0237-05

BEROTEC Metered Aerosol

Composition
1 metered dose (actuation) contains
1-(3,5-dihydroxy-phenyl)-2-[[1-(4-hydroxy-benzyl)-ethyl]-amino]-
ethanol hydrobromide (= fenoterol hydrobromide) 100 mcg

propellant : 1,1,1,2-Tetrafluoroethane (HFA 134a)
other excipients : citric acid anhydrous, purified water, ethanol absolute

Indications

a) Symptomatic treatment of acute asthma attacks.
b) Prophylaxis of exercise induced asthma.
c) Symptomatic treatment of bronchial asthma and other conditions with reversible airway narrowing e.g. chronic obstructive bronchitis. Concomitant anti-inflammatory therapy should be considered for patients with bronchial asthma and steroid responsive chronic obstructive pulmonary disease (COPD).

Dosage and Administration
a) Acute asthma episodes
1 actuation is sufficient for prompt symptom relief in many cases. If breathing has not noticeably improved after 5 minutes, a second actuation may be taken.

If an attack has not been relieved by actuations, further actuations may be required. In these cases, patients should consult the doctor or the nearest hospital immediately.

b) Prophylaxis of exercise induced asthma
1 - 2 actuations for each administration, up to a maximum of 8 actuations per day.

c) Bronchial asthma and other conditions with reversible airways narrowing
If repeated dosing is required, 1 – 2 actuations for each administration, up to a maximum of 8 actuations per day.

In children BEROTEC 100 mcg metered aerosol should only be used on medical advice and under the supervision of an adult.

Instruction for use
The correct administration of the metered aerosol is essential for successful therapy.

Depress the valve twice before the apparatus is used for the first time.
Before each use the following rules should be observed:
1. Remove protective cap.

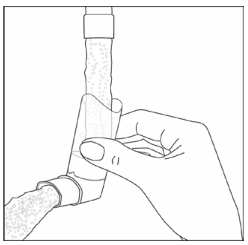
(fig. 1)

2. Breathe out deeply.

3. Hold the inhaler as shown in fig. 1, and close lips over the mouthpiece. The arrow and the base of the container should be pointing upwards.
4. Breathe in as deeply as possible, pressing the base of the container firmly at the same time, this releases one metered dose. Hold the breath for a few seconds, then remove the mouthpiece and breathe out.
   If a second inhalation is required, the same action (steps 2-4) should be repeated.
5. Replace the protective cap after use.
6. After not using the inhaler for three days the valve has to be actuated once.

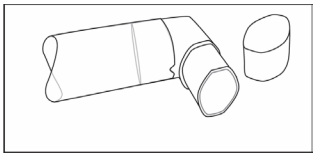
The container is not transparent. It is therefore not possible to see when it is empty. The inhaler will deliver **200** puffs. When the labelled number of doses have been used the canister may still appear to contain a small amount of fluid. The inhaler should, however be replaced so that you can be certain that you are getting the right amount of your medicine in each actuation.

Clean your mouthpiece at least once a week.
It is important to keep the mouthpiece of your inhaler clean to ensure that medicine does not build up and block the spray.
For cleaning, first take off the dust cap and remove the canister from the mouthpiece. Rinse warm water through the mouthpiece until no medication build-up and/or dirt is visible.



(fig. 2)

After cleaning shake out the mouthpiece and let it air-dry **without** using any heating system. Once the mouthpiece is dry, replace the canister and the dust cap.



(fig. 3)

WARNING:
The plastic mouthpiece has been specially designed for use with BEROTEC 100 mcg to ensure that you always get the right amount of the medicine. The mouthpiece must never be used with any other metered aerosol nor must the BEROTEC 100 mcg be used with any mouthpiece other than the one supplied with the product.

The container is under pressure and should by no account be opened by force or exposed to temperatures above 50°C.

Contraindications
BEROTEC is contraindicated in patients with:

- hypertrophic obstructive cardiomyopathy
- tachyarrhythmia
- hypersensitivity to fenoterol hydrobromide or to any of the excipients of the product

Special Warnings and Precautions

In the following conditions BEROTEC should only be used after careful risk/benefit assessment, especially when highest recommended doses are utilized:
• insufficiently controlled diabetes mellitus
• recent myocardial infarction
• severe organic heart or vascular disorders
• hyperthyroidism
• phaeochromocytoma

Paradoxical bronchospasm

As with other inhaled medicines BEROTEC may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs BEROTEC should be discontinued immediately and substituted with an alternative therapy.

Cardiovascular effects

Cardiovascular effects may be seen with sympathomimetic drugs, including BEROTEC. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta agonists.
Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving BEROTEC 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 as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin

Hypokalaemia

Potentially serious hypokalaemia may result from $beta_2$-agonist therapy. Particular caution is advised in severe asthma, as hypokalaemia may be potentiated by concomitant treatment with xanthine derivatives, glucocorticosteroids and diuretics. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm. Hypokalaemia may result in an increased susceptibility to arrhythmias in patients receiving digoxin.
It is recommended that serum potassium levels are monitored in such situations.

Acute progressive dyspnoea

The patient should be advised to consult a physician immediately in the case of acute, rapidly worsening dyspnea.

Particular warning for regular use

- On demand (symptom-oriented) treatment is preferable to regular use.
- Patients must be evaluated for the addition or the increase of anti-inflammatory therapy (e.g. inhaled corticosteroids) to control airway inflammation and to prevent long-term lung damage.

If bronchial obstruction deteriorates it is inappropriate and possibly hazardous to simply increase the use of $beta_2$-agonist containing drugs such as BEROTEC beyond the recommended dose over extended periods of time. The use of increasing amounts of $beta_2$-agonist containing products like BEROTEC on a regular basis to control symptoms of bronchial obstruction may suggest declining disease control. In this situation, the patient's therapy plan, and in particular the adequacy of the anti-inflammatory therapy, should be reviewed to prevent potentially life threatening deterioration of disease control.

Concomitant use with sympathomimetic and anticholinergic bronchodilators

Other sympathomimetic bronchodilators should only be used with BEROTEC□ under medical supervision (see section Interactions). Anticholinergic bronchodilators may however be inhaled at the same time.

Interferance with laboratory tests or other diagnostic measures

The use of BEROTEC may lead to positive results on fenoterol in tests for nonclinical substance abuse, e.g. in the context of athletic performance enhancement (doping).

Fertility, Pregnancy and Lactation

Pregnancy
Nonclinical data, combined with available experience in humans have shown no evidence of adverse effects of BEROTEC in pregnancy. Nonetheless, the usual precautions regarding the use of drugs during pregnancy, especially during the first trimester, should be exercised.
The inhibitory effect of fenoterol on uterine contraction should be taken into account.

Lactation
Nonclinical studies have shown that fenoterol is excreted into breastmilk. Safety during breastfeeding has not been established. Caution should be exercised when BEROTEC is administered to a nursing woman.

Fertility
Clinical data on fertility are not available for fenoterol. Nonclinical studies performed with fenoterol showed no adverse effect on fertility (see section Toxicology).

Driving and Using Machines
No studies on the effect on the ability to drive and use machines have been performed.

However, patients should be advised that symptoms such as dizziness have been reported in clinical trials. Therefore, caution should be recommended when driving a car or operating machinery.

Interactions
Beta-adrenergics, anticholinergics, and xanthine derivatives (such as theophylline) may enhance the effects of fenoterol. The concurrent administration of other beta-mimetics, systemically available anticholinergics and xanthine derivatives (e.g. theophylline) may increase the side effects.
Hypokalaemia induced by $beta_2$-agonists may be increased by concomitant treatment with xanthine derivatives, corticosteroids, and diuretics. This should be taken into account particularly in patients with severe airway obstruction (see section Special warnings and precautions).

A potentially serious reduction in bronchodilatation may occur during concurrent administration of beta-blockers.

Beta-adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta adrenergic agonists may be enhanced.

Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may increase the susceptibility to the cardiovascular effects of beta-agonists.

Side Effects
As with all inhalation therapy **BEROTEC** may show symptoms of local irritation.

The following adverse reactions have been reported during use of **BEROTEC** in clinical trials and during the post-marketing experience.

Immune system disorders
Hypersensitivity

Metabolism and nutrition disorders
Hypokalaemia including serious hypokalaemia

Psychiatric disorders
Agitation, nervousness

Nervous system disorders
Tremor, headache, dizziness

Cardiac disorders
myocardial ischaemia, arrhythmia, tachycardia, palpitations

Respiratory, thoracic and mediastinal disorders (only applicable to inhalative formulations)
bronchospasm paradoxical, cough, throat irritation

Gastrointestinal disorders
nausea, vomiting

Skin and subcutaneous tissue disorders
hyperhidrosis, skin reaction such as rash, pruritus, urticaria

Musculoskeletal, connective tissue and bone disorders
muscle spasm, myalgia, muscular weakness

Investigations
blood pressure systolic increased, blood pressure diastolic decreased

Overdosage
Symptoms
The expected symptoms with overdosage are those of excessive beta-adrenergic-stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, arrhythmias, and flushing. Metabolic acidosis and hypokalaemia have also been observed with fenoterol when applied in doses higher than recommended for the approved indications of BEROTEC.

Therapy
Treatment with BEROTEC should be discontinued. Acid base and electrolyte monitoring should be considered.

Administration of sedatives and, in severe cases intensive therapy may be needed.
Beta-receptor blockers, preferably $beta_1$-selective, are suitable as specific antidotes; however, a possible increase in bronchial obstruction must be taken into account and the dose should be adjusted carefully in patients suffering from bronchial asthma.

Pharmacological Properties
Pharmacotherapeutic group: Adrenergics for inalative use in obstructive airway diseases, selective beta-2-adrenoreceptor agonists
ATC code: R03AC04

BEROTEC is an effective bronchodilator for use in acute asthma and in other conditions with reversible airway narrowing such as chronic obstructive bronchitis with or without pulmonary emphysema. After oral administration BEROTEC acts within a few minutes with a duration of action up to 8 hours.

Following inhalation of fenoterol hydrobromide in obstructive lung diseases, bronchodilatation occurs within a few minutes. The bronchodilator effect lasts 3 -5 hours.

Mode of Action
Fenoterol hydrobromide is a direct acting sympathomimetic agent, selectively stimulating $beta_2$-receptors in the therapeutic dose range. The stimulation of $beta_1$-receptors comes into effect at a higher dose range. Occupation of $beta_2$-receptors activates adenyl cyclase via a stimulatory G_s-protein. The increase in cyclic AMP activates protein kinase A which then phosphorylates target proteins in smooth muscle cells. This in turn leads to the phosphorylation of myosin light chain kinase, inhibition of phosphoinositide hydrolysis, and the opening of large-conductance calcium-activated potassium channels. There is some evidence that the "maxi-K channel" can be directly activated via the G_s-protein.

Pharmacodynamics
Fenoterol relaxes bronchial and vascular smooth muscle and protects against bronchoconstricting stimuli such as histamine, methacholine, cold air, and allergen (early response).
After acute administration the release of bronchoconstricting and pro-inflammatory mediators from mast cells is inhibited. Further, an increase in mucociliary clearance has been demonstrated after administration of doses of fenoterol (0.6 mg).

Higher plasma concentrations, which are more frequently achieved with oral, or even more so, with intravenous administration inhibit uterine motility. Also at higher doses, metabolic effects are observed: Lipolysis, glycogenolysis, hyperglycaemia and hypokalaemia, the latter caused by increased K^+-uptake primarily into skeletal muscle. Beta-adrenergic effects on the heart such as increase in heart rate and contractility, are caused by the vascular effects of fenoterol, cardiac $beta_2$-receptor stimulation, and at supratherapeutic doses, by $beta_1$-receptor stimulation. As with other beta-adrenergic agents, QTc prolongation has been reported. For fenoterol MDIs these events were discrete and observed at doses higher than recommended. However, systemic exposure after adminstration with nebulisers (UDVs, solution for inhalation) might be higher than with recommended MDI doses (refer to dosage and administration). The clinical significance has not been established. Tremor is a more frequently observed effect of beta-agonists.

In clinical studies fenoterol was shown to be highly efficacious in manifest bronchospasm. It prevents bronchoconstriction following exposure to various stimuli such as exercise cold air, and the early response following allergen exposure.

Pharmacokinetics
The pharmacokinetics of fenoterol were studied after intravenous, inhaled and oral dosing.
The therapeutic effect of BEROTEC is produced by local action in the airway. Thus, drug concentrations in plasma are not necessarily correlated with a bronchodilatory effect.
Following inhalation, 10 - 30% of the active ingredient released from the aerosol preparation reaches the lower respiratory tract, depending on the method of inhalation and the system

used. The remainder is deposited in the upper respiratory tract and the mouth and is subsequently swallowed.

Absorption
The absolute bioavailability of fenoterol following inhalation from BEROTEC metered aerosol is 18.7%. Absorption from the lung follows a biphasic course. 30% of the fenoterol hydrobromide dose is rapidly absorbed with a half-life of 11 minutes, and 70% is slowly absorbed with a half-life of 120 minutes.

Maximum plasma concentrations (geometric mean) following inhalation of a single dose of 200 µg fenoterol via HFA-MDI was 66.9 pg/mL with a t_{max} –value of 15 minutes).

After oral administration, approximately 60% of the fenoterol hydrobromide dose is absorbed. The amount absorbed undergoes extensive first-pass metabolism resulting in an oral bioavailability of about 1.5%. Thus, the contribution of the swallowed portion of the active ingredient to the plasma concentration following inhalation is minor.

Distribution
Fenoterol distributes widely throughout the body. The volume of distribution at steady state following intravenous administration (V_{ss}) is 1.9 – 2.7 L/kg. The disposition of fenoterol in plasma following intravenous administration is adequately described by a 3-compartment pharmacokinetic model.The half-lives are t_{α} = 0.42 minutes, t_{β} = 14.3 minutes, and t_{γ} = 3.2 hours. The plasma protein binding is 40 to 55%.

Biotransformation
Fenoterol undergoes extensive metabolism by conjugation to glucuronides and sulphates in humans. Following oral administration, fenoterol is metabolised predominantly by sulphation. This metabolic inactivation of the parent compound starts already in the intestinal wall.

Excretion
The renal clearance of fenoterol (0.27 L/min) corresponds to about 15% of the mean total clearance of a systemically available dose. Taking into account the fraction of drug bound to plasma protein, the value of renal clearance suggest tubular secretion of fenoterol in addition to glomerular filtration.

Total radioactivity excreted in urine following oral administration is approximately 39% of the dose, and total radioactivity excreted in faeces is 40.2% of the dose within 48 hours. 0.38% of the dose is excreted as parent compound in urine after oral administration. Following inhalation from a metered dose inhaler, 2% of the dose is excreted renally unchanged within 24 hours.

In its non-metabolised state, fenoterol hydrobromide can pass through the placenta and enter the maternal milk.

There is insufficient data on the effects of fenoterol hydrobromide in the diabetic metabolic state.

Toxicology
Single-dose toxicity
The oral LD_{50} values in adult mice, rats and rabbits were in the ranges of 1600 - 7400 mg/kg and 150 - 433 mg/kg in dogs. Intravenous LD_{50} values for mouse, rat, rabbit and dog were between 30 and 81 mg/kg. The acute toxicity after inhalation was very low in rats, dogs and monkeys. Depending on the experimental set-up, mortality was not observed at inhalation doses of 0.58 - 670 mg/kg.

Repeat-dose toxicity
Repeat-dose toxicity studies were performed in mice, rats and dogs for periods of up to 78 weeks and by varying routes of administration (per os, subcutaneous, intravenous, intraperitoneal, inhalation).
Summarising, these toxicity studies revealed findings in the respective species typical for administration of beta-sympathomimetics (e.g. depletion of liver glycogen, reduced serum potassium levels, tachycardia). Myocardial hypertrophy and/or lesions were observed in rat, mouse, and rabbit at various administration routes at doses > 1 mg/kg/day. In the dog – the most sensitive species to beta-adrenergics - these lesions were discerned at inhalation doses > 0.019 mg/kg/day onwards. Subacute inhalation studies in monkeys revealed no direct substance related toxic effects.

Reproduction toxicity
Inhalation reproduction toxicity studies in rats and rabbits revealed no teratogenic or embryotoxic changes and fertility and rearing were not impaired. Oral doses up to 40mg/kg/day had no deleterious effects on male or female fertility in rats. Oral doses up to 25 mg/kg/day in rabbits, and up to 38.5 mg/kg/day in mice showed neither embryotoxic nor teratogenic effects. In rats tocolytic effects were observed at doses of 3.5 mg/kg/day per os, and at 25 mg/kg/day, a slightly increased fetal and/or neonatal mortality occurred. Extremely high doses of 300 mg/kg/day per os and 20 mg/kg/day i.v. revealed an increased rate of malformations.

Genotoxicity
Fenoterol hydrobromide did not show any mutagenic activity *in vitro* and *in vivo*.

Carcinogenicity
Carcinogenicity studies were performed after oral (mouse, 18 months, rat, 24 months) and inhalation administration (rat, 24 months). At oral doses of 25 mg/kg/day an increased incidence of uterine leiomyomas with variable mitotic activity in mice and mesovarial leiomyomas in rats were observed.

These findings are recognised effects caused by the local action of beta-adrenergic agents on the uterine smooth muscle cell in mice and rats. These results are not believed to be applicable to man. All other neoplasias found were considered to be common types of neoplasia spontaneously occurring in the strains used and did not show a biologically relevant increased incidence resulting from treatment with fenoterol.

Local tolerance
In local tolerance studies with different amplication routes (i.v., i.a., dermal, ocular) fenoterol hydrobromide was well tolerated.

Availability
BEROTEC 100 mcg M.A. 100 mcg/actuation Reg. No DKI0252501439A1
Canister 10 ml of 200 actuations

Store below 30°C
Store in a safe place out of the reach of children

Only on doctor's prescription.
Harus dengan resep dokter.

Manufactured by :
Boehringer Ingelheim Pharma GmbH & Co. KG

For :
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

Imported by:
PT Tunggal Idaman Abdi
Jakarta, Indonesia