SEREVENT™ Evohaler™
Salmeterol xinafoate

QUALITATIVE AND QUANTITATIVE COMPOSITION
Pressurised metered-dose inhaler delivering 25 micrograms of salmeterol as salmeterol xinafoate per actuation through the mouthpiece of the actuator. In addition to salmeterol xinafoate, the inhaler also contains q.s. ad 75 mg of the chlorofluorocarbon (CFC)-free propellant Norflurane (also known as HFA 134a or 1,1,1,2 -tetrafluoroethane).
PHARMACEUTICAL FORM
Pressurised inhalation, suspension.
Each canister contains 120 actuations.
CLINICAL PARTICULARS
Therapeutic indications
- Continual symptomatic treatment of asthma:
  - in patients requiringdaily doses of rapid-acting short-duration beta-2 agonists;
  - and/or for nocturnal symptoms;
  in combination with continual anti-inflammatory treatment, such as inhaled corticosteroids.
- Preventive treatment of exercise-induced asthma.
  N.B. salmeterol is not a suitable treatment for an asthma attack. In the event of an asthma attack, use a rapid-acting short-duration beta-2 mimetic by inhalationor, depending on the severity, by injection.
- Symptomatic treatment of chronic obstructive pulmonary disease.
  N.B. an inhaled corticosteroid should not be combined routinely with a bronchodilator in the treatment of chronic obstructive pulmonary disease.

Dosage and method of administration
As there may be adverse effects associated with excessive dosing of this class of drug, the dosage or frequency of administration shouldonly be increased on medical advice.
SEREVENT is administered by the inhaled route only.
Dosage
For adults and children over 4 years old only:
+ Continual symptomatic treatment of asthma:
- Usual dose: 50 µg morning and evening (2 inhalations of 25 µg morning and evening)
- Maximum dose:
- in adults: 100 µg morning and evening (4 inhalations of 25 µg morning and evening)
- in children over 4 years old: there are no data available on the use of dosages above 50 µg twice daily in this indication.
+ Preventive treatment of exercise-induced asthma:
- 50 µg (2 inhalations of 25 µg) ½ to 1 hour before exercise.
+ Symptomatic treatment of chronicobstructive pulmonarydisease:
- in adults: 50 µg morning and evening (2 inhalations of 25 µg morning and evening).

Contraindications
- Intolerance of this medicinal product (appearance of cough or bronchospasm after inhalation of the product). In this case the treatment should be stopped and other treatments or other forms of administration considered.
- Hypersensitivityto any ingredient of the preparation

Warnings and Precautions
The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.
SEREVENT should not be initiated in patients with significantly worsening or acutely deteriorating asthma.
Sudden and progressive deterioration of asthma is potentially life threatening and considerations should be given to starting or increasing corticosteroidtherapy. Inpatients at risk, daily peak flow monitoring may be instituted.
Bronchodilators should not be the only or the main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment, including lung functiontesting, as patients are at risk of severeattacksand even death. Physicians shouldconsider using oral corticosteroid therapy and/or maximum recommended dose of inhaled corticosteroid in these patients.
Increasing useof bronchodilators, in particular short-acting inhaled beta-2 agonists, torelieve symptoms indicates deterioration ofasthma control. If patients find that short-acting relief bronchodilator treatment becomes less effective ortheyneed more inhalations than usual, medical attention must be sought. In this situationpatients should be reassessed andconsideration given to the need for increasedanti-inflammatory therapy (e.g. higher doses of inhaled corticosteroids or a course of oral corticosteroids). Severe exacerbations of asthma must be treated in the normal way.
SEREVENT is not a replacement for oral or inhaled corticosteroids. Its use is complementary to them. Patients must be warned not to stop steroidtherapy and not to reduce it without medicaladvice even if they feel better on *SEREVENT*.
SEREVENT is not designed to relieve acute asthma symptoms, for which an inhaled short-acting bronchodilator (e.g. salbutamol) is required. Patients should be advised to have such relief medication available.
There havebeenveryrare reportsof increases in blood glucoselevels (seeAdverse Reactions) andthis should be consideredwhen prescribing to patients with a history of diabetes mellitus.
SEREVENT should be administered with caution in patients with thyrotoxicosis.
Cardiovascular effects, such as increases in systolic blood pressure and heart rate, may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses. For this reason, SEREVENT should be used with caution in patients with pre-existing cardiovascular diseases.
A transient decrease in serum potassium may occur with all sympathomimetic drugs at higher than therapeutic doses. Therefore, SEREVENT should be used with caution in patients predisposed to low levels of serum potassium.
Patients' inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of the drug to the lungs.
Interactions
Both non-selective and selective beta-blockers should be avoided in patients with reversible obstructive airways disease, unless there are compelling reasonsfor their use.
Pregnancyand Lactation
In animal studies, some effects on the foetus, typical for a beta-2 agonist, occurred at exposure levels substantially higher than those that occur with therapeutic use.Extensive experience with otherbeta-2 agonists has provided no evidence that such effects are relevant forwomen receiving clinical doses.
As yet, experience of the use of salmeterol during pregnancy is limited.
As with any medicine, use duringpregnancy should be considered only if the expected benefit to the mother is greater than any possible risk to the foetus.
As there is limited experience of the use of salmeterol in nursingmothers its use in such circumstances should only be considered if the expected benefit to the mother is greater than any possible risk to the infant.
Studies in lactating animals support the view that salmeterol is likely to be secreted in only very small amounts into breast milk.
Norflurane (or tetrafluoroethane or HFA 134a): propellant gas
The study of reproductive functions conducted in animals has failed to demonstrate any harmful effects of the administration of norflurane (tetrafluoroethane or HFA 134a) contained in this medicinal product. In the absence of teratogenic effects in animals, a malformation effect in humans is not expected. There are, however, no relevant data currently available in sufficient amounts to evaluate the possible malformation or fetotoxic effect of norflurane when administered during pregnancy.
Effects on Ability to Drive and Use Machines
None reported.
Adverse Reactions
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Common and uncommon events were generally determined from clinical trial data. The incidence of placebo was not taken into account. Very rare events were generally determined from post-marketing spontaneous data.
The following frequencies are estimated at the standard dose of 50 micrograms twice daily. Frequencies at the higher dose of 100 micrograms twicedaily have also been taken to accountwhere appropriate.
Immune system disorders
Hypersensitivity Reactions:
Uncommon: Rash.
Very rare: Anaphylactic reactions including oedema and angioedema, bronchospasm and anaphylactic shock.
Metabolism and nutrition disorders
Very rare: Hyperglycaemia.
Nervous system disorders
Common: Tremor and headache.
The pharmacological side-effects of beta-2 agonist treatment, such as tremor and headache have been reported, but tend to be transient and to reduce with regular therapy. Tremor occurs more commonly when administered at doses higher than 50 micrograms twice daily.
Cardiac disorders
Common: Palpitations.
The pharmacological side-effects of beta-2 agonist treatment, such as subjective palpitations have been reported, but tend to be transient and to reduce with regular therapy.
Uncommon: Tachycardia.
Tachycardia occurs more commonly when administered at doses higher than 50 micrograms twice daily.
Very rare: CardiacArrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles.
Respiratory, thoracic and mediastinal disorders
Very rare: Oropharyngeal irritation and paradoxical bronchospasm.
As with other inhalational therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. *SEREVENT* Evohaler should be discontinued immediately, the patient assessed, and if necessaryalternative therapy instituted.

Musculoskeletal and connective tissue disorders
Common: Musclecramps.
Veryrare: Arthralgia.
Overdose
The expected symptoms and signs of SEREVENT overdosage are those typical of excessive beta2-adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic bloodpressure, hyperglycaemia and hypokalaemia.
The preferred antidote for overdosage with *SEREVENT* is a cardioselective beta- blocking agent. Cardioselective beta-blocking drugs should be used with caution in patients with history of bronchospasm.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
Mechanism of Action
Salmeterol is a selective long-acting (12 h) beta-2 adrenoceptor agonist with a long side- chain which binds to the exo-site of the receptor.
Pharmacodynamic properties
Pharmacotherapeutic class: SELECTIVE BETA-2 ADRENERGIC AGONIST
ATC code: R03AC12
Inhaleddelayed-action long-duration beta-2mimetic bronchodilator.
After inhalation, salmeterol exerts selective stimulant action on the beta-2 receptors of bronchial smooth muscle.
After inhalation of a single dose, bronchodilation begins only 15 minutes after administration and persists for about 12hours.
Pharmacokinetics
Salmeterol acts locally in the lung therefore plasmalevels arenot predicative of therapeutic effect. In addition thereare only limited data availa ble on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma because of the very low plasma concentrations (approximately 200 picograms/ml or less) achieved after inhaled dosing.
Absorption
After regular dosing with salmeterol xinafoate, hydroxynaphthoic acid can be detected in the systemic circulation, reaching steady state concentrations of approximately 100 nanograms/ml.These concentrations are up to 1000 fold lower than steadystate levels observed in toxicity studies and in long term regular dosing (more than 12 months) in patients with airways obstruction, have been shown to produce no ill effects.
Norflurane (or tetrafluoroethane or HFA 134a): propellant gas
After inhalation of a puff, HFA 134a is absor bed rapidly in very small amounts, with peak concentration being reached in less than 6 minutes.
A very low level of hepatic meta bolism with formation of trifluoroacetic acid and trifluoroacetaldehyde has been demonstrated in animals (miceand rats).
Nevertheless, kinetic studiescarried out in patients after administration of HFA 134a in a pathological situation have failed to demonstrate the formation of trifluoroacetic acid.
Pre-clinical SafetyData
Not applica ble.
PHARMACEUTICAL PARTICULARS
List of Excipients
Norflurane (also known as HFA 134a or 1,1,1,2-tetrafluoroethane).
Incompatibilities
None reported.
Shelf Life
The expiry dateis indicated on the packaging.
Special Precautions for Storage
SEREVENT Evohaler should be stored below 30°C
Protectfromfrostand directsunlight.
As with most inhaled medications in pressurised metered-dose inhalers, the therapeutic effect of this medication may decrease when the canister is cold.
Thecanister should not be broken, punctured or burnt, evenwhen apparentlyempty.
Nature and Contents of Container
Pressurised container (aluminium) with a metering valve (polypropylene) dispensing 120 doses.
Instructions for Use/Handling
SEREVENT Evohaler has been reformulated to remove the chlorofluorocar bon (CFC) propellant. There are no concerns regarding the patient safety of these propellants but they may damage the ozone layer in the atmosphere. *SEREVENT* Evohaler contains a CFC-free propellant Norflurane (HFA 134a) which is kinder to the environment.
If you have used the original *SEREVENT* inhaler you may find that your new *SEREVENT* Evohaler tastes and feels slightly different from the original inhaler.
Please read the section on how to clean your *SEREVENT* Evohaler carefully. The *SEREVENT* Evohaler must not be washed with water.
INSTRUCTIONS FOR USE:




1. Remove the mouthpiece cover bygently squeezing the sidesof the cover and checkthe mouthpiece inside and outside tosee that it is clean.
2. Shake the inhalerwell.
3. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece.
4. Breatheout as far as is comfortableand thenplace the mouthpiece inyour mouth betweenyour teeth and close yourlips aroundit but do not bite it.
5. Just after starting to breathe in through your mouth press down on the top of the inhaler to release *SEREVENT* while still breathing in steadily and deeply.
6. While holding your breath, take the inhaler from your mouth and take your finger from the top of the inhaler. Continue holding your breath for as long as is comforta ble.
7. If you are to take a further puffkeepthe inhalerupright and wait about half a minute beforerepeatingsteps 2 to 6.
8. Afteruse always replace the mouthpiececover to keep out dustand fluff.

The mouthpiece cover is replaced by firmly pushing and snapping thecap into position.
Important:
Do not rush stages 4, 5 and 6. It is important thatyou start to breathe in as slowly as possible just before operatingyour inhaler.
Practise in front of a mirror for the first few times. If you see "mist" coming from the top of your inhaler or the sides of your mouth you should start again fromstage2.
If your doctor has given you different instructions for using your inhaler, please follow them carefully. Tell your doctor if you haveany difficulties.
Children:
Young children mayneed help and theirparents mayneed to operate the inhaler for them. Encourage the child to breathe out and operate the inhaler justafter the child starts to breathein. Practice the technique together. Olderchildren or people with weak hands should hold the inhaler with both hands. Put the two forefingers on top of the inhaler and both thumbs on the base below the mouthpiece.
Cleaning:
Your inhaler should be cleaned atleastonce a week.
1. Remove the mouth piece cover.
2. Do not remove the canister fromthe plasticcasing.
3. Wipe theinsideand outsideof the mouthpiece andthe plasticcasing with a dry cloth or tissue.
4. Replace the mouthpiececover.

DO NOT PUT THE METAL CANISTER INTO WATER.
Testing your inhaler:
If your inhalerhas not been used for a week or morerelease onepuff into the air to makesurethat it works.
Version number: GDS21/IPI04
Date of issue: 6th June 2005
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THIS IS A MEDICAMENT
Medicament is a product whichaffects yourhealth and its consumption contrary to instructions is dangerous foryou.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist arethe expertsin medicines, their benefits and risks.
- Do not by yourselfinterrupt the periodof treatmentprescribed.
- Donot repeat the same prescription without consultingyour doctor.
- Keepall medicaments out of reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists.

GlaxoSmithKline