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 acute 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-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.

4.5 Interactions 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.

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-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® Respimat®

SUMMARY OF PRODUCT CHARACTERISTICS (ENGLISH TRANSLATION OF A GERMAN FACHINFORMATION (SPC))

Boehringer Ingelheim

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 1 Accurating to the WHO System Organ Class

<table>
<thead>
<tr>
<th>WHO Preferred Term</th>
<th>Frequency²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site disorder</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Application site reaction (i.e. burning throat)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Body as a whole-general</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Headache</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hypertension aggrivated</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Central and peripheral nervous system</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hoarseness, nervousness, tremor</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastro-intestinal system</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Glossitis, mouth dry, nausea, stomatitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Heart rate &amp; rhythm disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Palpitation, pulse rate increased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Respiratory system disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Coughing; pharyngitis,</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Special senses other</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Urinary system disorders</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vascular (extracardiac)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

¹ considered at least possibly related by the investigator and the sponsor in the clinical trials
² uncommon (>0.1 % but < 1 %)

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.

Beta₂-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 beta₂-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 β₂-adrenergic stimulation, the most prominent being tachycardia, palpitation, tremor, hyper tension, 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, tranquillisers; 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

Pharmaco therapeutic 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 β₂-sympathomimetic agent. The β₂-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 adenylylcyclase system in such a way that the binding of the β₂-agonist to its receptor — mediated by guanosine-binding protein — leads to the activation of the adenylylcyclase. 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 related hyperglycaemia due to increased K⁺ uptake in the skeletal muscle are pharmacological effects which only occur with higher doses.

Due to the density of β₂-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 30% 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 (α-phenylacrylic acid and the phenylacetic acid-N-isopropyl) nortropane ester methobromide, and the N-isopropyl-N-nortropane 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 is renal.
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 in 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.
Once the dose indicator has reached the end of the scale (i.e. all 120 actuations have been used), the Respimat® inhaler locks automatically. The base cannot be turned anymore.

At the latest three months after first use, the Respimat® 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® inhaler performance.

If necessary, wipe the outside of your Respimat® 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.