1. NAME OF THE MEDICINAL PRODUCT

Berodual Respimat, oplossing voor inhalatie 20 microgram/ 50 microgram

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The delivered dose (the dose that leaves the mouthpiece of the Berodual Respimat) is 20 microgram ipratropium bromide monohydrate (equivalent to 19 microgram ipratropium bromide anhydrous) and 50 microgram fenoterol hydrobromide per puff.

Excipient with known effect: This medicine contains 1.12 microgram benzalkonium chloride in each actuation.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation solution
Clear, colourless, inhalation solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Berodual Respimat is indicated for the prevention and treatment of bronchospasm in asthma and chronic obstructive pulmonary disease (COPD).

Concomitant anti-inflammatory therapy should be considered.

4.2 Posology and method of administration

Posology

The dosage should be adapted to the individual requirements. The following dosages are recommended for adults.

Acute asthma episodes
One actuation of Berodual Respimat is sufficient for prompt relief in many cases. In more severe cases, if breathing has not noticeably improved after 5 minutes, one further actuation may be taken. If an attack has not been relieved by 2 actuations, further actuations 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 Respimat should be used only on an as-needed basis)

Adults: 1 actuation per administation of Berodual Respimat up to 4 times a day.

The total daily dose should not exceed 6 actuations, because generally a higher dose is not likely to provide increased efficacy. However, the risk of potentially serious adverse reaction may be increased.

Paediatric population:

Berodual Respimat is not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

Method of administration

This medicinal product is intended for inhalation use only. The cartridge can only be inserted and used in the Respimat device. Respimat is an inhaler device that generates a spray for inhalation. It is a single patient device intended for multiple uses.

Patients should read the instructions on How to use the Respimat inhaler device before they start using Berodual Respimat. To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler by a physician or other health care professional.

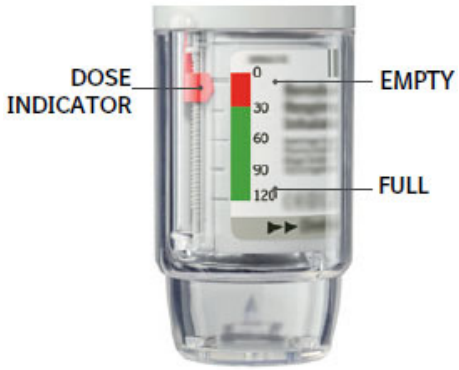
Instructions for handling and use of the Respimat inhaler

- If Berodual Respimat has not been used for more than 7 days release one puff towards the ground.
- If Berodual Respimat has not been used for more than 21 days repeat steps 4 to 6 under ‘Prepare for first use’ until a cloud is visible. Then repeat steps 4 to 6 three more times.
- Do not touch the piercing element inside the clear base.

How to care for Berodual Respimat
Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week.
Any minor discoloration in the mouthpiece does not affect Berodual Respimat inhaler performance.

If necessary, wipe the outside of Berodual Respimat inhaler with a damp cloth.

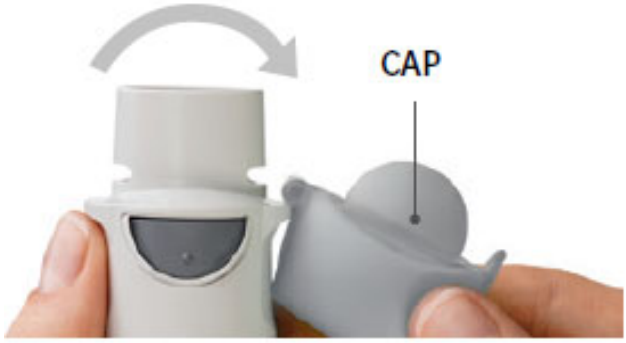
When to get a new Berodual Respimat



- Berodual Respimat inhaler contains 120 puffs (120 doses) if used as indicated.
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale the patient needs to get a new prescription; there is approximately medication for 7 days left (28 puffs).
- Once the dose indicator reaches the end of the red scale, BERODUAL RESPIMAT locks automatically – no more doses can be released. At this point, the clear base cannot be turned any further.
- Berodual Respimat should be discarded three months after the patient has prepared it for first use, even if it has not been fully used or used at all.

Prepare for first use

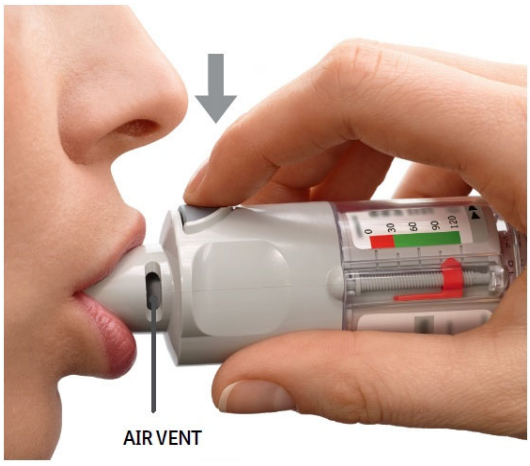
1. Remove clear base • Keep the cap closed. • Press the safety catch while firmly pulling off the clear base with the other hand.	

2. Insert cartridge • Insert the narrow end of the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it clicks into place. • Do not remove the cartridge once it has been inserted into the inhaler.	
3. Replace clear base • Put the clear base back into place until it clicks. • Do not remove the clear base again.	
4. Turn • Keep the cap closed. • Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).	
5. Open • Open the cap until it snaps fully open	

6. Press • Point the inhaler toward the ground • Press the dose-release button. • Close the cap. • Repeat steps 4-6 until a cloud is visible. • **After a cloud is visible**, repeat steps 4-6 three more times. The inhaler is now ready to use. These steps will not affect the number of doses available. After preparation the inhaler will be able to deliver 120 puffs (120 doses).	

Daily use

TURN • Keep the cap closed. • **TURN** the clear base in the direction of the arrows on the label until it clicks (half a turn).	
OPEN • **OPEN** the cap until it snaps fully open.	

PRESS • Breathe out slowly and fully. • Close the lips around the mouthpiece without covering the air vents. Point the Inhaler to the back of the throat. • While taking a slow, deep breath through the mouth, **PRESS** the dose-release button and continue to breathe in slowly for as long as comfortable. • Hold the breath for 10 seconds or for as long as comfortable. • Close the cap until the inhaler is used again.	

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in section 6.1, or to other atropine like substances.
Hypertrophic obstructive cardiomyopathy or tachyarrhythmia.

4.4 Special warnings and precautions for use

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

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

Ocular complications
Berodual Respimat, like other medicinal products containing anticholinergic active substances, 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 and eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic $beta_2$-agonist, has come into 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 eye drops should be initiated and specialist advice should be sought immediately.
Thus patients must be instructed in the correct administration of Berodual Respimat.
Care must be taken not to allow the product to enter the eyes.

Systemic effects

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

Cardiovascular effects
Cardiovascular effects may be seen with sympathicomimetic drugs, including Berodual Respimat. 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 Respimat, 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 hypokalemia may result from $beta_2$-agonist therapy (see also section 4.9).

Gastro-intestinal motility disturbances
Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances when treated with inhaled anticholinergics.

Dyspnoea

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

Prolonged use
- In patients with bronchial asthma Berodual Respimat should be used only on an as-needed basis. In patients with mild COPD, on demand treatment (symptom-oriented) 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 asthma and with steroid-responsive COPD.

In asthmatic patients, the use of increasing amounts of $beta_2$-agonist containing medicinal products, such as Berodual Respimat, 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 medicinal 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 to prevent potentially life-threatening deterioration of disease control.

Other sympathomimetic bronchodilators should only be used in combination with Berodual Respimat under medical supervision (see section 4.5).

Excipients
Benzalkonium chloride may cause wheezing and breathing difficulties. Patients with asthma are at an increased risk for these adverse events.

4.5 Interaction with other medicinal products and other forms of interaction

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

Other beta-adrenergics, 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 may increase the adverse reactions.

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

Hypokalemia induced by beta$_2$-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.

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

Beta$_2$-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 (e.g. halothane, trichloroethylene and enflurane) can increase the susceptibility on the cardiovascular effects of beta$_2$-agonists.

The risk of acute glaucoma (see section 4.4) may be increased when nebulised ipratropium bromide and beta$_2$-agonists come into contact with the eyes simultaneously.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no sufficient data from the use of Berodual Respimat in pregnant women. Animal studies do not indicate direct or indirect harmful effect with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women.
The potential of beta 2-agonists to inhibit uterine contraction should be taken into account.

Use of ß-2 sympathomimetics in the end of the pregnancy or in high doses may cause negative effects in the newborn baby (tremor, tachycardia, blood glucose fluctuations, hypokalaemia).

Breastfeeding
Non-clinical studies have shown that fenoterol hydrobromide is excreted into breast milk. It is not known 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 inhalation. However, because many active substances are excreted into breast milk, caution should be exercised when Berodual Respimat is administered to nursing mothers.

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 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 Respimat. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Many of the listed undesirable effects can be assigned to the anticholinergic and beta-adrenergic properties of Berodual Respimat. As with all inhalation therapy Berodual Respimat may show symptoms of local irritation. Adverse drug reactions were identified from data obtained in clinical trials and pharmacovigilance during post approval use of the drug.

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.

Adverse reactions have been ranked using the following convention:
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)

a) <u>General description</u>

The reported incidences of adverse reactions to Berodual Respimat are based on three multiple-dose clinical trials [mean duration of treatment was 62 days and maximum was 107 days] and one phase IIIb trial comparing Berodual Respimat with Berodual HFA MDI involving 802 patients. Furthermore two phase III studies with Berodual HFA MDI are included resulting in a total of 2009 patients. Most adverse reactions are uncommon (<1/100) or rare (<1/1,000) and are mainly due to the pharmacological effects of the medicinal product. Cough and pharyngitis fall under the category common as local side effects.

b) Table of Adverse Reactions According to the MedDRA terminology

System Organ Class	**Frequency**
Immune System Disorders	
Anaphylactic reaction	Rare*
Hypersensitivity	Rare*
Metabolism and nutricional disorders	
Hypokalemia	Rare*
Psychiatric Disorders	
Nervousness	Uncommon
Agitation	Rare
Mental disorder	Rare
Nervous System Disorders	
Headache	Uncommon
Tremor	Uncommon
Dizziness	Uncommon
Hyperactivity	Not known
Eye Disorders	
Glaucoma	Rare*
Intraocular pressure increased	Rare*
Accommodation disorder	Rare*
Mydriasis	Rare*
Vision blurred	Rare*
Eye pain	Rare*
Corneal oedema	Rare*
Conjunctival hyperaemia	Rare*
Halo vision	Rare*
Cardiac disorders	
Tachycardia, heart rate increased	Uncommon
Palpitations	Uncommon
Arrhythmia	Rare
Atrial fibrillation	Rare
Supraventricular tachycardia	Rare*
Myocardial ischaemia	Rare*
Respiratory, Thoracic and Mediastinal Disorders	
Cough	Common
Pharyngitis	Uncommon
Dysphonia	Uncommon
Bronchospasm	Rare
Throat irritation	Rare
Pharyngeal oedema	Rare
Laryngospasm	Rare*
Bronchospasm paradoxical	Rare*

Dry throat	Rare*
Gastro-intestinal Disorders	
Vomiting	Uncommon
Nausea	Uncommon
Dry mouth	Uncommon
Stomatitis	Rare
Glossitis	Rare
Gastrointestinal motility disorder	Rare
Diarrhoeia	Rare
Constipation	Rare*
Oedema mouth	Rare*
Skin and Subcutaneous Disorders	
Urticaria	Rare
Rash	Rare
Pruritus	Rare
Angioedema	Rare*
Hyperhidrosis	Rare*
Musculoskeletal and connective Tissue Disorders	
Myalgia	Rare
Muscle spasms	Rare
Muscular weakness	Rare
Renal and Urinary Disorders	
Urinary retention	Rare
Investigations	
Blood pressure systolic increased	Uncommon
Blood pressure diastolic decreased	Rare

* Side effect has not been observed in any of the selected BERODUAL® 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 = 0.00060 which relates to "rare").

c) Individual serious and/or frequently occurring adverse reactions

Coughing, pharyngitis, throat irritation, hoarseness, taste perversion, glossitis and stomatitis are being considered as local irritation phenomena, mainly due to the inhaled route of administration.

d) Pharmacological class-adverse reactions

The following reactions were not observed in clinical trials but are known to be associated with medicinal products in the same pharmacological class as the components of Berodual Respimat.

Beta$_2$-agonists: sweating and weakness (muscle) may occur. In rare cases decreased diastolic blood pressure, increased systolic blood pressure, particularly after higher doses, have been observed. Potentially serious hypokalemia and myocardial ischaemia may result from beta$_2$-agonist therapy.

Anticholinergic active substances: supraventricular tachycardia, gastro intestinal motility disturbances and urinary retention may occur. Ocular adverse reactions like visual accommodation disturbances, mydriasis, increased intraocular pressure and eye pain have been reported (see section 4.4).

Hypersensitivity reactions such as angio-oedema of the tongue, lips and face may occur.

As with other inhalation therapy, inhalation induced bronchospasm may occur immediately after dosing.

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 via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

The effects of overdose are expected to be primarily related to fenoterol.
The expected symptoms with overdose are those of excessive ß-adrenergic stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, arrhythmias, and flushing.
Metabolic acidosis has also been observed with fenoterol when applied in doses higher than recommended for the approved indications of Berodual. Hypokalaemia may occur following overdose with fenoterol. Serum potassium levels should be monitored.

Expected symptoms of overdose with ipratropium bromide (such as dry mouth, visual accommodation disorder, increase of heart rate) are mild and because the systemic bioavailability of inhaled ipratropium is very low.

Treatment of overdose

Treatment with Berodual Respimat should be discontinued. Acid base and electrolyte monitoring should be considered.
Administration of sedatives, tranquilisers; in severe cases intensive care treatment. Beta-receptor blockers, preferably $beta_1$-selective, may be used 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 asthma or COPD because of the risk of precipitating severe bronchospasm, which may be fatal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergics in combination with anticholinergics for obstructive airway diseases
ATC code: R03AL01

Following inhalation, both active substances, fenoterol hydrobromide and ipratropium bromide, induce bronchodilatation within a few minutes. The bronchodilator effect persists for 3-5 hours for Fenoterol and up to 6 hours for ipratropium bromide. Due to the local effect in the airways the time course of plasma concentrations does not correlate with the pharmacodynamic time-response curve after inhalation.

Fenoterol hydrobromide

Fenoterol hydrobromide is a $ß_2$-sympathomimetic agent. The $ß_1$-receptors are only stimulated with higher doses.
Fenoterol hydrobromide relaxes the smooth muscles in the bronchi and blood vessels. The relaxation of the smooth muscles is dose-dependent. It is induced via effects on the adenylate cyclase system in such a way that the binding of the ß-agonist to its receptor - mediated by guanosine-binding protein - leads to the activation of the adenylate cyclase. Increased intracellular cAMP then causes the smooth muscles to relax via protein phosphorylation (protein kinase A). In high doses fenoterol also affects the striated muscles (tremor). Furthermore, fenoterol inhibits mediator release from the mast cells.
Increased mucociliary clearance is demonstrated after administration of fenoterol in a dose of 0.6 mg. There may be little or no effect in neonates or infants up to about 20 months.
Fenoterol has a positive isotropic and chronotropic (direct and/or reflex) effect on the heart.
As with other beta-adrenergic agents, QTc prolongations have been reported. For fenoterol pressurised inhalation, solutions these were discrete and observed at doses higher than recommended. The clinical significance has not been established.
The influence on lipid and sugar metabolism (lipolysis, glycogenolysis and hyperglycaemia) and relative hypokalaemia due to increased K^+ uptake in the skeletal muscle are pharmacological effects which only occur with higher doses.

Due to the density of $ß_2$-receptors in the myometrium, fenoterol also relaxes the uterine muscles. This effect is particularly pronounced in the pregnant uterus and at considerably higher doses.

Ipratropium bromide

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In preclinical 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.

Combination of active substances

The effects of fenoterol hydrobromide and ipratropium bromide interact through functional synergism. Therefore, the dose of fenoterol hydrobromide can be kept particularly low.

5.2 Pharmacokinetic properties

The delivery of active substances via inhalation is strongly dependent on the formulation, the device and the technique used. Generally approximately 10-30% of inhaled polar, water-soluble active substances reach the lower parts of the airways, while the remainder is deposited in the mouth and the upper part of the respiratory tract (oropharynx). In particular, after inhalation via Respimat, a lung deposition of fenoterol of 39% is experimentally observed. The oropharyngeal deposition is correspondingly decreased. The amount of the active substance deposited in the oropharynx is slowly swallowed and passes the gastrointestinal tract. Inhaled doses of fenoterol hydrobromide and ipratropium bromide follow this general pattern of distribution.

Fenoterol hydrobromide

Absorption
After oral administration, fenoterol hydrobromide is absorbed for approximately 60%. Due to first pass metabolism, the oral bioavailability of the swallowed portion is low (approximately 1.5%). Based on urinary excretion data, the total systemic bioavailability of inhaled doses of fenoterol hydrobromide is estimated at 7%.

Distribution
Following intravenous administration, the apparent volume of distribution of fenoterol at steady state (Vdss) is approximately 189 L (≈ 2.7 L/kg).
Fenoterol is bound to plasma proteins to approximately 40%-55%.
Preclinical studies with rats revealed that fenoterol and its metabolites do not cross the blood-brain barrier.

Metabolism
Fenoterol is predominantly metabolised to sulphate conjugates in the liver.

Elimination
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. 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

Absorption
Ipratropium bromide is barely absorbed by the respiratory tract (approximately 4%). The absorption of the swallowed portion is approximately 10%. Due to first pass metabolism, the oral bioavailability of the swallowed portion is low (approximately 2%).

Distribution
Less than 20% of ipratropium bromide is bound to plasma proteins, and it does not pass the placenta or blood-brain barrier.

Metabolism
After intravenous administration approximately 60% of a dose is metabolised, the major portion probably in the liver by oxidation. Ipratropium bromide is metabolised in the liver to mainly 3 metabolites (α-phenylacrylic acid and the phenylacetic acid-N-isopropyl nortropine ester methobromide, and the N-isopropylnortropine methobromide). Binding of the main urinary metabolites to the muscarinic receptor is negligible.

Elimination
Total clearance is approximately 2.3 l/min, 40% of which renal. Elimination occurs in approx. 1.6 hours. 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 occures via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.6 hours.

5.3 Preclinical safety data

Animal tests have not produced evidence to suggest that there might be a safety risk for humans. This is based on data from pharmacological studies regarding safety, and data on toxicity following repeated administration, genotoxicity, carcinogenicity and reproduction studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride, Disodium edetate, Water, purified, Hydrochloric acid for pH adjustment

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
This includes a 3 months in-use period. The cartridge has an in-use shelf life of 3 months after insertion in the Respimat.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Type and material of the container in contact with the medicinal product:

Solution filled into a 4.5 ml polyethylene / polypropylene cartridge with a polypropylene cap with integrated silicone sealing ring. The cartridge is enclosed within an aluminium cylinder.

Pack sizes and devices supplied:
- Original package: 1 Respimat inhaler and one 4.5 ml cartridge, delivering 120 metered doses.
- Double package: 2 single packages, each containing 1 Respimat inhaler and one 4.5 ml cartridge, each delivering 120 metered doses.
- Hospital package: 8 single packages, each containing 1 Respimat inhaler and one 4.5 ml cartridge, each delivering 120 metered doses.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Straße 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

Berodual Respimat, oplossing voor inhalatie 20 microgram/ 50 microgram: RVG 26896

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2 oktober 2002 / 2 oktober 2007

10. DATE OF REVISION OF THE TEXT

Laatste wijziging betreft de opmaak: 14 juli 2022.