Public Assessment Report

Decentralised Procedure

Zulavent 250 Micrograms per ml Nebuliser Solution
(ipratropium bromide)

Procedure No: UK/H/3401/001/DC

UK Licence No: PL 14825/0002

Institut Dr Zoeller
On 26 October 2011 the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Institut Dr. Zoeller for the medicinal product Zulavent 250 micrograms per ml nebuliser solution (PL 14825/0002; UK/H/3401/001/DC). The medicinal product will be referred to as Zulavent in this report. This is a prescription-only medicine (POM) that helps to make breathing easier in patients with asthma and other breathing difficulties, such as chronic obstructive pulmonary disease (COPD). Zulavent can be used at the same time as salbutamol, a β2 agonist bronchodilator or ‘reliever’ medicine and also used for breathing problems.

Zulavent should not be used as the first treatment, when a rapid response is required, for acute wheezing, shortness of breath or tightness of the chest in adults, adolescents and children 6 years of age; instead, a rapid-acting β2 agonist bronchodilator or ‘reliever’ medicine or ‘reliever inhaler should be used. However in children 5 years of age and younger Zulavent is only used to treat acute episodes of asthma.

Zulavent contains the active ingredient, ipratropium bromide, which belongs to a group of medicines called ‘bronchodilators’ that help to open up the airways in the lungs so that breathing is easier. Zulavent is used with a device called a ‘nebuliser’, which changes the medicine into a mist for breathing in.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Zulavent outweigh the risks; therefore, a Marketing Authorisation has been granted.
# TABLE OF CONTENTS

| Module 1: Information about initial procedure | Page 4 |
| Module 2: Summary of Product Characteristics | Page 5 |
| Module 3: Product Information Leaflet | Page 11 |
| Module 4: Labelling | Page 23 |
| Module 5: Scientific Discussion | Page 30 |
| 1 Introduction | |
| 2 Quality aspects | |
| 3 Non-clinical aspects | |
| 4 Clinical aspects | |
| 5 Overall conclusions | |
| Module 6: Steps taken after initial procedure | |
Module 1

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Zulavent 250 micrograms per ml nebuliser solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10.3</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Ipratropium bromide</td>
</tr>
<tr>
<td>Form</td>
<td>Nebulising Solution</td>
</tr>
<tr>
<td>Strength</td>
<td>250 micrograms/ml</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Institut Dr. Zoeller Kriemhildstr. 17 69469 Weinheim Germany</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
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<tr>
<td>Concerned Member States (CMS)</td>
<td>Austria and Germany</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/3401/001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210 – 08 March 2011</td>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Zulavent 250 micrograms per ml nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ampoule contains ipratropium bromide 250 micrograms per ml i.e. 250 micrograms in 1 ml and 500 micrograms in 2 ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Nebuliser solution.

A clear, colourless solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Zulavent is indicated for the treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD).

Zulavent is indicated, when used concomitantly with inhaled \( \beta_2 \) agonists, for treatment of reversible airways obstruction in patients with acute and chronic asthma.

4.2 Posology and method of administration
For inhalation use.

The dosage should be adapted to the individual needs of the patient. In children aged 12 years and under, only 1 ml ampoules of Zulavent nebuliser solution should be used. The following doses are recommended:

Adults (including the elderly) and adolescents over 12 years of age:
250–500 micrograms (i.e. one or two ampoules of 250 micrograms in 1 ml) 3 to 4 times daily.
A dose of 500 micrograms can be administered from one ampoule containing 500 micrograms in 2 ml.

For treatment of acute bronchospasm: 500 micrograms.
Repeated doses can be administered until the patient is stable. The time interval between the doses may be determined by the physician.

It is advisable not to exceed the recommended total daily dose during either acute or maintenance treatment. Daily doses exceeding 2 mg in adults and adolescents over 12 years of age should only be given under medical supervision.

Children 6–12 years of age:
250 micrograms (i.e. one ampoule of 250 micrograms in 1 ml) up to a total daily dose of 1 mg (4 ampoules).

The time interval between doses may be determined by the physician.

Children 0–5 years of age (for treatment of acute asthma only):
125–250 micrograms (i.e. half to one ampoule of 250 micrograms in 1 ml) up to a total daily dose of 1 mg (4 ampoules).

Zulavent should be administered no more frequently than 6 hourly in children under 5 years of age.

For acute bronchospasm, repeated doses may be administered until the patient is stable.

If therapy does not produce a significant improvement or if the patient's condition gets worse, medical advice must be sought. In the case of acute or rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately.
Renal or hepatic impairment
Zulavent has not been studied in patients with renal or hepatic insufficiency. It should be used with caution in these patient groups.

The dose of nebuliser solution may need to be diluted in order to obtain a final volume suitable for the particular nebuliser being used (usually 2–4 ml); if dilution is necessary use only sterile sodium chloride 0.9 % solution.

Zulavent may be combined with salbutamol nebuliser solution, a short-acting β₂ agonist, in the same nebuliser chamber, for simultaneous administration where co-administration is required. The solution should be used as soon as possible after mixing and any unused solution should be discarded. Compatibility studies with the short-acting β₂ agonist, salbutamol nebuliser solution have been carried out.

This medicinal product must not be mixed with any other short-acting β₂ agonists or any other medicinal products.

Zulavent and sodium cromoglycate inhalation solutions that contain the preservative benzalkonium chloride should not be administered simultaneously in the same nebuliser as precipitation may occur.

Drug delivery characteristics were studied in vitro using the PARI LC Sprint Junior nebuliser device. Two formulations were tested:

<table>
<thead>
<tr>
<th>Nebuliser system: PARI LC Sprint Junior</th>
<th>1 ml Zulavent nebuliser solution diluted with 1 ml sterile sodium chloride 0.9 % solution</th>
<th>2 ml Zulavent nebuliser solution</th>
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<tbody>
<tr>
<td>Droplet size distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D₁₀ [µm]</td>
<td>0.97</td>
<td>0.92</td>
</tr>
<tr>
<td>D₅₀ (MMD) [µm]</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td>D₉₀ [µm]</td>
<td>10.66</td>
<td>8.29</td>
</tr>
<tr>
<td>Drug Delivery Rate [µg / min]</td>
<td>9.25</td>
<td>17.5</td>
</tr>
<tr>
<td>Total drug delivered [µg]</td>
<td>49.25</td>
<td>102.5</td>
</tr>
</tbody>
</table>

* MMD - Median Mass Diameter

No information is available in respect of pulmonary inhalation and deposition patterns across nebuliser systems that have not been studied.

The use of an alternative untested nebuliser system may alter the pulmonary deposition of the active substance, this in turn may alter the efficacy and safety of the product and dose adjustment may then become necessary.

Instructions for use with the PARI LC Sprint Junior
1. The nebuliser is operated with the PARI Junior BOY S Compressor (Type 053) and should be prepared by following the manufacturer’s instructions.
2. A new ampoule should be separated from the strip carefully and the rest of the strip returned to the foil pack which is then put back into the carton. An ampoule which has been opened previously should NOT be used again.
3. The ampoule should be held upright and opened by simply twisting off the top.
4. The closure on the nebuliser upper section should be released by pressing the thumb against the underside of the cap.
5. The prescribed quantity of solution should be squeezed into the nebuliser chamber. If dilution of the ampoule contents is necessary, this should be done using ONLY sterile 0.9 % sodium chloride solution.
6. The nebuliser chamber should be filled with solution to a level no higher than the upper scale marking (max level 8 ml).
7. The cap of the nebuliser should be closed. The cap should snap into place. All parts of the nebuliser should be firmly connected to each other.
8. The patient should sit in an upright position and relax. The compressor should be switched on. The mouthpiece should be taken between the teeth and the lips should be closed around it or the mask should be tightly pressed over mouth and nose. The patient should be instructed to breathe in through the mouthpiece or mask as slowly and as deeply as possible and to breathe out in their own time.
9. For inhalation with babybend and babymask, the bend should be swivelled so that it corresponds with the position of the baby or infant. The nebuliser should always be held upright. The
compressor should be switched on and the mask pressed gently but firmly over mouth and nose. The infant or child should be allowed to breathe in and out in their own time.

10. The inhalation should be continued until the solution in the nebuliser chamber is used up (signalled by a change in the sound of the nebuliser).

11. The compressor should be switched off as soon as inhalation is finished. Any remaining solution from the nebuliser chamber should be thrown away.

12. The manufacturer’s instructions should be followed for cleaning the nebuliser. It is important that the nebuliser is kept clean.

The full instructions for use of the nebuliser in the leaflet provided with PARI LC Sprint Junior should be read before starting the inhalation.

4.3 **Contraindications**

Hypersensitivity to ipratropium bromide, atropine or other derivatives or to any of the excipients.

4.4 **Special warnings and precautions for use**

Use of the nebuliser solution should be subject to close medical supervision during initial dosing.

Caution is advocated in the use of anticholinergic agents in patients predisposed to or with narrow-angle glaucoma, or with prostatic hyperplasia or bladder-outflow obstruction.

As patients with cystic fibrosis may be prone to gastro-intestinal motility disturbances, ipratropium bromide, as with other anticholinergics, should be used with caution in these patients.

Immediate hypersensitivity reactions following the use of ipratropium bromide have been demonstrated by rare cases of urticaria, angiooedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis. Caution should be used in patients with cardiac disease.

Ipratropium bromide should not be used for the initial treatment of acute episodes of bronchospasm when a rapid response is required.

If it is necessary to use higher doses than recommended to control the symptoms of bronchoconstriction (or bronchospasm), the patient’s treatment plan should be reassessed.

There have been isolated reports of ocular complications (i.e. mydriasis, increased intra-ocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide, either alone or in combination with an adrenergic β₂ agonist, has come into contact with the eyes during nebuliser therapy.

Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be symptoms or signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

Patients must be instructed in the correct administration of Zulavent. Care must be taken not to allow the solution or mist to enter the eyes. It is recommended that the nebulised solution is administered via a mouthpiece. If this is not available and a nebuliser mask is used, it must fit properly. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Ipratropium bromide should be discontinued immediately, the patient should be assessed and alternative therapy instituted if necessary.

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

There is evidence that the administration of ipratropium bromide with beta-adrenergic drugs and xanthine preparations may produce an additive bronchodilatory effect.

Concomitant use of other anticholinergics may intensify the effect as well as the side effects of ipratropium bromide.
The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see section ‘4.4 Special warnings and precautions for use’) may be increased when nebulised ipratropium bromide and β2 agonists are administered simultaneously.

4.6 Pregnancy and lactation
The safety of Zulavent during human pregnancy has not been established. The benefits of using Zulavent during a confirmed or suspected pregnancy must be weighed against the possible hazards to the unborn child. Preclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man.

It is not known whether ipratropium bromide is excreted into breast milk. It is unlikely that ipratropium bromide would reach the infant to an important extent; however caution should be exercised when Zulavent is administered to nursing mothers.

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. Up to now there is no evidence that Zulavent essentially affects the ability to drive or to use machines. However, when driving or using machines account should be taken of the possible side effects, e.g. dizziness and impaired vision.

4.8 Undesirable effects
The following terminology has been used in order to classify the frequency of undesirable 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
Uncommon: Rash, urticaria (1), hypersensitivity
Rare: Anaphylactic reaction, angiooedema of tongue, lips, face

Nervous system disorders
Common: Headache, dizziness

Eye disorders
Uncommon: Ocular accommodation disturbances, angle closure glaucoma (2), (3)
Rare: Eye pain (2), mydriasis (2), intraocular pressure increased (2)

Cardiac disorders
Uncommon: Tachycardia
Rare: Palpitations, supraventricular tachycardia, atrial fibrillation

Respiratory, thoracic and mediastinal disorders
Common: Cough, local irritation, inhalation induced bronchospasm
Uncommon: Bronchospasm (other than paradoxical bronchospasm), pharyngeal oedema, dry throat
Rare: Laryngospasm

Gastro-intestinal disorders
Common: Dry mouth, vomiting, gastro-intestinal motility disorder (4), nausea
Uncommon: Stomatitis

Skin and subcutaneous disorders
Uncommon: Rash, pruritus

Renal and urinary disorders
Rare: Urinary retention (5)

Investigations
Rare: Intraocular pressure increased (2)
(1) including giant urticaria
(2) ocular effects – such as eye pain, mydriasis, angle closure glaucoma, increased intraocular pressure - have been reported when aerolised ipratropium bromide, either alone or in combination with an adrenergic beta-agonist, has come into contact with the eyes during nebuliser therapy – see section 4.4.
(3) Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be symptoms or signs of acute narrow-angle glaucoma.
(4) e.g. constipation, diarrhoea
(5) the risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Ipratropium bromide should be discontinued immediately, the patient should be assessed and alternative therapy instituted if necessary.

4.9 Overdose
No symptoms specific to over dosage have been encountered. In view of the wide therapeutic window and topical administration of Zulavent, no serious anticholinergic symptoms are to be expected. As with other anticholinergics, dry mouth, visual accommodation disturbances and tachycardia would be the expected symptoms and signs of overdose.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: drugs for obstructive airway diseases, other drugs for obstructive airway diseases, inhalants, anticholinergics.
ATC code: R03BB01

Ipratropium bromide is a competitive antagonist of muscarinic acetylcholine receptors. It prevents the activation of G-protein coupled receptors caused by the interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Due to its chemical property as quaternary ammonium compound inhaled ipratropium bromide acts selectively and locally on muscarinic acetylcholine receptors at the bronchial smooth muscle and leads to bronchodilation.

Ipratropium bromide is able to inhibit reflex-induced bronchoconstriction following exercise, inhalation of cold air and the early response to inhaled antigens. It also reverses the bronchoconstriction induced by inhaled cholinergic agonists.

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

5.2 Pharmacokinetic properties
Depending on the formulation and the inhalation technique, approximately 10-30 % of the inhaled dose reaches the lungs. The major part of the dose is swallowed.

Because of the negligible gastro-intestinal absorption, the bioavailability of the swallowed dose is only about 2 % of the total dose administered. The part of the dose that reaches the lungs has an almost complete systemic bioavailability and reaches the circulation within a few minutes.

From data on renal excretion (0-24 h) the total systemic bioavailability of inhaled ipratropium bromide is estimated to be 7-28 % (averages from three studies).

The kinetic parameters have been calculated from plasma concentrations after intravenous administration. The plasma concentration falls rapidly. The volume of distribution ($V_d$) is 338 l (approximately 4.6 l/kg). Ipratropium bromide has a low degree of protein binding (< 20 %). Because of its ammonium ion structure, ipratropium does not pass the blood-brain barrier. The elimination of ipratropium is biphasic. The half-life of the terminal elimination phase is about 1.6 hours.

The average total clearance has been estimated to be 2.3 l/min. About 60 % of the systemic available dose is metabolised, probably in the liver. The main metabolites that are found in the urine have a low affinity for muscarinic receptors and do not possess significant anticholinergic activity.

About 40 % of the systemic available dose is excreted via the kidneys, which corresponds to a renal clearance of 0.9 l/min.
From studies using radioactively labelled ipratropium bromide, less than 10 % of the dose (ipratropium bromide and metabolites) is excreted via bile and faeces. The major part of the radio labelled dose is excreted via the kidneys.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, or toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium chloride
Water for injections
Concentrated hydrochloric acid (for pH adjustment)

6.2 Incompatibilities
Zulavent and sodium cromoglycate nebuliser solution containing benzalkonium chloride should not be administered simultaneously in the same nebuliser as precipitation may occur.

6.3 Shelf life
Unopened: 3 years
After opening the ampoule: Use immediately; discard any unused contents.

6.4 Special precautions for storage
Do not store above 25 °C. Store in the original package.

6.5 Nature and contents of container
Sterile unit dose polyethylene ampoules containing either 1 ml or 2 ml of solution. Pack sizes: 10, 20, 50 or 60 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
For single use only. Use immediately after first opening the ampoules.
Discard immediately after first use.
Any unused product or waste material should be disposed of in accordance with local requirements.
For user instructions refer to section 4.2.

7 MARKETING AUTHORISATION HOLDER
Institut Dr. Zoeller
Kriemhildstr. 17
69469 Weinheim
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 14825/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/10/2011

10 DATE OF REVISION OF THE TEXT
26/10/2011
The leaflet text below is that agreed at the end of the Decentralised Procedure. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities, as appropriate.

PACKAGE LEAFLET: INFORMATION FOR THE USER

ZULAVENT 250 micrograms per ml nebuliser solution

ipratropium bromide

1 ml

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, asthma nurse or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, asthma nurse or pharmacist.

In this leaflet:
1. What ZULAVENT is and what it is used for
2. Before you use ZULAVENT
3. How to use ZULAVENT
4. Possible side effects
5. How to store ZULAVENT
6. Further information

1. WHAT ZULAVENT IS AND WHAT IT IS USED FOR

The full name of your medicine is ZULAVENT 250 micrograms per ml nebuliser solution. However the full name will be shortened to ZULAVENT in the general text of this leaflet.

ZULAVENT contains a medicine called ipratropium bromide. This belongs to a group of medicines called ‘bronchodilators’ which help to open up the air passages in your lungs so that you can breathe more easily. You use it with a device called a ‘nebuliser’. This changes your medicine into a mist for you to breathe in.

This medicine helps to make breathing easier in patients with asthma and other breathing difficulties such as chronic obstructive pulmonary disease (COPD). However ZULAVENT should not be used as the first treatment for acute wheezing, shortness of breath or tightness of the chest in adults, adolescents and children 6 years of age and older when a rapid response is required. A rapid-acting \( \beta_2 \) agonist bronchodilator or “reliever” medicine or “reliever” inhaler should be used.

However in children 5 years of age and younger ZULAVENT is ONLY used to treat acute episodes of asthma.

ZULAVENT can be used at the same time as salbutamol, a \( \beta_2 \) agonist bronchodilator or “reliever” medicine and also used for breathing problems.

2. BEFORE YOU USE ZULAVENT

Do not use ZULAVENT

- If you are allergic (hypersensitive) to ipratropium bromide or medicines, that are similar to ZULAVENT such as atropine
- If you are allergic to any of the other ingredients of ZULAVENT (these are listed in section ‘6. FURTHER INFORMATION’).

Do not use this medicine if either of the above apply to you. If you are not sure talk to your doctor, asthma nurse or pharmacist before using ZULAVENT.
Take special care with ZULAVENT
Talk to your doctor before using this medicine if any of the following apply to you:
- if you suffer from cystic fibrosis
- if you suffer from raised pressure in the eyes (glaucoma) or have been told that you may develop it, as you will need to make sure the mist does not get into your eyes
- if you are a man suffering from prostate problems
- if you have a condition which makes passing urine (passing water) difficult
- if you have heart problems
- if you have liver problems
- if you have kidney problems
- if you are pregnant, likely to get pregnant or if you are breast-feeding

Taking other medicines
Please tell your doctor, asthma nurse or pharmacist if you are taking or have recently taken other medicines, including medicines obtained without a prescription and herbal medicines. This is because ZULAVENT can affect the way some other medicines work. Also some other medicines can affect the way ZULAVENT works.
In particular, tell your doctor, asthma nurse or pharmacist if you are taking any of the following:
- other medicines for breathing problems called "beta2 agonist bronchodilators" or "reliever" medicines such as salbutamol or terbutaline
- medicines for breathing problems called "xanthines" such as theophylline or aminophylline
- medicines belonging to the same group as ZULAVENT (so-called "anticholinergic agents" such as atropine or hyoscymine)
If you are not sure if any of the above apply to you, talk to your doctor, asthma nurse or pharmacist before using ZULAVENT.

Pregnancy and breast-feeding
If you are pregnant, think that you might be pregnant, are planning to become pregnant or are breast-feeding talk to your doctor or asthma nurse. You should not use ZULAVENT unless your doctor tells you to.

If you become pregnant whilst using this medicine you should tell your doctor as soon as possible.

Driving and using machines
ZULAVENT has no known effects on the ability to drive and use machines.
However, if you do experience any side effects, such as dizziness or blurred vision, do not drive or operate machines and talk to your doctor, asthma nurse or pharmacist.

3. HOW TO USE ZULAVENT

For inhalation use,
ZULAVENT nebuliser solution should not be swallowed or given by injection.

Always use ZULAVENT exactly as your doctor has told you. You should check with your doctor, asthma nurse or pharmacist if you are not sure.

Your doctor or asthma nurse will tell you when and how often to use your nebuliser.

How much to take

Adults (including the elderly) and adolescents over 12 years
- The usual dose is the contents of 1 or 2 ampoules containing 250 micrograms in 1 ml, that is a dose of either 250 or 500 micrograms, inhaled from the nebuliser three to four times a day.
A larger ampoule is available, so if the dose required is 500 micrograms 1 ampoule containing 500 micrograms in 2 ml can be used.

If you are acutely wheezy or breathless you can take a dose of 500 micrograms which is made up from either 2 ampoules each containing 250 micrograms in 1ml OR 1 larger ampoule containing 500 micrograms in 2 ml.

The time between doses will be decided by your doctor or asthma nurse.

**Children 6-12 years**

- The usual dose is 1 ampoule (250 micrograms) up to a total daily dose of 4 ampoules (1000 micrograms).
- The time between doses should be decided by your doctor or asthma nurse.

**Children 0-5 years (for treatment of acute asthma only)**

- The usual dose is ½ to 1 ampoule (125-250 micrograms) up to a total daily dose of 4 ampoules (1000 micrograms).
- Doses should **NOT** be administered more frequently than every 6 hours.

When children are using ZULAVENT nebuliser solution they must be supervised at all times by a responsible adult.

In all cases, if breathlessness does not go away or becomes worse, tell your doctor or asthma nurse; if you feel that your breathing is getting worse rapidly you must contact your doctor immediately.

If your doctor or asthma nurse has told you to dilute the solution, use ONLY sterile sodium chloride 0.9% solution. ZULAVENT can be mixed with salbutamol nebuliser solution, another medicine for breathing problems called a "β2 agonist bronchodilator" or "reliever" medicine, in the same nebuliser chamber. The solution should be used as soon as possible after mixing with salbutamol nebuliser solution and any unused solution should be thrown away. Do **NOT** mix ZULAVENT with any other medicine.

**General instructions:**

ZULAVENT should be used with a suitable nebuliser (e.g. PARI LC Sprint). The mist produced is then preferably inhaled through a mouthpiece. If you are unable to inhale through a mouthpiece, you may use a face mask. Your doctor or asthma nurse will advise you on choosing an appropriate nebuliser and how it should be used.

When starting treatment with ZULAVENT the use of the nebuliser should be closely supervised by your doctor or asthma nurse.

Sometimes, this medicine is given using an intermittent positive pressure ventilator, in which case treatment will be started by your hospital specialist.

ZULAVENT has been studied using a PARI LC Sprint nebuliser. There is no information available on the use of ZULAVENT with other nebuliser systems. If an alternative untested nebuliser system is used your doctor may need to adjust your dose of ZULAVENT.

**How to use your nebuliser**

1. The nebuliser is operated with the PARI Junior BOY'S Compressor (Type 053) and should be prepared by following the manufacturer’s instructions.
2. Separate a new ampoule carefully from the strip (Diagram 1) and replace the rest of the strip back in the foil pack which is then placed back within the carton. **NEVER** use an ampoule which is already open.
3. Hold the ampoule upright and open by simply twisting off the top (diagram 2).
4. Release the closure on the nebuliser upper section by pressing your thumb against the underside of the cap.
5. Squeeze the quantity of solution prescribed by your doctor into the nebuliser chamber. If dilution of the ampoule contents is necessary, this should be done using ONLY sterile 0.9% sodium chloride solution as directed by your doctor.
6. Ensure that the nebuliser chamber is not filled with solution to a level higher than the upper scale marking (max level 8 ml).
7. Close the cap of the nebuliser. Make sure that the cap snaps into place. Ensure that all parts of the nebuliser are firmly connected to each other.
8. Use the nebuliser as directed by your doctor or asthma nurse. Sit in an upright position and relax. Switch the compressor on. Take the mouthpiece between your teeth and close your lips around it or press the mask lightly over mouth and nose. Breathe in through the mouthpiece or mask as slowly and deeply as possible and then out again in your own time.
9. For inhalation with babybend and babymask, swivel the bend so that it corresponds with the position of the baby or infant. Always hold the nebuliser upright. Switch the compressor on and press the mask gently but firmly over the mouth and nose. The infant or child should be allowed to breathe in and out in their own time.
10. The inhalation should be continued until the solution in the nebuliser chamber is used up (signalled by a change in the sound of the nebuliser).
11. Switch the compressor off as soon as you have finished the inhalation. Throw away any remaining solution from the nebuliser chamber.
12. Follow the manufacturer's instructions for cleaning the nebuliser. It is important that the nebuliser is kept clean.

Please read the full instructions for use of the nebuliser in the leaflet provided with PARI LC Sprint Junior before starting the inhalation.

Contact your doctor immediately if:
- You are not getting relief from your current dose of ZULAVENT or you feel that ZULAVENT is not working as well as usual or you feel that you need to use the nebuliser more than your doctor has recommended.
- Your breathing is getting worse
- Your chest feels tight

These are signs that your condition is not being controlled and you may need different or additional treatment.

Patients with kidney or liver problems
Please talk to your doctor before using ZULAVENT, if you suffer from kidney or liver problems.

If you use more ZULAVENT than you should
You may feel that your heart is beating faster than usual. You may have a dry mouth or problems with your eyes or vision.

Call your doctor immediately or go to the nearest hospital casualty department. Take ZULAVENT in its packaging with you, so that the doctor will know what you have taken. You should also take all other medicines and any inhalers that you take, including medicines bought from the pharmacy without a prescription, and in the original packaging, if possible.

If you forget to use ZULAVENT
- If you forget a dose, take it as soon as you remember.
- However, if it is nearly time for the next dose, skip the missed dose.
• Do not use a double dose to make up for the one that you missed.

If you stop using ZULAVENT
• This may make your condition worse.
• Do not stop using ZULAVENT unless your doctor tells you to do so.

If you have any further question on the use of this product, ask your doctor, asthma nurse or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ZULAVENT can cause side effects, although not everybody gets them.

Stop using ZULAVENT and see a doctor straight away, if you notice any of the following serious side effects - you may need urgent medical treatment:
• If after using ZULAVENT you are wheezy or have other difficulties in breathing, do not use any more (unless you have been told to by your doctor).
• Allergic reactions - the signs may include skin rash, itching and nettle rash (affects less than 1 in 100 people). In severe cases the signs include swelling of your tongue, lips and face, sudden difficulties in breathing, reduction of your blood pressure, tightening of your throat (affects less than 1 in 1000 people)
• If you feel your heart is beating unevenly or faster or stronger than usual (palpitations, atrial fibrillation or supraventricular tachycardia) (affects less than 1 in 1000 people)

Other side effects include:

Common (affects less than 1 in 10 people)
• Unexpected tightness of the chest, cough and local irritation when you have just used ZULAVENT
• Headache, dizziness
• Nausea (feeling sick), vomiting (being sick), diarrhoea or constipation
• Dry mouth

Uncommon (affects less than 1 in 100 people)
• Itching, skin rash, nettle rash (urticaria)
• Blurred vision, difficulty focusing or a specific eye disorder including visual halos, coloured images and red eyes (angle closure glaucoma)
• Allergy (hypersensitivity)
• Breathlessness due to airway constriction, swelling of the throat (pharyngeal oedema), dry throat
• Inflammation of oral mucosa ( stomatitis)

Rare (affects less than 1 in 1000 people)
• Problems passing water (urine), especially if you already have problems passing urine
• Eye pain, dilated pupils or increased pressure in the eyes
• Uncontrolled contraction of the vocal cords (laryngospasm)

If any of the solution or mist accidentally gets into your eyes you may get painful, stinging or red eyes, dilated pupils, blurred vision, see colours or lights. If you experience any eye problems due to mist getting into your eyes, talk to your doctor or asthma nurse for advice, immediately. If affected, do not drive or use any tools or machines. If you get problems with your eyes at any other time, talk to your doctor for advice.

If any of the side effects gets troublesome or serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, asthma nurse or pharmacist.
5. **HOW TO STORE ZULAVENT**

Keep out of the reach and sight of children.

Do not use ZULAVENT after the expiry date. This is stated on the ampoule label, foil sachet and carton after EXP. The expiry date refers to the last day of that month.

Do not store ZULAVENT above 25 °C. Store in the original package.

Each ampoule is for single use only and should be opened immediately before use. Discard any unused contents after each use.

Do not use ZULAVENT if you notice any cloudiness when the solution is poured into the nebuliser chamber. Discard the solution and wash the nebuliser cup before selecting a fresh ampoule for use.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What ZULAVENT contains**

- The active ingredient is ipratropium bromide
- 1 ml of the solution contains 250 micrograms of ipratropium bromide
- The other ingredients are sodium chloride, water for injections and hydrochloric acid (for pH adjustment of the nebuliser solution)

**What ZULAVENT looks like and contents of the pack**

Your medicine comes in the form of plastic ampoules containing a clear colourless solution to be nebulised (made into a fine mist for inhalation).

1 ampoule contains 1 ml of solution (corresponding to 250 micrograms of ipratropium bromide)

The ampoules are packed in strips of 10 inside a foil sachet which are then packed into a carton. Cartons are available in packs of 10, 20, 50 or 60 ampoules. Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**

Institut Dr. Zoeller
Kriemhildstr. 17
69469 Weinheim
Germany

**Manufacturer:**

LPU
Fraunhoferstraße 11a
82152 Martinsried
Germany

This medicinal product is authorised in the Member States under the following names:

- Austria: IPRABRONCH 250 Mikrogramm/ml Lösung für einen Venehler
- Germany: IPRABRONCH 250 Mikrogramm/ml Lösung für einen Venehler
- United Kingdom: ZULAVENT 250 Micrograms per ml nebuliser solution

This leaflet was last approved in 05/2011
PACKAGE LEAFLET: INFORMATION FOR THE USER

Zulavent 250 micrograms per ml nebuliser solution
iopratropium bromide
2 ml

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Zulavent is and what it is used for
2. Before you use Zulavent
3. How to use Zulavent
4. Possible side effects
5. How to store Zulavent
6. Further information

1. WHAT ZULAVENT IS AND WHAT IT IS USED FOR

The full name of your medicine is Zulavent 250 micrograms per ml nebuliser solution. However the full name will be shortened to Zulavent in the general text of this Leaflet.

Zulavent contains a medicine called iopratropium bromide. This belongs to a group of medicines called ‘bronchodilators’ which help to open up the air passages in your lungs so that you can breathe more easily. You use it with a device called a ‘nebuliser’. This changes your medicine into a mist for you to breathe in.

This medicine helps to make breathing easier in patients with asthma and other breathing difficulties such as chronic obstructive pulmonary disease (COPD). However Zulavent should not be used as the first treatment for acute wheezing, shortness of breath or tightness of the chest in adults, adolescents and children 6 years of age and older when a rapid response is required. A rapid-acting \( \beta_2 \) agonist bronchodilator or “reliever” medicine or “reliever” inhaler should be used.

However in children 5 years of age and younger Zulavent is ONLY used to treat acute episodes of asthma.

Zulavent can be used at the same time as salbutamol, a \( \beta_2 \) agonist bronchodilator or “reliever” medicine and also used for breathing problems.

2. BEFORE YOU USE ZULAVENT

Do not use Zulavent

- If you are allergic (hypersensitive) to iopratropium bromide or medicines, that are similar to Zulavent such as atropine
- If you are allergic to any of the other ingredients of Zulavent (these are listed in section 6. FURTHER INFORMATION).

Do not use this medicine if either of the above apply to you. If you are not sure talk to your doctor, asthma nurse or pharmacist before using Zulavent.
Take special care with Zulavent
Talk to your doctor before using this medicine if any of the following apply to you:
- if you suffer from cystic fibrosis
- if you suffer from raised pressure in the eyes (glaucoma) or have been told that you may develop it, as you will need to make sure the mist does not get into your eyes
- if you are a man suffering from prostate problems
- if you have a condition which makes passing urine (passing water) difficult
- if you have heart problems
- if you have liver problems
- if you have kidney problems
- if you are pregnant, likely to get pregnant or if you are breast-feeding

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken other medicines, including medicines obtained without a prescription and herbal medicines. This is because Zulavent can affect the way some other medicines work. Also some other medicines can affect the way Zulavent works.
In particular, tell your doctor or pharmacist if you are taking any of the following:
- other medicines for breathing problems called ‘β₂ agonist bronchodilators’ or “reliever” medicines such as salbutamol or terbutaline
- medicines for breathing problems called ‘xanthines’ such as theophylline or aminophylline
- medicines belonging to the same group as Zulavent (so-called ‘anticholinergic agents’ such as atropine or tiotropium)

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before using Zulavent.

Pregnancy and breast-feeding
If you are pregnant, think that you might be pregnant, are planning to become pregnant or are breast-feeding talk to your doctor or asthma nurse. You should not use Zulavent unless your doctor tells you to.
If you become pregnant whilst using this medicine you should tell your doctor as soon as possible.

Driving and using machines
Zulavent has no known effects on the ability to drive and use machines. However, if you do experience any side effects, such as dizziness or blurred vision, do not drive or operate machines and talk to your doctor or pharmacist.

3. HOW TO USE ZULAVENT

For inhalation use.
Zulavent nebuliser solution should not be swallowed or given by injection.

Always use Zulavent exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Your doctor or asthma nurse will tell you when and how often to use your nebuliser.

How much to take

Adults (including the elderly) and adolescents over 12 years
- The usual dose is the contents ¼ or 1 ampoules containing 500 micrograms in 2 ml, that is a dose of either 250 or 500 micrograms, inhaled from the nebuliser three to four times a day.
- A smaller ampoule is available so if the dose required is 250 micrograms 1 ampoule containing 250 micrograms in 1 ml can be used.
- If you are acutely wheezy or breathless you can take a dose of 500 micrograms which is made up from either 1 ampoule containing 500 micrograms in 2ml OR 2 smaller ampoules containing 250 micrograms in 1 ml.
- The time between doses will be decided by your doctor or asthma nurse.

**Children under 12 years**
- Not recommended for use, a smaller ampoule is available.

In all cases, if breathlessness does not go away or becomes worse, tell your doctor; if you feel that your breathing is getting worse rapidly you must contact your doctor immediately.

If your doctor has told you to dilute the solution, use ONLY sterile sodium chloride 0.9% solution. Zulavent can be mixed with salbutamol nebuliser solution, another medicine for breathing problems called a ‘β₂ agonist bronchodilator or “reliever” medicine in the same nebuliser chamber. The solution should be used as soon as possible after mixing with salbutamol nebuliser solution and any unused solution should be thrown away. Do NOT mix Zulavent with any other medicine.

**General instructions:**
Zulavent should be used with a suitable nebuliser (e.g. PARI LC Sprint). The mist produced is then preferably inhaled through a mouthpiece. If you are unable to inhale through a mouthpiece, you may use a face mask. Your doctor will advise you on choosing an appropriate nebuliser and how it should be used.

When starting treatment with Zulavent the use of the nebuliser should be closely supervised by your doctor or asthma nurse. Sometimes, this medicine is given using an intermittent positive pressure ventilator, in which case treatment will be started by your hospital specialist.
Zulavent has been studied using a PARI LC Sprint nebuliser. There is no information available on the use of Zulavent with other nebuliser systems. If an alternative untested nebuliser system is used your doctor may need to adjust your dose of Zulavent.

**How to use your nebuliser**

1. The nebuliser is operated with the PARI Junior BOY S Compressor (Type 053) and should be prepared by following the manufacturer's instructions.
2. Separate a new ampoule carefully from the strip (diagram 1) and replace the rest of the strip back in the foil pack which is then placed back within the carton. NEVER use an ampoule which is already open.

   ![Diagram 1](image1)

   ![Diagram 2](image2)

3. Hold the ampoule upright and open by simply twisting off the top (diagram 2).
4. Release the closure on the nebuliser upper section by pressing your thumb against the underside of the cap.
5. Squeeze the quantity of solution prescribed by your doctor into the nebuliser chamber. If dilution of the ampoule contents is necessary, this should be done using ONLY sterile 0.9% sodium chloride solution as directed by your doctor.
6. Ensure that the nebuliser chamber is not filled with solution to a level higher than the upper scale marking (max level 8 ml).
7. Close the cap of the nebuliser. Make sure that the cap snaps into place. Ensure that all parts of the nebuliser are firmly connected to each other.
8. Use the nebuliser as directed by your doctor. Sit in an upright position and relax. Switch the compressor on. Take the mouthpiece between your teeth and close your lips around it or press the mask lightly over mouth and nose. Breathe in through the mouthpiece or mask as slowly and deeply as possible and then out again in your own time.
9. The inhalation should be continued until the solution in the nebuliser chamber is used up (signalled by a change in the sound of the nebuliser).
10. Switch the compressor off as soon as you have finished the inhalation. Throw away any remaining solution from the nebuliser chamber.
11. Follow the manufacturer’s instructions for cleaning the nebuliser. It is important that the nebuliser is kept clean.

Please read the full instructions for use of the nebuliser in the leaflet provided with PARI LC Sprint Junior before starting the inhalation.

Contact your doctor immediately if:
- You are not getting relief from your current dose of Zulavent or you feel that Zulavent is not working as well as usual or you feel that you need to use the nebuliser more than your doctor has recommended.
- Your breathing is getting worse
- Your chest feels tight

These are signs that your condition is not being controlled and you may need different or additional treatment.

Patients with kidney or liver problems
Please talk to your doctor before using Zulavent, if you suffer from kidney or liver problems.

If you use more Zulavent than you should
You may feel that your heart is beating faster than usual. You may have a dry mouth or problems with your eyes or vision.

Call your doctor immediately or go to the nearest hospital casualty department. Take Zulavent in its packaging with you, so that the doctor will know what you have taken. You should also take all other medicines and any inhalers that you take, including medicines bought from the pharmacy without a prescription, and in the original packaging, if possible.
If you forget to use Zulavent
- If you forget a dose, take it as soon as you remember.
- However, if it is nearly time for the next dose, skip the missed dose.
- Do not use a double dose to make up for the one that you missed.

If you stop using Zulavent
- This may make your condition worse.
- Do not stop using Zulavent unless your doctor tells you to do so.

If you have any further question on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zulavent can cause side effects, although not everybody gets them.

Stop using Zulavent and see a doctor straight away, if you notice any of the following serious side effects: you may need urgent medical treatment:
- If after using Zulavent you are wheezy or have other difficulties in breathing, do not use any more (unless you have been told to by your doctor).
- Allergic reactions - the signs may include skin rash, itching and nettle rash (affects less than 1 in 100 people). In severe cases the signs include swelling of your tongue, lips and face, sudden difficulties in breathing, reduction of your blood pressure, tightening of your throat (affects less than 1 in 1000 people).
- If you feel your heart is beating unevenly or faster or stronger than usual (palpitations, atrial fibrillation or supraventricular tachycardia) (affects less than 1 in 1000 people).

Other side effects include:

Common (affects less than 1 in 10 people)
- Unexpected tightness of the chest, cough and local irritation when you have just used Zulavent.
- Headache, dizziness.
- Nausea (feeling sick), vomiting (being sick), diarrhoea or constipation.
- Dry mouth.

Uncommon (affects less than 1 in 100 people)
- Itching, skin rash, nettle rash (urticaria).
- Blurred vision, difficulty focusing or a specific eye disorder including visual halos, coloured images and red eyes (angle closure glaucoma).
- Allergy (hypersensitivity).
- Breathlessness due to airway constriction, swelling of the throat (pharyngeal oedema), dry throat.
- Inflammation of oral mucosa ( stomatitis).

 Rare (affects less than 1 in 1000 people)
- Problems passing water (urine), especially if you already have problems passing urine.
- Eye pain, dilated pupils or increased pressure in the eyes.
- Uncontrolled contraction of the vocal cords (laryngospasm).

If any of the solution or mist accidentally gets into your eyes you may get painful, stinging or red eyes, dilated pupils, blurred vision, see colours or lights. If you experience any eye problems due to mist getting into your eyes, talk to your doctor for advice, immediately. If affected, do not drive or use any tools or machines. If you get problems with your eyes at any other time, talk to your doctor for advice.

If any of the side effects gets troublesome or serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
5. HOW TO STORE ZULAVENT

Keep out of the reach and sight of children.

Do not use Zulavent after the expiry date. This is stated on the ampoule label, foil sachet and carton after EXP. The expiry date refers to the last day of that month.

Do not store Zulavent above 25°C. Store in the original package.

Each ampoule is for single use only and should be opened immediately before use. Discard any unused contents after each use.

Do not use Zulavent if you notice any cloudiness when the solution is poured into the nebuliser chamber. Discard the solution and wash the nebuliser cup before selecting a fresh ampoule for use.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Zulavent contains
- The active ingredient is ipratropium bromide
- 1 ml of the solution contains 250 micrograms of ipratropium bromide
- The other ingredients are sodium chloride, water for injections and hydrochloric acid (for pH adjustment of the nebuliser solution)

What Zulavent looks like and contents of the pack
Your medicine comes in the form of plastic ampoules containing a clear colourless solution to be nebulised (made into a fine mist for inhalation).

1 ampoule contains 2 ml of solution (corresponding to 500 micrograms of ipratropium bromide)

The ampoules are packed in strips of 10 inside a foil sachet which are then packed into a carton. Cartons are available in packs of 10, 20, 50 or 60 ampoules. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Institut Dr. Zoeller
Kriemhildstr. 17
69469 Weinheim
Germany

Manufacturer:
LPU
Fraunhoferstraße 11a
82152 Martinsried
Germany

This medicinal product is authorised in the Member States under the following names:
Austria: IPRABRONCH 250 Mikrogramm/ml Lösung für einen Vernebler
Germany: IPRABRONCH 250 Mikrogramm/ml Lösung für einen Vernebler
United Kingdom: ZULAVENT 250 Micrograms per ml nebuliser solution

This leaflet was last approved in: 05/2011
Module 4

The labelling text below is that agreed at the end of the Decentralised Procedure. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities, as appropriate.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOIL OVERWRAP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZULAVENT 250 micrograms per ml nebuliser solution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 micrograms in 1 ml</td>
</tr>
<tr>
<td>Each 1 ml ampoule contains 250 micrograms of ipratropium bromide.</td>
</tr>
<tr>
<td>500 micrograms in 2 ml</td>
</tr>
<tr>
<td>Each 2 ml ampoule contains 500 micrograms of ipratropium bromide.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Also contains sodium chloride, hydrochloric acid and water for injections.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ampoules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>For inhalation use.</td>
</tr>
<tr>
<td>Read the package leaflet carefully before use.</td>
</tr>
<tr>
<td>Use as directed by your doctor.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each ampoule is for single use only. Use immediately after first opening the ampoule. Discard any unused contents after first use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP (MM/YYYY)</td>
</tr>
</tbody>
</table>
9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Institut Dr. Zoeller
69469 Wenheim
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 14825/0002

13. MANUFACTURER’S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription. POM

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON

1. NAME OF THE MEDICINAL PRODUCT

ZULAVENT 250 micrograms per ml nebuliser solution
ipratropium bromide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

250 micrograms in 1 ml
Each 1 ml ampoule contains 250 micrograms of ipratropium bromide.

500 micrograms in 2 ml
Each 2 ml ampoule contains 500 micrograms of ipratropium bromide

3. LIST OF EXCIPIENTS

Also contains sodium chloride, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

10 ampoules
20 ampoules
50 ampoules
60 ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use.
Read the package leaflet carefully before use.
Use as directed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Each ampoule is for single use only. Use immediately after first opening the ampoule. Discard any unused contents after first use.

8. EXPIRY DATE

EXP {MM/YYYY}
9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25 °C. Store in the original package.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Institut Dr. Zoeller
69469 Weinheim
Germany

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 14825/0002

13. **MANUFACTURER'S BATCH NUMBER**

Batch

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.
POM

15. **INSTRUCTIONS ON USE**

Optional: pictogram of the pharmaceutical form or the route of administration

16. **INFORMATION IN BRAILLE**

ZULAVENT 1 ml

ZULAVENT 2 ml
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bundling label

1. NAME OF THE MEDICINAL PRODUCT

ZULAVENT 250 micrograms per ml nebuliser solution
ipratropium bromide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

(See Information on the box, which will remain visible after bundling)

3. LIST OF EXCIPIENTS

See 2.

4. PHARMACEUTICAL FORM AND CONTENTS

Bundle pack
20 (2x10) ampoules
50 (5x10) ampoules
60 (6x10) ampoules
60 (3x20) ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

See 2.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

See 2.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

See 2.

8. EXPIRY DATE

See 13.
9. SPECIAL STORAGE CONDITIONS

See 2.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Institut Dr. Zoeller
69469 Wemheim
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 14825/0002

13. MANUFACTURER’S BATCH NUMBER

EXP. Batch No. and further product information please find on box and leaflet.

14. GENERAL CLASSIFICATION FOR SUPPLY

See 2.

15. INSTRUCTIONS ON USE

See 2.

16. INFORMATION IN BRAILLE

See 2.
<table>
<thead>
<tr>
<th><strong>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMPOULES</strong></td>
</tr>
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<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ZULAVENT 250 mcg/ml nebuliser solution</td>
</tr>
<tr>
<td>ipratropium bromide</td>
</tr>
<tr>
<td>For inhalation use</td>
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</table>

<table>
<thead>
<tr>
<th><strong>2. METHOD OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>(see section 1)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>3. EXPIRY DATE</strong></th>
</tr>
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<tbody>
<tr>
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</table>

<table>
<thead>
<tr>
<th><strong>4. BATCH NUMBER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch {number}</td>
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</table>

<table>
<thead>
<tr>
<th><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml</td>
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<td>2 ml</td>
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<th><strong>6. OTHER</strong></th>
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Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Zulavent 250 micrograms per ml nebuliser solution (PL 14825/0002; UK/H/3401/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for the treatment of reversible:
• bronchospasm associated with chronic obstructive pulmonary disease (COPD)
• airways obstruction in patients with acute and chronic asthma, when used concomitantly with inhaled β₂ agonists.

This application was submitted using the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria and Germany as Concerned Member States (CMS). The application was submitted under Article 10.3 of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Atrovent 250 UDVs, 1ml and Atrovent UDVs, 2ml (Boehringer Ingelheim Limited, UK) which was first authorised in the UK on 27 August 1986.

Ipratropium bromide is a non-selective antagonist of the muscarinic receptors M₁, M₂, M₃, M₄, and M₅. Although ipratropium bromide blocks all five muscarinic receptor subtypes with similar affinity, it is likely that M₃-receptor antagonism alone accounts for the bronchodilating effect. However, the blockade of the M₂-receptor subtype allows further release of presynaptic acetylcholine and may antagonise the bronchodilatory effect of blocking the M₃-receptor.

No new non-clinical or clinical data have been submitted, which is acceptable given that this is a hybrid application based on an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 08 March 2011. After a subsequent national phase, a licence was granted in the UK on 26 October 2011.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Zulavent 250 micrograms per ml nebuliser solution</th>
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</thead>
<tbody>
<tr>
<td>Name of the active substance(s) (INN)</td>
<td>Ipratropium bromide</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Drugs for obstructive airway diseases, other drugs for obstructive airway diseases, inhalants, anticholinergics (R03BB01)</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Nebuliser solution; 250 micrograms/ml</td>
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<tr>
<td>Reference number for the Mutual Recognition Procedure</td>
<td>UK/H/3401/001/DC</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>Austria and Germany</td>
</tr>
<tr>
<td>Marketing Authorisation Number</td>
<td>PL 14825/0002</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Institut Dr. Zoeller</td>
</tr>
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<td>Kriemhildstr. 17</td>
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<td></td>
<td>69469 Weinheim</td>
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<td>Germany</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Ipratropium bromide

Chemical name: \((1R,3r,5S,8r)-3-[[2RS]-3-Hydroxy-2-phenylpropanoyl]oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide monohydrate\)

Structure:

![Ipratropium Bromide Structure](image)

Molecular formula: \(C_{20}H_{30}BrNO_{3}\cdot H_{2}O\)
Molecular mass: 430.4
Appearance: A white or almost white crystalline powder, soluble in water, freely soluble in methanol and slightly soluble in ethanol (96%).

Ipratropium bromide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance ipratropium bromide monohydrate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.
Medicinal Product
Other Ingredients
Other ingredients consist of the pharmaceutical excipients sodium chloride, water for injections and concentrated hydrochloric acid (for pH adjustment). Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development
The objective of the pharmaceutical development programme was to produce a safe, efficacious, product that was comparable in performance to the originator product, Atrovent UDVs 250 micrograms/ml Nebuliser Solution (Boehringer Ingelheim Limited, UK).

The physico-chemical properties of the drug product and the reference product, Atrovent 250 UDVs, 1ml and Atrovent UDVs, 2ml (Boehringer Ingelheim Limited, UK) have been found to be comparable.

Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro data have been provided for this product and the reference product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is supplied in sterile unit dose polyethylene ampoules containing either 1ml or 2ml of solution. The product is packaged with the Product Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 10x1ml, 10x2ml, 20x1ml, 20x2ml, 50x1ml, 50x2ml, 60x1ml and 60x2ml ampoules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging. All primary packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.

Suitable post approval commitment has been provided to submit data on analytical test methods used in the routine control of a component of the secondary packaging (the overwrap), as soon as it is available.
Stability of the product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been proposed for the unopened ampoule, with the storage conditions “Do not store above 25°C. Store in the original package.”

It has been stipulated that the medicine should be used immediately after opening the ampoule; unused contents should be discarded.

Bioequivalence
As the product provides local therapeutic activity (that is, not systemic), investigation of bioequivalence is not appropriate for this product.

Summary of Product Characteristics (SmPC), Patient Information Leaflets (PILs), Labels
The SmPC, PILs and labels are acceptable from a pharmaceutical perspective. Final text versions of the labelling and PIL have been provided. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities, as appropriate.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

MAA form
The MAA form is satisfactory.

Expert report
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of ipratropium bromide are well-known, no new non-clinical data have been submitted and none are required.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of a Marketing Authorisation is recommended.
III.3 CLINICAL ASPECTS

The clinical pharmacology of ipratropium bromide is well known.

No clinical studies have been conducted to support the application and none are required for an application of this type. Essential similarity with the originator product is based on the comparative quality attributes of the product. This application is being made under Article 10.3 (hybrid) of Directive 2001/83/EC, which states that bioequivalence cannot be demonstrated through bioavailability studies for products for local use intended to act without systemic absorption - in this case – after inhalant administration.

Efficacy

The efficacy profile of ipratropium bromide is well-known. Efficacy is reviewed in the clinical overview. No new efficacy data have been submitted and none are required for this application.

Safety

The safety profile of ipratropium bromide is well-known. The safety profile of ipratropium bromide is reviewed in the clinical overview. No new safety data have been submitted with this application and none are required.

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

Summary of Product Characteristics (SmPC), Product Information Leaflets (PILs), Labels

The SmPC, PILs and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the originator product. The PILs are consistent with the details in the SmPC and is in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion

The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Zulavent are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of ipratropium bromide are well-known, no additional data were required.

EFFICACY
No clinical studies have been conducted to support the application and none are required for an application of this type. Essential similarity with the originator product is based on the comparative quality attributes of the product. This application is being made under Article 10.3 (hybrid) of Directive 2001/83/EC, which states that bioequivalence cannot be demonstrated through bioavailability studies for products for local use intended to act without systemic absorption - in this case – after inhalant administration.

SAFETY
The safety profile of ipratropium bromide is well-known. No new safety data were submitted and none were required for this application.

PRODUCT LITERATURE
The SmPC, PILs and labelling are satisfactory and consistent with those for the originator product, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ipratropium bromide is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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