therapy with beclomethasone dipropionate may need to be temporarily interrupted under close medical supervision. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

#### *Deterioration of Asthma and Acute Episodes*

Beclomethasone dipropionate is not indicated for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta<sub>2</sub>-agonist, not beclomethasone dipropionate, should be used to relieve acute symptoms such as shortness of breath. Instruct patients to contact their physician immediately if

episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with beclomethasone dipropionate. During such episodes, patients may require therapy with oral corticosteroids.

#### *Transferring Patients from Systemic Corticosteroid Therapy*

Particular care is needed in patients who are transferred from systemically active corticosteroids to beclomethasone dipropionate 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 hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections (particularly gastroenteritis) or other conditions with severe electrolyte loss. Although beclomethasone dipropionate may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid that is necessary for coping with these emergencies. During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack.

Patients requiring oral or other systemic corticosteroids should be weaned slowly from oral or other systemic corticosteroid use after transferring to beclomethasone dipropionate. Lung function (FEV<sub>1</sub> or PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral or other systemic corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to beclomethasone dipropionate may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions. During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

#### *Immunosuppression*

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune patients on corticosteroids. In such patients who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. It is not known how the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection, and nor is the contribution of the underlying disease and/or prior corticosteroid treatment known. If exposed to chickenpox, prophylaxis with varicella-zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, parasitic or viral infections; or ocular herpes simplex.

#### *Paradoxical Bronchospasm*

Inhaled corticosteroids may produce inhalation-induced bronchospasm with an immediate increase in wheezing after dosing that may be life-threatening. If inhalation induced bronchospasm occurs following dosing with beclomethasone dipropionate, it should be treated immediately with an inhaled, short-acting bronchodilator. Treatment with

beclomethasone dipropionate should be discontinued and alternate therapy instituted.

#### *Immediate Hypersensitivity Reactions*

Hypersensitivity reactions, such as urticaria, angioedema, rash, and bronchospasm, may occur after administration of beclomethasone dipropionate. Discontinue beclomethasone dipropionate if such reactions occur.

#### *Hypercorticism and Adrenal Suppression*

Beclomethasone dipropionate will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since beclomethasone dipropionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of beclomethasone dipropionate in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with beclomethasone dipropionate should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when beclomethasone dipropionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of beclomethasone dipropionate should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

#### *Effects on Growth*

Orally inhaled corticosteroids, including beclomethasone dipropionate, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving beclomethasone dipropionate routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including beclomethasone dipropionate, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms.

#### *Reduction in Bone Mineral Density*

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term outcomes, such as fracture, is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids) should be monitored and treated with established standards of care.

#### *Eye Disorders*

Glaucoma, increased intraocular pressure, blurred vision and cataracts have been reported following the use of long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, blurred vision, glaucoma, and/or cataracts while using beclomethasone dipropionate.

### ▶ Drug Interactions

#### *Levosalbutamol*

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with levosalbutamol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

#### *Beta-Blockers*

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-adrenergic agonists, such as levosalbutamol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should

not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution.

#### *Diuretics*

The ECG changes or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop and thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta agonists with non-potassium-sparing diuretics. Consider monitoring potassium levels.

#### *Digoxin*

Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic salbutamol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving levosalbutamol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and levosalbutamol.

#### *Monoamine Oxidase Inhibitors or Tricyclic Antidepressants*

Levosalbutamol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salbutamol on the vascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

#### *Beclomethasone Dipropionate*

Beclomethasone 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 agents

#### ► Pregnancy

#### *Levosalbutamol*

##### *Pregnancy Category C*

There are no adequate and well-controlled studies of levosalbutamol in pregnant women. Because animal reproduction studies are not always predictive of human response, levosalbutamol should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. There are clinical considerations with the use of levosalbutamol in pregnant women.

##### *Clinical Considerations Disease-Associated Maternal and/or Embryo/Fetal Risk*

In women with poorly or moderately controlled asthma, there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women should be closely monitored and medication adjusted as necessary to maintain optimal control.

#### *Beclomethasone Dipropionate*

There is inadequate evidence of the safety of beclomethasone dipropionate in human pregnancy. Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

There are clinical considerations with the use of inhaled corticosteroids (ICS),

##### *Clinical Considerations Disease-Associated Maternal and/or Embryo/Fetal Risk*

The risk of complications to the mother and developing fetus from inadequate control of asthma must be balanced against the risks from exposure to beclomethasone dipropionate. In women with poorly or moderately controlled asthma,

evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age for the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted to maintain optimal control.

#### ▶ Labor or Delivery

##### *Levosalbutamol*

Levosalbutamol has not been approved for the management of preterm labor. The benefit:risk ratio when levosalbutamol tartrate is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta<sub>2</sub>-agonists, including racemic salbutamol.

##### *Beclomethasone Dipropionate*

There are no specific human data regarding any adverse effects of inhaled beclomethasone dipropionate on labor and delivery.

#### ▶ Lactation

##### *Levosalbutamol*

Plasma levels of levosalbutamol after inhalation of therapeutic doses are very low in humans, but it is not known whether levosalbutamol is excreted in human milk.

##### *Beclomethasone Dipropionate*

No specific studies examining the transference of beclomethasone dipropionate into the milk of lactating animals have been performed. However, other inhaled corticosteroids have been detected in human milk.

#### ▶ Females and Males of Reproductive Potential Impairment of Fertility

Females and males of reproductive potential impairment of fertility was observed in rats and dogs at oral doses of beclomethasone dipropionate corresponding to 250 and 25 times the MRHDID for adults on an mg/m<sup>2</sup> basis, respectively.

#### ▶ Pediatric Use

##### *Levosalbutamol*

The safety and effectiveness of levosalbutamol in paediatric patients below the age of 4 years have not been established

##### *Beclomethasone Dipropionate*

The safety and effectiveness of beclomethasone dipropionate in children below 4 years of age have not been established.

#### ▶ Geriatric Use

##### *Levosalbutamol*

Clinical studies of levosalbutamol tartrate did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseases or other drug therapy.

Salbutamol is known to be substantially excreted by the kidneys, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

##### *Beclomethasone Dipropionate*

Clinical studies of beclomethasone dipropionate did not include sufficient numbers of patients aged 65 and over to

determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## Undesirable Effects

As AEROCORT Inhaler contain levosalbutamol and beclomethasone dipropionate, the type and severity of adverse reactions associated with each of the compounds may be expected.

### *Levosalbutamol*

Common side effects reported by greater than 2% in adults and adolescents were pain, dizziness, asthma, pharyngitis, and rhinitis whereas those observed in children were vomiting, bronchitis and pharyngitis; less than 2% were cyst, flu syndrome, viral infection, constipation, gastroenteritis, myalgia, hypertension, epistaxis, lung disorder, acne, herpes simplex, conjunctivitis, ear pain, dysmenorrhea, hematuria, and vaginal moniliasis. In children, frequently occurring adverse events were accidental injury, vomiting, bronchitis, pharyngitis.

The incidence of systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) was low.

Potentially serious hypokalaemia may result from beta<sub>2</sub>-agonist therapy. This effect may be potentiated by hypoxia. Particular caution is advised in severe asthma in such cases, monitoring of serum potassium levels is recommended.

### *Postmarketing Experience*

In addition to the adverse reactions reported in clinical trials, the following adverse reactions have been observed in post-approval use of levosalbutamol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to their seriousness, their frequency of reporting, or their likely beta-mediated mechanism: angioedema, anaphylaxis, arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), asthma, chest pain, cough increased, dysphonia, dyspnea, gastroesophageal reflux disease (GERD), metabolic acidosis, nausea, nervousness, rash, tachycardia, tremor, urticaria.

In addition, levosalbutamol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, sleeplessness, headache, and drying or irritation of the oropharynx.

### *Beclomethasone Dipropionate*

Candidiasis of the mouth and throat (thrush) may occur in some patients (Gargling with water after inhalation may relieve this), hypersensitivity reactions, easy bruising of the skin, skin thinning, adrenal suppression, growth retardation in children and adolescents, hoarseness and throat irritation, upper respiratory tract infection, nasopharyngitis, oropharyngeal pain, viral upper respiratory tract infection, sinusitis, rhinitis allergic, cough, vomiting, headache, pyrexia are common.

Very rare include Cushing's syndrome, Cushingoid features, decrease in bone mineral density, cataract, glaucoma, paradoxical bronchospasm, rashes, urticaria, pruritus, erythema, oedema of the eyes, face, lips and throat, respiratory symptoms (dyspnoea and/or bronchospasm), eosinophilic pneumonia and anaphylactoid/anaphylactic reactions, anxiety, sleep disorders and behavioural changes, including psychomotor hyperactivity, irritability (predominantly in children), depression and aggression. Other common respiratory effects were throat irritation and pharyngitis. Other adverse events reported with beclomethasone were nausea, pain, myalgia, diarrhea, ear infection, influenza, gastroenteritis viral. In some patients, inhaled beclomethasone dipropionate may cause hoarseness or throat irritation. It may be helpful to rinse out the mouth with water immediately after inhalation.

### *Postmarketing Experience*

In addition to the adverse reactions reported from clinical trials with beclomethasone dipropionate, the following adverse

reactions have been identified during post-approval use of beclomethasone dipropionate and other inhaled corticosteroids. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Local Effects:** Localized infections with *Candida albicans* have occurred in patients treated with beclomethasone dipropionate or other orally inhaled corticosteroids.

**Psychiatric and Behavioral Changes:** Aggression, depression, sleep disorders, psychomotor hyperactivity, and suicidal ideation have been reported (primarily in children).

**Eye Disorders:** Blurred vision, central serous chorioretinopathy (CSC).

If you experience any side-effects, talk to your doctor or pharmacist or write to [drugsafety@cipla.com](mailto:drugsafety@cipla.com). You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side-effects, you can help provide more information on the safety of this product.

## Overdosage

### *Levosalbutamol*

The expected symptoms with overdosage are those of excessive beta-adrenergic receptor stimulation, e.g. seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitations, nausea, dizziness, fatigue, malaise, and sleeplessness, and/or occurrence or exaggeration of any of the symptoms listed under UNDESIRABLE EFFECTS. Hypokalaemia also may occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with the abuse of levosalbutamol. Treatment consists of discontinuation of levosalbutamol together with appropriate symptomatic therapy.

The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial in treating overdosage of levosalbutamol.

### *Beclomethasone Dipropionate*

If higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression may result. Monitoring of adrenal reserve may be necessary. In cases of beclomethasone dipropionate overdose, therapy may still be continued at a suitable dosage for symptom control. Treatment should be continued at a dose sufficient to control asthma.

## Storage And Handling Instructions

Store below 30°C

Do not freeze.

## Packaging Information

AEROCORT Inhaler with *Dose Counter* .....Canister containing 200 metered doses

Last Updated: *January 2019*

Last Reviewed: *January 2019*

# AEROCORT Inhaler

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