Xaltide® HFA

(Salbutamol+Beclomethasone dipropionate)
CFC Free Inhaler 100mcg+50mcg

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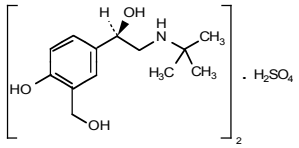
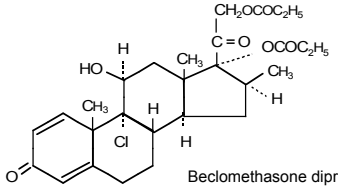
DESCRIPTION
XALTIDE HFA is a metered dose inhaler that delivers 100mcg salbutamol and 50mcg beclomethasone dipropionate per actuation into the mouth piece of specially designed actuator.
XALTIDE HFA (Salbutamol + Beclomethasone dipropionate) Inhaler contains a new propellant (HFA 134a) and does not contain any chlorofluorocarbons.
Salbutamol is a short-acting bronchodilator having the chemical name Bis[(1RS)-2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-hydroxymethyl)phenyl]ethanol] sulphate. Its molecular formula is $(C_{13}H_{21}NO_3)_2.H_2SO_4$ and the structural formula is:



Salbutamol Sulphate

Beclomethasone dipropionate is an anti-inflammatory corticosteroid having the chemical name 9-chloro-11ß,17,21-trihydroxy-16ß methylpregna-1,4-diene-3,20-dione17,21-dipropionate.Its molecular formula is $C_{28}H_{37}ClO_7$ and the structural formula is:



Beclomethasone dipropionate

QUALITATIVE & QUANTITATIVE COMPOSITION
XALTIDE HFA (Salbutamol + Beclomethasone dipropionate) Inhaler is available for administration as:

XALTIDE HFA Inhaler 100mcg + 50mcg.
Each metered dose contains:
Salbutamol… 100mcg (as salbutamol sulphate BP)
Beclomethasone dipropionate BP …50mcg

CLINICAL PHARMACOLOGY
Mechanism of Action
Salbutamol:
Salbutamol is a selective ß$_2$-adrenoceptor agonist. At therapeutic doses it acts on the ß$_2$-adrenoceptors of bronchial muscle providing short acting (4-6 hours) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

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

Pharmacokinetics
Absorption/Distribution

Salbutamol: After administration by the inhalation route, between 10% and 20% of the dose of salbutamol reaches the lower airways. The remainder is retained in the delivery system or is deposited in the oropharynx from where it is swallowed. The fraction deposited in the airways is absorbed into the pulmonary tissues and circulation, but is not metabolized by the lungs. Salbutamol is bound to plasma proteins to the extent of 10%.

Beclomethasone dipropionate: Systemic absorption of unchanged beclomethasone dipropionate occurs through the lungs. There is negligible oral absorption of the swallowed dose of unchanged beclomethasone dipropionate. Prior to absorption there is extensive conversion of beclomethasone dipropionate 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 beclomethasone dipropionate and B-17-MP, respectively. Beclomethasone dipropionate is absorbed rapidly with peak plasma concentrations observed T_{max} at 0.3 hour. 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.

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

Metabolism/Excretion

Salbutamol: The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulphate. The portion deposited in the lungs is not metabolized by the lungs. On reaching the systemic circulation it becomes accessible to hepatic metabolism and is excreted primarily in the urine as unchanged drug and as the phenolic sulphate. Most of the dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours.

Beclomethasone dipropionate: Beclomethasone dipropionate 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, beclomethasone-21-monopropionate (B-21-MP) and beclomethasone (BOH), are also formed but these contribute little to the systemic exposure. The elimination of beclomethasone dipropionate 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 hour and 2.7 hour. Following oral administration of tritiated 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. The renal clearance of beclomethasone dipropionate and its metabolites is negligible.

THERAPEUTIC INDICATIONS
XALTIDE HFA (Salbutamol+Beclomethasone dipropionate) Inhaler is indicated for the long term management of asthma only when the need for inhaled corticosteroid and bronchodilator therapy has been established.

DOSAGE AND ADMINISTRATION
The association of salbutamol with beclomethasone dipropionate is specially provided for those patients who require regular doses of both drugs treatment. XALTIDE HFA (Salbutamol+Beclomethasone dipropionate) Inhaler is not intended for use as a first-line treatment but is for use once the need for inhaled corticosteroid therapy has been established.

Adults: 2 Inhalations three to four times daily.
Children: 1-2 Inhalations two to four times daily.

ADVERSE EFFECTS
Salbutamol:
Tremor, headache, tachycardia, palpitations, mouth and throat irritation, muscle cramps, hypokalemia, peripheral vasodilatation, hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse, hyperactivity, cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles), paradoxical bronchospasm, myocardial ischemia.

Beclomethasone dipropionate:
Adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma, paradoxical bronchospasm with an immediate increase in wheezing, shortness of breath and cough after dosing, hypersensitivity reactions including rashes, urticaria, pruritus, erythema, oedema of the eyes, face, lips and throat, candidiasis of the mouth and throat, hoarseness or throat irritation, psychiatric disorders including psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression and behavioural changes (predominantly in children).

CONTRAINDICATIONS
- Salbutamol+Beclomethasone dipropionate is contraindicated in patients with hypersensitivity to the drug or any component of the product.
- Inhaled salbutamol is not appropriate for managing premature labour; therefore salbutamol inhaler should not be used for threatened abortion.

PRECAUTIONS
- Patient's inhaler technique should be checked to make sure that inhaler actuation is synchronised with inspiration of breath for optimum delivery of drug to the lungs.
- In the event of a previously effective dose of inhaled salbutamol failing to give relief for at least three hours, the patient should be advised to seek medical advice in order that any necessary additional steps may be taken.
- Salbutamol should be administered cautiously to patients with hyperthyroidism, myocardial insufficiency, arrhythmias, susceptibility to QT-interval prolongation, hypertension and diabetes mellitus.
- Potentially serious hypokalemia may result from ß$_2$-agonist therapy mainly from parenteral and nebulised administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics and by hypoxia. It is recommended that serum potassium levels are monitered in such situations.

- Patients requiring long-term management with bronchodilators should be kept under regular surveillance.
- Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. Patients with underlying severe heart disease (e.g., ischemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease.
- Attention should be paid to assessment of symptoms such as dyspnea and chest pain as they may be of either resipratory or cardiac origin.
- Increasing use of short-acting inhaled $ß_2$-agonists to control symptoms indicates deterioration of asthma control. Consideration should be given to starting or increasing corticosteroid therapy.
- Inhaled salbutamol can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, salbutamol should be discontinued immediately and alternative therapy instituted.
- If immediate hypersensitivity reactions occur, discontinue salbutamol.
- It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slow, 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.
- Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression.
- As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.

Pregnancy
The use of salbutamol and beclomethasone dipropionate during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Nursing Mothers
Salbutamol and beclomethasone dipropionate are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Drug Interactions
- Salbutamol 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 cardiovascular system may be potentiated.
- Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers.
- Use of salbutamol and other $ß_2$-agonists with corticosteroids, diuretics or xanthines increases the risk of hypokalemia and monitoring of potassium concentrations is recommended in severe asthma where such combination therapy is common.
- Care should be taken when co-administering beclomethasone dipropionate with known strong CYP 3A4 inhibitors (e.g. ketoconazole, itraconazole, nelfinavir, ritonavir) as there is a potential for increased systemic exposure to beclomethasone.

OVERDOSAGE
Salbutamol:
The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events, including tachycardia, tremor, hyperactivity and metabolic effects including hypokalemia. Serum potassium levels should be monitored. Consideration should be given to discontinuation of treatment and appropriate symptomatic therapy such as cardio-selective beta-blocking agents in patients presenting with cardiac symptoms (e.g.,tachycardia, palpitations). Beta-blocking drugs should be used with caution in patients with a history of bronchospasm.

Beclomethasone dipropionate:
Acute: Inhalation of doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not require emergency action. In these patients treatment should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol.
Chronic: Use of inhaled beclomethasone dipropionate in daily doses in excess of 1,500 micrograms over prolonged periods may lead to adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment should be continued at a dose sufficient to control asthma.

STORAGE
Store below 30°C.
Protect from direct sunlight, heat and frost.
Shake well before use.

As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. The canister should not be broken, punctured or burnt, even when apparently empty.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
XALTIDE HFA (Salbutamol+Beclomethasone dipropionate) 100mcg + 50 mcg Inhaler is available as metered dose inhaler with specially designed actuator. Each canister provides 200 inhalations.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Jewim Pharmaceutical (Shandong) Co. Ltd.
Taian High-Tech Industrial Development Zone
Shandong, China.

Manufactured for:

Getz pharma (PVT) LIMITED
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