

## 1. NAME OF THE MEDICINAL PRODUCT

Berodual® Respimat® 20/50 Microgram/  
Dose Solution for Inhalation

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The delivered dose (the dose that leaves the mouthpiece of the Berodual Respimat) is 20 µg ipratropium bromide monohydrate and 50 µg fenoterol hydrobromide

For excipients, see 6.1

## 3. PHARMACEUTICAL FORM

Solution for inhalation

Clear, colorless solution for inhalation

## 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

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

One administration 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 administration may be taken. If an attack has not been relieved by 2 administrations, further administrations may be required. In these cases, patients should consult the doctor or the nearest hospital immediately.

#### Intermittent and long-term treatment

Adults:

1 actuation per administration of Berodual Respimat up to 4 times a day.

Children (over 6 years of age):

Berodual Respimat should only be used on medical advice and under the supervision of an adult.

1 actuation of Berodual Respimat, up to a maximum of 3 actuations per day.

### 4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients (see 6.1 List of excipients), or to other atropine like substances. Hypertrophic obstructive cardiomyopathy or tachyarrhythmia.

### 4.4 Special warnings and precautions for use

In the case of acute, rapidly worsening of dyspnoea the patient should be advised that a doctor should be consulted immediately.

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.

Berodual Respimat, like other products containing anticholinergic drugs, should be used with caution in patients with prostatic hyperplasia or bladder-neck obstruction or 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<sub>2</sub>-agonist, has come into contact with the eyes. Thus patients must be instructed in the correct administration of Berodual Respimat. Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival and corneal congestion 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.

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

#### Prolonged use

In patients with asthma and 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<sub>2</sub>-agonist containing 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<sub>2</sub>-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 to prevent potentially life-threatening deterioration of disease control.

Other sympathomimetic bronchodilators should only be used in combination with Berodual Respimat under medical supervision.

Potentially serious hypokalemia may result from excessive beta<sub>2</sub>-agonist therapy.

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

### 4.5 Interaction with other medicinal products and other forms of interaction

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 side effects.

Hypokalemia induced by beta<sub>2</sub>-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<sub>2</sub>-agonist containing 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.

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

Inhalation of halogenated hydrocarbon anaesthetics (e.g. halothane, trichloroethylene and enflurane) can increase the susceptibility on the cardiovascular effects of beta<sub>2</sub>-agonists.

The risk of acute glaucoma (see special warnings and precautions for use) may be increased when nebulised ipratropium bromide and beta<sub>2</sub>-agonists come into contact with the eyes simultaneously.

### 4.6 Pregnancy and lactation

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<sub>2</sub>-agonists to inhibit uterine contraction should be taken into account. Preclinical 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 drugs are excreted into breast milk, caution should be exercised when Berodual Respimat is administered to nursing mothers.

### 4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile and the reported adverse drug reactions it is not likely that ipratropium bromide and fenoterol hydrobromide have an effect on the ability to drive or use machines.

### 4.8 Undesirable effects

#### a) General description

The reported incidences of adverse reactions to Berodual Respimat are based on three multiple-dose clinical trials [mean du-

# Berodual<sup>®</sup> Respimat<sup>®</sup>



ration of treatment was 62 days and maximum was 107 days] involving 565 patients. Adverse drug reactions are uncommon (< 1/100) and are mainly due to the pharmacological effects of the medicinal product.

## b) Table of Adverse Reactions<sup>1</sup> According to the WHO System Organ Class

WHO Preferred Term	Frequency <sup>2</sup>
Application site disorder Application site reaction (i.e. burning throat)	Uncommon
Body as a whole-general Headache	Uncommon
Cardiovascular disorders Hypertension aggravated	Uncommon
Central and peripheral nervous system Hoarseness, nervousness, tremor	Uncommon
Gastro-intestinal system Glossitis, mouth dry, nausea, stomatitis	Uncommon
Heart rate & rhythm disorders Palpitation, pulse rate increased	Uncommon
Respiratory system disorders Coughing; pharyngitis,	Uncommon
Special senses other Taste perversion	Uncommon
Urinary system disorders Urinary retention	Uncommon
Vascular (extracardiac) Hot flushes	Uncommon

<sup>1</sup> considered at least possibly related by the investigator and the sponsor in the clinical trials

<sup>2</sup> uncommon (>0.1 % but < 1 %)

## c) Individual serious and/or frequently occurring adverse reactions

Burning throat, hoarseness, glossitis, stomatitis, coughing and pharyngitis 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 products in the same pharmacological class as the components of Berodual Respimat.

Beta<sub>2</sub>-agonists: vomiting, sweating, weakness, myalgia/muscle cramps and psychological alterations may occur. In rare cases decrease in diastolic blood pressure, increase in systolic blood pressure, arrhythmias, particularly after higher doses, have been observed. Potentially serious hypokalaemia may result from beta<sub>2</sub>-agonist therapy.

**Anticholinergic drugs:** gastro-intestinal motility disturbances and urinary retention. Ocular side effects like visual accommodation disturbances, mydriasis, increased intraocular pressure, eye pain and glaucoma have been reported [see 4.4: **Special Precautions**].

Hypersensitivity reactions such as skin rash, angioedema of the tongue, lips and face and urticaria may occur.

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

## 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  $\beta$ -adrenergic stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, arrhythmias, and flushing.

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

### Therapy

Administration of sedatives, tranquilisers; in severe cases intensive therapy. Beta-receptor blockers, preferably beta1-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 and other anti-asthmatics ATC code: R03A K.

Following inhalation, both active ingredients, 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 is a  $\beta_2$ -sympathomimetic agent. The  $\beta_1$ -receptors are only stimulated with higher doses.

Fenoterol 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  $\beta$ -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.

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. The influence on lipid and sugar metabolism (lipolysis, glycogenolysis and hyperglycaemia) and relative hypokalaemia due to increased K<sup>+</sup> uptake in the skeletal muscle are pharmacological effects which only occur with higher doses.

Due to the density of  $\beta_2$ -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

Inhibition of vagally induced reflex bronchoconstriction. Inhibition of the release of bronchospastic mediators by decreasing the cyclic GMP in the mast cells (mast cell stabilisation), thus preventing allergic early phase reactions (type I).

#### Combination of active ingredients

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 drugs via inhalation is strongly dependent on the formulation, the device and the technique used. Generally approximately 10–30 % of inhaled polar, water-soluble drugs 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 drug 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

Fenoterol hydrobromide is barely absorbed by the respiratory tract. Its bioavailability following oral administration is low (approximately 1.5 %). In the liver, it is predominantly metabolised into sulphate conjugates. Fenoterol is bound to plasma proteins to approximately 40–55 %. Non-metabolised fenoterol hydrobromide may slowly pass the placenta and be secreted into the breast milk. Fenoterol and its conjugates are excreted via the kidneys (renal clearance: approx. 270 ml/min). Its elimination half-life is approximately 3 hours.

#### Ipratropium bromide

Ipratropium bromide is barely absorbed by the respiratory tract. The bioavailability of the swallowed portion is low (approximately 2 %). Ipratropium bromide is metabolised in the liver to mainly 3 metabolites ( $\alpha$ -phenylacrylic acid and the phenylacetic acid-N-isopropyl nortropine ester methobromide, and the N-isopropyl nortropine methobromide). Less than 20 % of ipratropium bromide is bound to plasma proteins, and it does not pass the placenta or blood-brain barrier. Total clearance is approximately 2.3 l/min, 40 % of which renal. The primary

metabolites in the urine barely bind to muscarinic receptors. Elimination occurs in approx. 1.6 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

### 6.2 Incompatibilities

No incompatibilities known at present.

### 6.3 Shelf life

The shelf life of the product is 24 months. 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 PE/PP cartridge with a PP cap

Pack sizes and devices supplied:

- Original package: 1 Respimat inhaler and one 4.5 ml cartridge, delivering 120 metered doses.
- Double package: 2 Respimat inhalers and two 4.5 ml cartridges, delivering 240 metered doses

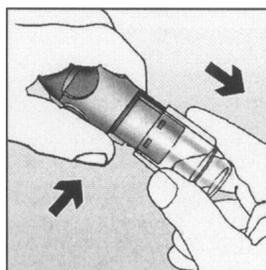
### 6.6 Instructions for use and handling

The correct administration of Berodual Respimat is essential for successful therapy.

#### Inserting the cartridge

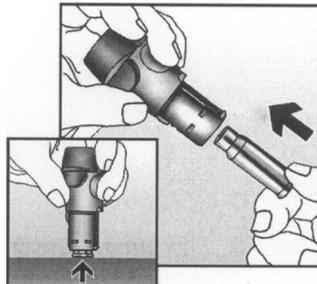
The following steps 1–3 are necessary before first use:

- 1 With the cap closed, press the safety catch and pull off the transparent base.



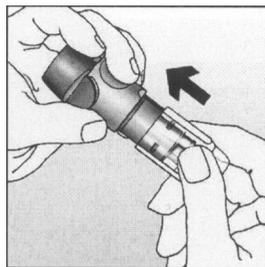
- 2 Take the cartridge out of the box. Push the narrow end of the cartridge into the inhaler until it clicks into place – if needed push it vertically against a firm surface.

Do not remove the cartridge once it has been inserted.



- 3 Replace the transparent base with the notch of the base in line with the safety catch.

Do not remove again the transparent base.

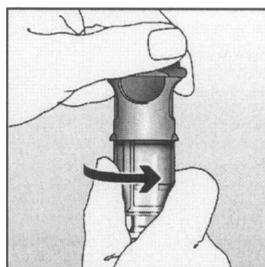


#### To prepare the Respimat® inhaler for use

As the Respimat® inhaler does not use any propellants, the following steps are needed to fill the dosing system.

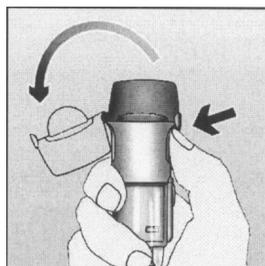
#### 4 To turn

Hold the Respimat® inhaler upright, with the cap closed. Turn the base in the direction of the arrow until it clicks (half a turn).



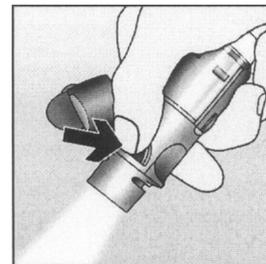
#### 5 To open

Open the cap until it snaps into position.



#### 6 To release the dose

Point the Respimat® inhaler towards the ground. Press the dose release button.

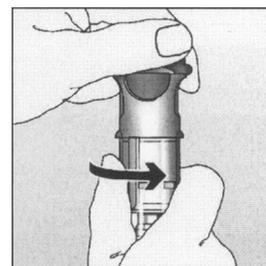


Repeat steps 4 to 6 until a cloud is visible. Then repeat steps 4 to 6 three more times.

#### Using Respimat® inhaler

- A Hold the Respimat® inhaler upright, with the cap closed, to avoid premature release of the dose.

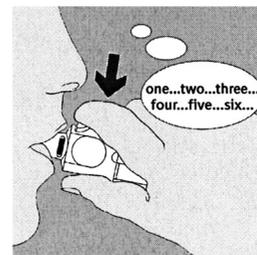
Turn the base in the direction of the arrow until it clicks (half a turn).



- B Open the cap until it snaps into position. Breathe out slowly and deeply, then... close your lips around the end of the mouthpiece without covering the air vents.

Point your Respimat® inhaler to the back of your throat.

While taking a slow, deep breath through your mouth, press the dose release button and continue to breathe in slowly for as long as you can. Hold your breath for 10 seconds or for as long as comfortable.



#### Close the cap until you use your Respimat® inhaler again.

If Berodual® Respimat® inhaler has not been used for more than 7 days ensure that the dosing system is full by releasing one actuation towards the ground. If Berodual® Respimat® inhaler has not been used for more than 21 days repeat steps 4 to 6 until a cloud is visible. Then repeat steps 4 to 6 three more times.

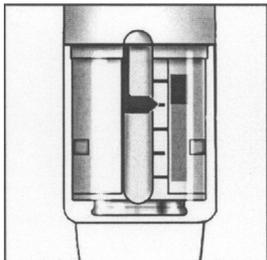
#### When to get a new Respimat® inhaler

The Berodual® Respimat® inhaler contains 120 doses. The dose indicator shows approximately how much medication is left. When the pointer enters the red area of the scale, there are approximately 30 doses left. This is when you need to get a new Berodual® Respimat® inhaler prescription.

# Berodual<sup>®</sup> Respimat<sup>®</sup>

Once the dose indicator has reached the end of the scale (ie all 120 actuations have been used), the Respimat<sup>®</sup> inhaler locks automatically. The base cannot be turned anymore.

At the latest three months after first use, the Respimat<sup>®</sup> inhaler should be discarded even if not all medication has been used.



## **Care of your inhaler**

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 the Respimat<sup>®</sup> inhaler performance.

If necessary, wipe the outside of your Respimat<sup>®</sup> inhaler with a damp cloth.

## **7. MARKETING AUTHORISATION HOLDER**

Boehringer Ingelheim International  
GmbH & Co. KG  
Binger Straße 173  
D-55216 Ingelheim am Rhein  
Germany

## **8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**

56712.00.00

## **9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION**

17. 9. 2003

## **10. DATE OF REVISION OF THE TEXT**

September 2003

Please note that the product BERODUAL RESPIMAT has been licensed and launched in Germany.

It is not available in any other country for the time being.