Boehringer Ingelheim

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Berodual®
250 µg/500 µg inhalation solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients: ipratropium bromide and fenoterol hydrobromide

1 ml (= 10 actuations with the solution dispenser) contains:
261 µg ipratropium bromide 1 H_2O (corresponds to 250 µg ipratropium bromide) and
500 µg fenoterol hydrobromide.

1 actuation contains:
26.1 µg ipratropium bromide 1 H_2O (corresponds to 25 µg ipratropium bromide) and
50 µg fenoterol hydrobromide.

Excipient with known effect: benzalkonium chloride (see Section 4.4).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Inhalation solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the prevention and treatment of dyspnoea in chronic obstructive airway disorders:

Allergic and non-allergic (endogenous) bronchial asthma, exercise-induced asthma and chronic obstructive bronchitis with and without emphysema.

Note

If long-term medication is necessary, it should always be accompanied by anti-inflammatory treatment.

4.2 Posology and method of administration

Only for inhalation with a nebulizer

Treatment should be initiated and administered under medical supervision, e.g. in the hospital setting. After consultation with an experienced physician, home-based treatment can be recommended in patients when a low dose rapid acting beta-agonist bronchodilator such

as Berodual pressurised inhalation solution has been insufficient in providing relief. It can also be recommended in patients who are in need for nebuliser treatment for other reasons (e.g. handling issues of pressurised inhalation solution) or requirement of higher doses in experienced patients.
The treatment with the nebuliser solution should always be started with the lowest recommended dose. The dosage should be adapted to the individual requirements and tailored according to the severity of the acute episode. Administration should be stopped when sufficient symptom relief is achieved.

The nebuliser solution is intended only for inhalation with suitable nebulising devices and must not be taken orally.

For administration, the recommended dose of Berodual inhalation solution should be diluted with physiological saline (0.9%) to a volume of 3-4 ml. The diluted, ready-to-use solution should be inhaled until sufficient symptom relief is achieved.

The diluted, ready-to-use solution should be freshly prepared each time before use. The diluted, ready-to-use solution should be inhaled immediately after preparation; any residual solution should be discarded. The instructions provided in the user guide for the inhalation device are to be followed.

It is recommended to administer the nebulized solution via a mouth-piece. If a mouth-piece is not available, and a nebulizing mask is used instead, then the mask must fit appropriately. Patients predisposed for glaucoma attacks should be warned to particularly protect their eyes.

The solution for inhalation can be administered using a range of commercially available nebulising devices. The lung and systemic drug exposure is dependent on the nebulizer used and may be higher than with Berodual metered dose aerosol, depending on the efficiency of the device.

Method of administration
The following dosages are recommended:

<u>Adults and adolescents over 12 years:</u>

For the **acute treatment** of sudden bronchial spasms, depending on the severity of the acute episode, 10-25 puffs (1.0-2.5 ml) of Berodual should be inhaled, after dilution with physiological saline to a volume of 3-4 ml.
In exceptional severe cases, up to 40 puffs (4 ml) of Berodual may be inhaled, after dilution with physiological saline to a volume of 3-4 ml.

For **targeted prevention** of exercise-induced asthma or predictable allergic contact,
1-2 puffs (0.1-0.2 ml) of Berodual, diluted with 2-3 ml of physiological saline, should be inhaled, if possible 10-15 minutes prior to the incident.

<u>Children aged 6 to 12 years:</u>

For the **acute treatment** of acute asthma episodes, depending on the severity of the acute episode and on age, 5-20 puffs (0.5-2.0 ml) of Berodual should be inhaled, after dilution with physiological saline to a volume of 3-4 ml.

For **targeted prevention** of exercise-induced asthma or predictable allergic contact, 1-2 puffs (0.1-0.2 ml) of Berodual, diluted with 2-3 ml of physiological saline, should be inhaled, if possible 10-15 minutes prior to the incident.

Children below the age of 6 years:

Because there is limited information in this age group, the following dose is recommended to be given under medical supervision only:
1 puff (0.1 ml) per kg body weight, up to a maximum of 5 puffs (0.5 ml) , after dilution with physiological saline to a volume of 3-4 ml.

4.3 Contraindications

Berodual is contraindicated in patients with known hypersensitivity to fenoterol hydrobromide and/or ipratropium bromide, atropine-like substances, or any of the excipients (see Section 6.1). Berodual is also contraindicated in patients with hypertrophic obstructive cardiomyopathy and tachyarrhythmia.

4.4 Special warnings and precautions for use

In the case of acute, rapidly worsening of dyspnoea the patients should be advised to consult a doctor immediately.

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

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,
- Myocarditis,
- Severe organic heart or vascular disorders (in particular in the presence of tachycardia),
- Hyperthyroidism,
- Phaeochromocytoma.

Cardiovascular effects may be seen with sympathicomimetic 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.

Berodual, like other anticholinergic products, should only be used with caution in patients with
- Predisposition to narrow-angle glaucoma,
- Pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-neck obstruction),
- Renal insufficiency,
- Hepatic insufficiency.

There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, angle-closure glaucoma and eye pain), when nebulized ipratropium bromide either alone or in combination with an adrenergic beta$_2$-agonist has come into contact with the eyes.

Attention! Patients must be instructed on the correct administration of Berodual. Care must be taken not to allow the product to enter the eyes.

Signs of acute narrow-angle glaucoma may include:
- Eye pain or discomfort,
- Blurred vision,
- Visual halos,
- Coloured images,
- Red eyes from conjunctival congestion and corneal oedema.

Should any of these symptoms develop, specialist advice should be sought immediately and treatment with miotic eye drops initiated.

Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances when treated with inhaled anticholinergics. This will reverse on discontinuation of treatment.

Long-term treatment
- In patients with asthma Berodual should be used only on an as-needed basis. In patients with mild COPD, on-demand (symptom-oriented) treatment may be preferable to regular use, circumstances permitting.
- The addition or the increase of anti-inflammatory therapy to control airway inflammation and prevent escalation of symptoms should be considered for patients with asthma and with steroid-responsive COPD.

In asthmatic patients, the use of increasing amounts of beta$_2$-agonist 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 beta$_2$-agonist containing products 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 or the dose of existing anti-inflammatory therapy adjusted or additional drugs administered to prevent potentially life-threatening deterioration of disease control.

Several cases of increased risk of serious complications in the primary disease as well as fatalities have been reported when bronchial asthma had been treated over a prolonged period of time with high and excessively high doses of inhaled beta$_2$-sympathomimetics without sufficient anti-inflammatory treatment. The causal relationship has not yet been fully explained. However, inadequate anti-inflammatory treatment seems to play a vital role.

Other sympathomimetic bronchodilators should only be used with Berodual under medical supervision (see Section 4.5).

Potentially serious hypokalaemia may result from high-dose beta$_2$-agonist therapy (see Section 4.9). With low baseline potassium levels, it is recommended to monitor the potassium levels.

The blood sugar level may increase. Therefore the blood sugar level should be monitored in patients with diabetes mellitus.

Immediate hypersensitivity reactions may occur after administration of Berodual, as demonstrated by rare cases of urticaria, angio-oedema, rash, bronchospasm; oropharyngeal oedema and allergic reactions.

This product contains the preservative benzalkoniumchloride and the stabiliser disodium ededate dihydrate. When inhaled these components may cause bronchospasm in sensitive patients with hyper reactive airways.

Using Berodual may cause a positive reaction to doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

The chronic co-administration of Berodual with other anticholinergic drugs has not been studied, and therefore is not recommended.

Concurrent administration of the following drugs/drug classes may influence the effect of Berodual.

- Enhanced effects and/or increased risk of adverse reactions:
  - Other beta-adrenergics (all types of administration),
  - Other anticholinergics (all types of administration),
  - Xanthine derivates (such as theophylline),
  - Anti-inflammatory substances (corticosteroids),
  - Monoamine oxidase inhibitors,
  - Tricyclic antidepressants,
  - Halogenated hydrocarbon anaesthetics (e.g. halothane, trichloroethylene and enflurane). In particular, they can increase the effects on the cardiovascular system.

- Reduced effects:
  - Concurrent administration of beta-receptor blockers.

- Other possible interactions:
  A $beta_2$-agonist induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, glucocorticosteroids 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.

  The risk of acute glaucoma attack (see Section 4.4) is increased if nebulized ipratropium bromide comes into direct contact with the eyes either alone or in combination with a $beta_2$-agonist.

4.6 Fertility, pregnancy and lactation

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 should be exercised.
The inhibitory effect of fenoterol on uterine contraction should be taken into account. The use of $beta_2$-sympathomimetics at the end of pregnancy or in high doses may cause negative effects in the newborn (tremor, tachycardia, blood glucose fluctuations, hypokalaemia).

Non-clinical studies have shown that fenoterol 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. Caution should be exercised when Berodual is administered to a nursing woman.

Clinical data on fertility are neither available for the combination of ipratropium bromide and fenoterol hydrobromide, nor for each of the two components separately. Non-clinical studies performed with the individual components ipratropium bromide and fenoterol hydrobromide showed no adverse effect on fertility (see Section 5.3).

4.7 Effects on ability to drive and use 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, accomodation disorder, mydriasis and blurred vision during treatment with Berodual. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience such undesirable effects they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Like all medicines, Berodual may have undesirable effects.

a) General description:
Many of the listed undesirable effects can be assigned to the anticholinergic and beta-adrenergic properties Berodual.

b) Table of undesirable effects:
The listed undesirable effects are based on data obtained in clinical trials and pharmacovigilance during post approval use of the drug.

The following frequencies are taken as the basis for the assessment of side effects:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10.000)
Not known (cannot be estimated from the available data)

Immune system disorders
Rare: Anaphylactic reactions *, hypersensitivity *

Metabolic and nutritional disorders
Rare: Hypokalaemia *
Very rare: Rise in blood sugar

Psychiatric disorders
Uncommon: Nervousness
Rare: Agitation, psychic alterations

Nervous system disorders
Uncommon: Headache, tremor, dizziness
Frequency unknown: Hyperactivity

Eye disorders
Rare: Glaucoma *, increased intraocular pressure *, accommodation disorder *, mydriasis *, blurred vision *, eye pain *, corneal oedema *, conjunctival hyperaemia *, halo vision *

Cardiac disorders
Uncommon: Tachycardia, palpitations
Rare: Arrhythmia, atrial fibrillation, supraventricular tachycardia *, myocardial ischaemia *

Respiratory, thoracic and mediastinal disorders
Common: Cough
Uncommon: Pharyngitis, dysphonia
Rare: Bronchospasm, throat irritations, pharyngeal oedema, laryngospasm *, paradoxical bronchospasm (caused by inhalation) *, dry throat *

Gastrointestinal disorders
Uncommon: Vomiting, nausea, dry mouth
Rare: Stomatitis, glossitis, gastrointestinal motility disorders **, diarrhoea, constipation *, mouth oedema *, heartburn

Skin and subcutaneous tissue disorders
Rare: Urticaria, skin rash, pruritus, angio-oedema *, petechias, hyperhidrosis *

Musculoskeletal and connective tissue disorders
Rare: Muscle weakness, muscle cramps, myalgia

Renal and urinary disorders
Rare: Urinary retention

Examinations
Uncommon: Increase in blood pressure (systolic)
Rare: Decrease in blood pressure (diastolic), thrombocytopenia

* These undesirable effects were not observed in any of the selected clinical trials. The estimate is based on the upper limit of its 95% confidence interval, calculated from the totality of treated patients in accordance with the EU SmPC guideline (3/4968 = 0.0006 which relates to “rare”).

** Especially patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances during treatment with inhaled anticholinergics (as contained in Berodual).

c) Remarks on common undesirable effects:
As with any inhalation therapy, signs of local irritations may also occur with Berodual treatment. In clinical trials, the most commonly reported undesirable effects were cough, dry mouth, headache, tremor, pharyngitis, nausea, dizziness, dysphonia, tachycardia, palpitations, vomiting, increase in systolic blood pressure, and nervousness.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

Federal Institute for Drugs and Medical Devices (BfArM),
Dept. of Pharmacovigilance, Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn,
Website: www.bfarm.de

4.9 Overdose

a) Symptoms of intoxication

Depending on the extent of overdosage, the following side effects - typical of beta$_2$-adrenergics - may occur:

Facial flush, light-headedness, headache, tachycardia, palpitations, arrhythmias, hypotension or even shock, increase in blood pressure, restlessness, chest pain, excitement, possibly extrasystoles and severe tremor especially in the fingers but also throughout the whole body. Hyperglycaemia may occur.

Gastrointestinal complaints including nausea and vomiting may occur, particularly following oral overdose.

Metabolic acidosis as well as hypokalaemia has been observed with fenoterol when applied in doses higher than recommended for the approved indications of Berodual.

Symptoms of overdose with ipratropium bromide (such as dry mouth, visual accommodation disturbances) are mild because the systemic availability of inhaled ipratropium is very low.

b) Therapy of intoxication

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

Administration of sedatives, tranquillisers; in severe cases intensive supportive therapy is indicated which may include hospitalisation. Beta-receptor blockers (preferably beta$_1$-selective) may be used as specific antidotes to fenoterol; 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways diseases, sympathomimetics in combination with anticholinergics. ATC Code: R03AL01

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 Calcium, caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle.

Calcium 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.

Fenoterol hydrobromide is a direct acting sympathomimetic agent, selectively stimulating $beta_2$-receptors in the therapeutic dose range. The $beta_1$-receptors are only stimulated with higher doses. Occupation of the $beta_2$-receptors activates adenyl cyclase system via a stimulatory Gs 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 specific 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 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 fenoterol (0.6 mg).

Higher plasma concentrations, which are more frequently achieved with oral - or even more frequently 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, prolongation of the QT interval has been reported. For fenoterol MDIs these were discrete and observed at doses higher than recommended. However, systemic exposure after administration with nebulisers (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 muscles, the systemic effects of beta-agonists on skeletal muscles 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/airways. The complementary action is such that only a very low proportion of the beta-adrenergic component is needed to obtain the desired effect, facilitating individual dosage suited to each patient with a minimum of adverse reactions.

5.2 Pharmacokinetic properties

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, 10-39% 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. 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
The swallowed portion is mainly metabolised to sulphate conjugates. The absolute bioavailability following oral administration is low (approx. 1.5%).
After intravenous administration, free fenoterol and conjugated fenoterol are approximated to 15% and 27% of the administered dose in the cumulative 24-hour urine. After inhalation via Berodual metered dose inhaler 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%.

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. In this 3-compartment model the apparent volume of distribution of fenoterol at steady state (Vdss) is approximately 189 l (about 2.7 l/kg).

About 40% of the drug are bound to plasma proteins.
Non-clinical studies with rats revealed that fenoterol and its metabolites do not cross the blood-brain barrier. Fenoterol has a total clearance of 1.8 l/min and a renal clearance of 0.27 l/min.
In an excretion balance study cumulative renal excretion (2 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 65% of dose after intravenous administration and total radioactivity excreted in faeces was 14.8% of dose. 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
Cumulative renal excretion (0-24 hrs) of ipratropium (parent compound) is approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3-13% of an inhaled dose via Berodual metered dose inhaler. Based on these data, the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7-28% respectively. Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.
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 (Vdss) is approximately 176 l (about 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.
The half-life of the terminal elimination phase is approximately 1.6 hours. Ipratropium has a total clearance of 2.3 l/min and a renal clearance of 0.9 l/min. After intravenous administration approximately 60% of a dose is metabolised probably mainly in the liver by oxidation.

In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity

excreted via the faeces was 6.3% following intravenous application, 88.5% following oral dosing and 69.4% after inhalation. Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occuress via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.6 hours. Binding of the main urinary metabolites to the muscarinic receptor is negligible and the metabolites have to be regarded as ineffective.

5.3 Preclinical safety data

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 LD_{50} values of the combination were determined more by the ipratropium bromide component than by fenoterol hydrobromide without any indication of potentiation.

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. 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 in only in one animal from the highest treatment group (84 mcg/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.

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 of ipratropium bromide and up to 40 mg/kg/day of fenoterol hydrobromide.

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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

100 µg benzalkonium chloride/ml, sodium chloride, sodium edetate (Ph. Eur.), purified water, hydrochloric acid 3.6% (for pH balance)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The individually prepared solutions are for immediate use.

Berodual inhalation solution should be used within 6 months after first opening.

The shelf-life is 3 years.

6.4 Special precautions for storage

None

6.5 Nature and contents of container

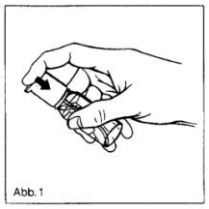
Clear, colourless solution for nebulizer, contained in an amber glass bottle with a dosing pump made of white plastic.

Pack sizes:
- Standard pack containing 20 ml solution

6.6 Special precautions for disposal and other handling instructions

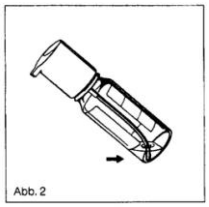
For administration, the recommended dose of Berodual inhalation solution should be diluted with physiological saline (0.9%) to a volume of 3-4 ml. The ready-to-use solution should be inhaled immediately after preparation. Inhale if possible while sitting or standing. The instructions for use of the inhalation device are to be followed.

1. To administer the solution, hold the bottle at an angle and fully depress the dosing head using your index finger (Fig. 1).



2. When using the device for the first time, press the pump a few times to ensure there is no air in the system. Discard the first released liquid.

3. When the liquid in the bottle decreases you must make sure that the dip-tube reaches into the solution (see Fig. 2).



This ensures that all the solution can be used except for a residual quantity which remains in the dispenser due to technical constraints.

Once air starts being drawn up with this residual quantity, exact dosage is no longer possible; therefore, the remaining solution should be discarded.

The inhalation duration can be controlled by the dilution volume.

Patients must be shown how to use the Berodual solution correctly. Care must be taken to avoid the solution/inhalation mist coming into contact with the eyes. The nebulized solution must be inhaled using a mouthpiece. If there is no mouthpiece and a nebulizer mask is used, care must be taken to ensure a proper fit for the mask. Patients who are prone to glaucoma must be expressly instructed to protect their eyes.

Berodual Solution is suitable for concomitant inhalation with Bisolvon® and Mucosolvan® inhalation solution.

7. MANUFACTURER

Istituto de Angeli
Loc. Prulli n.103/c 50066 Reggello (Firenze), ITALY
Uscita A1 - Incisa Valdarno/Reggello
Tel. 0558650001 Fax 0558650799
P.IVA 10274200152
E-mail: info@ida-pharma.com

8. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
55216 Ingelheim am Rhein, Germany
Phone: 0 800 / 77 90 900
Fax: 0 61 32 / 72 99 99
E-mail: info@boehringer-ingelheim.de

9. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.