Salbutamol and Beclometasone Dipropionate Pressurised Inhalation CFC-Free

NAME: Salbutamol and Beclometasone Dipropionate Pressurised Inhalation

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each canister provides 200 actuations. After priming, each actuation of the inhaler delivers 100 mcg of Salbutamol and 50 mcg of Beclometasone Dipropionate from the valve.

PHARMACEUTICAL FORM

Pressurised Inhalation

DESCRIPTION

Salbutamol and Beclometasone Dipropionate Pressurised Inhalation is a combination of salbutamol sulphate and beclometasone dipropionate, which have different modes of action and show additive effects. The combination of salbutamol sulphate and beclometasone dipropionate is specially provided for those patients who require regular doses of both drugs for treatment of their obstructive airways disease.

PHARMACOLOGICAL ACTION

►Salbutamol sulphate

In vitro studies and in vivo pharmacologic studies have demonstrated that salbutamol has a preferential effect on $beta_2$-adrenergic receptors compared with isoproterenol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective $beta_2$-agonists may have cardiac effects.

Activation of $beta_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenyl cyclase and to an increase in the intracellular concentration of cyclic-3′,5′-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Salbutamol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Salbutamol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

Salbutamol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled salbutamol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

►Beclometasone dipropionate

Beclometasone dipropionate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Corticosteroids have been shown to 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 contribute to their efficacy in asthma.

Beclometasone dipropionate is a prodrug that is rapidly activated by 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 beclometasone 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 recommended doses of Beclometasone dipropionate.

PHARMACOKINETICS

►Salbutamol sulphate

The systemic levels of salbutamol are low after inhalation of recommended doses. A trial conducted in 12 healthy male and female subjects using a higher dose (1,080 mcg of salbutamol base) showed that mean peak plasma concentrations of approximately 3 ng/mL occurred after dosing when salbutamol was delivered using propellant HFA-134a. The mean time to peak concentrations (Tmax) was delayed after administration of salbutamol sulphate (Tmax = 0.42 hours) as compared with CFC-propelled salbutamol inhaler (Tmax = 0.17 hours). Apparent terminal plasma half-life of salbutamol is approximately 4.6 hours. No further pharmacokinetic trials for salbutamol sulphate were conducted in neonates, children, or elderly subjects.

►Beclometasone dipropionate

Beclometasone dipropionate undergoes rapid and extensive conversion to beclomethasone-17-monopropionate (17-BMP) during absorption. The pharmacokinetics of beclometasone dipropionate and 17-BMP were studied in subjects given single doses.

Absorption

The mean peak plasma concentration (Cmax) of BDP was 6635 pg/mL at 2 minutes after inhalation of 320 mcg using beclometasone dipropionate. The mean peak plasma concentration of the major and most active metabolite, 17-BMP, was 1464 pg/mL at 10 minutes after inhalation of 320 mcg of beclometasone dipropionate.

Distribution

The in vitro protein binding for 17-BMP was reported to be 94-96% over the concentration range of 1000 to 5000 pg/mL. Protein binding was constant over the concentration range evaluated. There is no evidence of tissue storage of beclometasone dipropionate or its metabolites.

Elimination

The major route of elimination of inhaled beclometasone dipropionate appears to be via hydrolysis. More than 90% of inhaled beclometasone dipropionate is found as 17-BMP in the systemic circulation. The mean terminal half-life of 17-BMP is approximately 4 hours for beclometasone dipropionate.

Metabolism

Three major metabolites are formed via esterases:

- beclomethasone-17-monopropionate (17-BMP)
- beclomethasone-21-monopropionate (21-BMP)
- beclomethasone (BOH)

Lung slices metabolize beclometasone dipropionate rapidly to 17-BMP and more slowly to BOH. 17-BMP is the most active metabolite.

Excretion

Irrespective of the route of administration (injection, oral or inhalation), beclometasone dipropionate and its metabolites are mainly excreted in the feces. Less than 10% of the drug and its metabolites are excreted in the urine.

Specific Populations

Age: No pharmacokinetic studies for beclometasone dipropionate have been conducted in neonates or elderly subjects.

Pediatrics: No pharmacokinetic studies for beclometasone dipropionate have been conducted in pediatric subjects aged of 4 to 17 years. However, the pharmacokinetics of 17-BMP, including dose and strength proportionalities, is similar in children and adults using beclometasone dipropionate, although the exposure is highly variable. In 17 children (mean age 10 years), the Cmax of 17-BMP was 787 pg/mL at 0.6 hour after inhalation of 160 mcg. The systemic exposure to 17-BMP from 160 mcg of beclometasone dipropionate administered without a spacer was comparable to the systemic exposure to 17-BMP from 336 mcg CFC-BDP administered with a large volume spacer in 14 children (mean age 12 years). This implies that approximately twice the systemic exposure to 17-BMP would be expected for comparable mg doses of beclometasone dipropionate without a spacer and CFC-BDP with a large volume spacer.

Sex: The influence of sex on the pharmacokinetics of beclometasone dipropionate has not been studied.

Race: The influence of race on the pharmacokinetics of beclometasone dipropionate has not been studied.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of beclometasone dipropionate has not been evaluated.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of beclometasone dipropionate has not been evaluated.

Drug Interaction Studies: In vitro and in vivo drug interaction studies have not been conducted with beclometasone dipropionate.

INDICATIONS

It 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.

CONTRAINDICATIONS

Salbutamol and Beclometasone Dipropionate Pressurised Inhalation is contraindicated in patients with a history of hypersensitivity to any of the ingredients.

Salbutamol and Beclometasone Dipropionate Pressurised Inhalation is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

WARNINGS AND PRECAUTIONS

►Salbutamol sulphate

Paradoxical Bronchospasm

salbutamol sulphate can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with salbutamol sulphate, it should be discontinued immediately and alternative therapy should be instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

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 salbutamol sulphate than usual, this may be a marker of destabilization of asthma and requires reevaluation 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 beta-adrenergic agonist bronchodilators 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

salbutamol sulphate, like all other beta2-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients such as changes in pulse rate or blood pressure. If such effects occur, salbutamol sulphate 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 relevance of these findings is unknown. Therefore, salbutamol sulphate, like all other sympathomimetic amines, should be used with caution in patients with underlying 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 (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of salbutamol sulphate.

Coexisting Conditions

Salbutamol sulphate, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus and in patients who are unusually responsive to sympathomimetic amines. Large doses of intravenous salbutamol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

►Beclometasone dipropionate

Local Effects

Localized infections with Candida albicans have occurred in the mouth and pharynx in some patients receiving beclometasone dipropionate. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with beclometasone dipropionate therapy, but at times therapy with beclometasone 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

Beclometasone 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 beta2-agonist, not beclometasone 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 beclometasone 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 beclometasone 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 beclometasone 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 beclometasone dipropionate. Lung function (FEV1 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 beclometasone 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. 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 beclometasone dipropionate, it should be treated immediately with an inhaled, short-acting bronchodilator. Treatment with beclometasone 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 beclometasone dipropionate. Discontinue beclometasone dipropionate if such reactions occur.

Hypercorticism and Adrenal Suppression

Beclometasone dipropionate will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since beclometasone dipropionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of beclometasone 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 beclometasone 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 beclometasone dipropionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of beclometasone 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 beclometasone dipropionate, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving beclometasone dipropionate routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including beclometasone 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 beclometasone dipropionate.

ADVERSE REACTIONS

Use of Salbutamol and Beclometasone Dipropionate Pressurised Inhalation may be associated with the following:

- Paradoxical bronchospasm
- Cardiovascular effects
- Immediate hypersensitivity reactions
- Hypokalemia
- Candida albicans infection
- Immunosuppression
- Hypercorticism and adrenal suppression
- Growth effects
- Eye Disorders

DRUG INTERACTIONS

►Salbutamol sulphate

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

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, but may also produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

Non–Potassium-Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or 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 the product with non–potassium-sparing diuretics.

Digoxin

Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical relevance of these findings for patients with obstructive airway disease who are receiving inhaled albuterol 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 albuterol.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Salbutamol sulphate 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 albuterol on the vascular system may be potentiated.

►Beclometasone dipropionate

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 agents.

OVERDOSAGE

►Salbutamol sulphate

The expected signs and symptoms with overdosage of albuterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis).

As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of Salbutamol sulphate.

Treatment consists of discontinuation of Salbutamol sulphate 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 for overdosage of Salbutamol sulphate.

►Beclometasone dipropionate

Acute overdosage is unlikely to cause problems. The only harmful effect that follows inhalation of large amounts of the drug over a short time period is suppression of HPA axis function. Specific emergency action need not be taken. Treatment with Beclometasone dipropionate should be continued at the recommended dose to control the asthma; HPA axis function recovers in a day or two.

If excessive doses of beclometasone dipropionate were taken over a prolonged period a degree of atrophy of the adrenal cortex could occur in addition to HPA axis suppression. In this event the patient should be treated as steroid dependent and transferred to a suitable maintenance dose of a systemic steroid such as prednisolone.

STORAGE

Store below 30 °C. Protect from light.