

CCDS 0279-05

BERODUAL

Ipratropium bromide + Fenoterol hydrobromide

Composition

1 metered dose (puff) contains:

(8r)-3 α -hydroxy-8-isopropyl-1 α H,5 α H-tropanium bromide ($\pm$)-tropate monohydrate
(= ipratropium bromide) corresponding to 20 mcg ipratropium bromide anhydrous 0.020 mg1-(3,5-dihydroxy-phenyl)-2-[[1-(4-hydroxy-benzyl)-ethyl]-amino]-ethanol hydrobromide
(= fenoterol hydrobromide) 0.05 mg

Excipient**:

Propellant: 1,1,1,2-Tetrafluoroethane (HFA 134a)

Other excipients**: citric acid anhydrous, purified water, ethanol absolute, nitrogren (inert gas)

Indications

BERODUAL is a bronchodilator for the prevention and treatment of symptoms in chronic obstructive airway disorders with reversible bronchospasm such as bronchial asthma and especially chronic bronchitis with or without emphysema. Concomitant anti-inflammatory therapy should be considered for patients with bronchial asthma and steroid responsive chronic obstructive pulmonary disease (COPD).

Dosage and Administration

The dosage should be adapted to the individual requirements. Unless otherwise prescribed, the following dosages are recommended for adults and children over 6 years:

Acute asthma episodes (metered dose aerosol HFA)

2 actuations are sufficient for prompt symptom relief in many cases. In more severe cases, if breathing has not noticeably improved after 5 minutes, two further actuations may be taken.

If an attack has not been relieved by 4 puffs, further puffs may be required.

In these cases, patients should be advised to consult the doctor or the nearest hospital immediately.

Intermittent and long-term treatment (in asthma **BERODUAL** metered dose aerosol should be used only on an as-needed basis)

1 - 2 actuations for each administration, up to a maximum of 8 actuations per day (average 1- 2 actuations 3 times daily).

In children **BERODUAL** metered aerosol should only be used on medical advice and under the supervision of an adult.

Patients should be instructed in the correct administration of the metered aerosol to ensure successful therapy (see instructions for use).

Instruction for use:

Before first time use of the metered dose aerosol the following rules should be observed:

Remove protective cap and depress the valve twice.

Before each use of the metered dose aerosol the following rules should be observed:

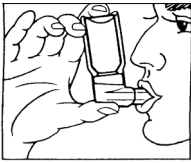
1. Remove protective cap
(If the metered aerosol has not been used for more than three days the valve has to be actuated once).

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2. Breathe out deeply.
3. Hold the inhaler as shown in fig. 1, and close lips around the mouthpiece. The arrow and the base of the canister should be pointing upwards.



(Fig. 1)

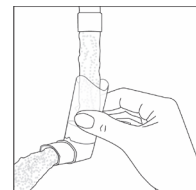
4. Breathe in as deeply as possible, pressing the base of the canister firmly at the same time, this releases one metered dose. Hold the breath for a few seconds, then remove the mouthpiece from the mouth and breathe out. The same action should be repeated for a second inhalation.
5. Replace the protective cap after use.

The container is not transparent. It is therefore not possible to see when it is empty. The inhaler will deliver 200 puffs or if available 300* doses. 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 because you may not get the right amount of treatment.

Clean your **mouthpiece** at least once a week.

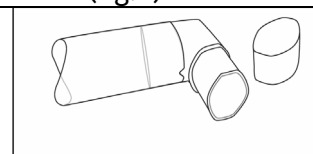
It is important to keep the mouthpiece of your inhaler clean to ensure that medicine does not build up and block the spray.

For cleaning, first take off the dust cap and remove the canister from the **mouthpiece**. Rinse with 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 **BERODUAL** 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 **BERODUAL** metered aerosol 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

BERODUAL is contraindicated in patients with known hypersensitivity to fenoterol hydrobromide or atropine-like substances or to any of the excipients of the product. **BERODUAL** is also contraindicated in patients with hypertrophic obstructive cardiomyopathy and tachyarrhythmia.

Special Warnings and Precautions

Hypersensitivity

Immediate hypersensitivity reactions may occur after administration of **BERODUAL** as demonstrated by rare cases of urticaria, angio-oedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

Paradoxical bronchospasm

As with other inhaled medicines Berodual may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs Berodual should be discontinued immediately and substituted [with an alternative therapy](#).

Ocular complications

BERODUAL should be used with caution in patients predisposed to narrow-angle glaucoma. There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta₂-agonist, has come in contact with the eyes. Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

Thus patients must be instructed in the correct administration of **BERODUAL**. Care must be taken not to allow the product to enter the eyes.

Systemic effects

In the following conditions **BERODUAL** should only be used after careful risk/benefit assessment, especially when doses higher than recommended are used: Insufficiently controlled diabetes mellitus, recent myocardial infarction, severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma, or with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-neck obstruction).

Cardiovascular effects

Cardiovascular effects may be seen with sympathomimetic drugs, including **BERODUAL**. 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 **BERODUAL**, 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 dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Hypokalaemia

Potentially serious hypokalaemia may result from beta₂-agonist therapy (see also section Overdose).

Gastro-intestinal motility disturbances

Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.

Dyspnoea

In the case of acute, rapidly worsening dyspnoea, [a physician should be consulted immediately](#).

Prolonged use

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- In patients with bronchial asthma BERODUAL should be used only on an as-needed basis. In patients with mild COPD [9,10] on demand (symptom-oriented) treatment may be preferable to regular use.
- The addition or the increase of anti-inflammatory therapy to control airway inflammation and to prevent deterioration of disease control should be considered for patients with bronchial asthma and with steroid-responsive COPD.

The use of increasing amounts of beta₂-agonists containing products such as **BERODUAL** on a regular basis to control symptoms of bronchial obstruction may suggest declining disease control. If bronchial obstruction deteriorates it is inappropriate and possibly hazardous to simply increase the use of beta₂-agonist containing products such as **BERODUAL** beyond the recommended dose over extended periods of time. In this situation, the patient's therapy plan, and in particular the adequacy of anti-inflammatory therapy with inhaled corticosteroids, should be reviewed to prevent potentially life threatening deterioration of disease control.

Concomitant use with other sympathomimetic bronchodilators

Other sympathomimetic bronchodilators should only be used with **BERODUAL** under medical supervision (see section Interactions).

Doping warning

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

Interactions

The chronic co-administration of BERODUAL with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of BERODUAL with other anticholinergic drugs is not recommended.

Other beta-adrenergics and anticholinergics and xanthine derivatives (such as theophylline) may enhance the bronchodilatory effect. The concurrent administration of other beta-mimetics, systemically available anticholinergics and xanthine derivatives (e.g. theophylline) may increase the adverse reactions.

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

Hypokalaemia induced by beta₂-agonist 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.

Hypokalaemia may result in an increased susceptibility to arrhythmias in patients receiving digoxin. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm. It is recommended that serum potassium levels are monitored in such situations.

Beta₂-agonist containing medicinal products 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 on the cardiovascular effects of beta-agonists.

Fertility, pregnancy and lactation

Pregnancy

Non-clinical data, combined with available experience in humans have shown no evidence of adverse effects in pregnancy of fenoterol or ipratropium. Nonetheless, the usual precautions regarding the use of drugs during pregnancy, especially during the first trimester, should be

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exercised.

The inhibitory effect of fenoterol on uterine contraction should be taken into account.

Lactation

Non-clinical studies have shown that fenoterol hydrobromide, is excreted into breast milk. It is unknown whether ipratropium is excreted into breast milk. But it is unlikely that ipratropium would reach the infant to an important extent, especially when taken by aerosol. However, caution should be exercised when **BERODUAL** is administered to a nursing woman.

Fertility

Clinical data on fertility are neither available for the combination of ipratropium bromide and fenoterol hydrobromide nor for each of the two components of the combination.

Non-clinical studies performed with the individual components ipratropium bromide and fenoterol hydrobromide showed no adverse effect on fertility (see section Toxicology).

Driving and Using Machines

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that they may experience undesirable effects such as dizziness, tremor, accommodation disorder, mydriasis and blurred vision during treatment with **BERODUAL**. Therefore, caution should be recommended when driving a car or operating machinery.

Side Effects

Many of the listed undesirable effects can be assigned to the anticholinergic and beta-adrenergic properties of **BERODUAL**. As with all inhalation therapy **BERODUAL** may show symptoms of local irritation.

The most frequent side effects reported in clinical trials were cough, dry mouth, headache, tremor, pharyngitis, nausea, dizziness, dysphonia, tachycardia, palpitations, vomiting, blood pressure systolic increased and nervousness.

Tabulated summary of adverse reactions

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

MedDRA System Organ Class	BERODUAL adverse reactions
Immune system disorders	Anaphylactic reaction Hypersensitivity
Metabolism and nutritional disorders	Hypokalaemia
Psychiatric disorders	Nervousness Agitation Mental disorder
Nervous system disorders	Headach Tremor Dizziness

Eye disorders	Glaucoma Intraocular pressure increased Accommodation disorder Mydriasis Vision blurred Eye pain Corneal oedema Conjunctival hyperaemia Halo vision
Cardiac disorders	Tachycardia, heart rate increased Palpitations Arrhythmia Atrial fibrillation Supraventricular tachycardia Myocardial ischaemia
Respiratory, thoracic and mediastinal disorders	Cough Pharyngitis Dysphonia Bronchospasm Throat irritation Pharyngeal oedema Laryngospasm Bronchospasm paradoxical Dry throat
Gastrointestinal disorders	Vomiting Nausea Dry mouth Stomatitis Glossitis Gastrointestinal motility disorder Diarrhoea Constipation Oedema mouth
Skin and subcutaneous tissue disorders	Urticaria Rash Pruritus Angioedema Hyperhidrosis
Musculoskeletal and connective tissue disorders	Muscular weakness Muscle spasms Myalgia
Renal and urinary disorders	Urinary retention
Investigations	Blood pressure systolic increased Blood pressure diastolic decreased

Overdose

Symptoms

The effects of overdose are expected to be primarily related to fenoterol. The expected symptoms with overdose 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 **BERODUAL**. Expected symptoms of overdose with ipratropium bromide (such as dry mouth, visual accommodation disorder) are mild because the systemic availability of inhaled ipratropium is very low.

Therapy

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

Administration of sedatives, and in severe cases intensive care treatment may be needed. Beta-receptor blockers, preferably beta₁-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 or COPD because of the risk of precipitating severe bronchospasm, which may be fatal.

Pharmacological Properties

Pharmacotherapeutic group:

Adrenergics in combination with anticholinergics for obstructive airway diseases.

ATC code:

R03AL01

Mode of Action

BERODUAL contains two active bronchodilating ingredients: ipratropium bromide, exhibiting an anticholinergic effect and fenoterol hydrobromide a beta-adrenergic agent.

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In non-clinical studies, it inhibits vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of Ca⁺⁺ which is caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Ca⁺⁺ release is mediated by the second messenger system consisting of IP₃ (inositol triphosphate) and DAG (diacylglycerol).

The bronchodilatation following inhalation of ipratropium bromide is primarily a local, site-specific effect, not a systemic one.

Preclinical and clinical evidence suggest no deleterious effect of ipratropium bromide on airway mucous secretion, mucociliary clearance or gas exchange.

Fenoterol hydrobromide is a direct acting sympathomimetic agent, selectively stimulating beta₂-receptors in the therapeutic dose range. The stimulation of beta₁-receptors comes into effect at a higher dose range. Occupation of beta₂-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.

Fenoterol hydrobromide 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 [68] 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 β_2 -receptor stimulation, and at supratherapeutic doses, by β_1 -receptor stimulation. As with other beta-adrenergic agents, QTc prolongations have been reported. For fenoterol MDIs these were discrete and observed at doses higher than recommended. However, systemic exposure after administration with nebulisers (UDVs, solution for inhalation) might be higher than with recommended MDI doses. The clinical significance has not been established. Tremor is a more frequently observed effect of beta-agonists. Unlike the effects on the bronchial smooth muscle, the systemic effects on skeletal muscle of β -agonists are subject to the development of tolerance.

Concurrent use of these two active ingredients dilates the bronchi by affecting different pharmacological sites of action. The two active substances thus complement each other in their spasmolytic action on the bronchial muscles and allow a broad therapeutic use in the field of bronchopulmonary disorders associated with constriction of the respiratory tract. The complementary action is such that only a very low proportion of the β -adrenergic component is needed to obtain the desired effect, facilitating individual dosage suited to each patient with a minimum of adverse reactions.

In patients with asthma and COPD, better efficacy compared to its components ipratropium or fenoterol was demonstrated. Two studies (one with asthma patients, one with COPD patients) have shown that **BERODUAL** is as efficacious as double the dose of fenoterol administered without ipratropium but was better tolerated in cumulative dose response studies.

In acute bronchoconstriction **BERODUAL** is effective shortly after administration and is therefore also suitable for treating acute episodes of reversible bronchospasm.

Pharmacokinetics

The therapeutic effect of the combination ipratropium bromide and fenoterol hydrobromide is produced by a local action in the airway. The pharmacodynamics of the bronchodilation are therefore not related to the pharmacokinetics of the active constituents of the preparation.

Following inhalation 10 to 39% of a dose is generally deposited in lungs, depending on the formulation, inhalation technique and device, while the remainder of the delivered dose is deposited in the mouthpiece, mouth and the upper part of the respiratory tract (oropharynx). A similar amount of the dose is deposited in the respiratory tract following inhalation by metered aerosol either with HFA 134a. In particular after inhalation of the aqueous solution via the RESPIMAT inhaler, a more than 2-fold higher lung deposition is experimentally observed as compared to the metered aerosol inhaler. The oropharyngeal deposition is correspondingly decreased and is significantly lower for the RESPIMAT inhaler as compared to the metered aerosol. The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes). The amount of the active substance deposited in the oropharynx is slowly swallowed and passes the gastrointestinal tract. Therefore the systemic exposure is a function of both oral and lung bioavailability.

There is no evidence that the pharmacokinetics of both ingredients in the combination differ from those of the mono-substance.

Fenoterol hydrobromide

Absorption

The absolute bioavailability following oral administration is low (approx. 1.5%). The absolute bioavailability of fenoterol following inhalation 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.

Distribution

Fenoterol distributes widely throughout the body. About 40 % of the drug are bound to plasma proteins. In this 3-compartment model the apparent volume of distribution of fenoterol at steady state (V_{dss}) is approximately 189 L (≈ 2.7 L/kg).

Non-clinical studies with rats revealed that fenoterol and its metabolites do not cross the blood-brain barrier.

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.

Elimination

After inhalation via **BERODUAL** pressurised inhalation, solution approximately 1% of an inhaled dose is excreted as free fenoterol in the 24-hour urine. Based on these data, the total systemic bioavailability of inhaled doses of fenoterol hydrobromide is estimated at 7%. Fenoterol has a total clearance of 1.8 L/min and a renal clearance of 0.27 L/min.

Kinetic parameters describing the disposition of fenoterol were calculated from plasma concentrations after i.v. administration. Following intravenous administration, plasma concentration-time profiles can be described by a 3-compartment model, whereby the terminal half-life is approximately 3 hours.

Following oral administration, total radioactivity excreted in urine was approximately 39% of dose and total radioactivity excreted in faeces was 40.2% of dose within 48 hours.

Ipratropium bromide

Absorption

Cumulative renal excretion (0-24 hrs) of ipratropium (parent compound) is below 1% of an oral dose and approximately 3 to 13% of an inhaled dose via **BERODUAL** pressurised inhalation, solution. Based on these data, the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 28% respectively. Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.

Distribution

Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after i.v. administration. A rapid biphasic decline in plasma concentrations is observed. The apparent volume of distribution at steady-state (V_{dss}) is approximately 176 L (≈ 2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Non-clinical studies with rats and dogs, revealed that the quarternary amine ipratropium does not cross the blood-brain barrier.

Binding of the main urinary metabolites to the muscarinic receptor is negligible and the metabolites have to be regarded as ineffective.

Biotransformation

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After intravenous administration approximately 60% of a dose is metabolised probably mainly in the liver by oxidation.

Elimination

The half-life of the terminal elimination phase is approximately 1.6 hours [116, 117]. Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min.

In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 88.5% following oral dosing and 69.4% after inhalation.

Toxicology

Single-dose toxicity

Single-dose toxicity studies with the combination ipratropium bromide and fenoterol hydrobromide in a ratio of 1/2.5 (ipratropium bromide/fenoterol hydrobromide) in mice and rats after oral, intravenous and inhalation administration revealed a low level of acute toxicity. In comparison to the individual components, the LD₅₀ values of the combination were determined more by the ipratropium bromide component than by fenoterol hydrobromide without any indication of potentiation.

Repeat-dose toxicity

Repeat-dose toxicity studies with the combination ipratropium bromide and fenoterol hydrobromide were performed in rats (oral, inhalation) and dogs (intravenous, inhalation) for up to 13 weeks [U78-0081; U84-0699]. Only minor toxic effects at concentrations up to several hundred times greater than that recommended in man were observed. Left ventricular myocardial scars were seen only in one animal from the highest treatment group (84µ/kg/day) of the 4-week intravenous study in dogs. The 13-week oral study in rats and the 13-week inhalation study in dogs did not show any toxicological changes beyond that proportional to the individual components.

There was no indication of potentiation with the combination in comparison to the individual components. All of the adverse effects observed are well known for fenoterol hydrobromide and ipratropium bromide.

Reproduction toxicity

After inhalation administration of the combination ipratropium bromide and fenoterol hydrobromide in rats and rabbits no teratogenic effects occurred. Also no teratogenic effects were seen after ipratropium bromide, and after inhalation administration of fenoterol hydrobromide. After oral dosing, at doses >25 mg/kg/day (rabbits) and >38.5 mg/kg/day (mice) fenoterol hydrobromide induced an increase rate of malformations.

The malformations observed are considered a class effect for beta-agonists. Fertility was not impaired in rats at oral doses up to 90 mg/kg/day ipratropium bromide and up to 40 mg/kg/day fenoterol hydrobromide.

Genotoxicity

Genotoxicity studies for the combination were not performed. *In vitro* and *in vivo* assays revealed that neither fenoterol hydrobromide nor ipratropium bromide have a mutagenic potential.

Carcinogenicity

Carcinogenicity studies for the combination were not performed. No tumorigenic or carcinogenic effects were demonstrated in long term studies in mice and rats with ipratropium bromide. For fenoterol hydrobromide, 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. Taking into account the present level of research, these results are not 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 hydrobromide.

Availability

BERODUAL

Box, 1 Canister @200 doses (10ml)

Reg. No. DKI0952502339A1

Store below 30°C.

Store in a safe place out of the reach of children.

Only on doctor's prescription.

Manufactured by:

Boehringer Ingelheim Pharma GmbH & Co.KG

Ingelheim am Rhein, Germany.

Imported by:

PT. Boehringer Ingelheim Indonesia

Bogor, Indonesia