Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Duovent UDVs 0.5mg/1.25mg per 4ml Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4 ml single dose unit contains 0.5 mg of ipratropium bromide (as monohydrate) and 1.25 mg of fenoterol hydrobromide.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution
A clear, colourless or almost colourless solution, free from suspended particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The management of acute severe asthma or reversible obstructive airways disorders requiring treatment by nebuliser, in patients who have not responded sufficiently well to anticholinergic therapy or in situations where the $beta_2$ agonist alone has produced unacceptable levels of side effects.

4.2 Posology and method of administration

Adults:

The recommended dose for adults and children over 14 years is one vial (4 ml) three or at maximum four times daily.

Children:

Use in children below the age of 14 years is not recommended.

Use in children should be supervised by a responsible adult.

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

4.3 Contraindications

Hypertrophic obstructive cardiomyopathy, tachyarrhythmia. Hypersensitivity to fenoterol hydrobromide or atropine-like substances or to any of the excipients of the product.

4.4 Special warnings and precautions for use

It is dangerous to exceed the recommended dose.

In the case of acute, rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately.

For prolonged use, on demand (symptom-oriented) treatment may be preferable to regular use. Patients should be

evaluated for the addition or the increase of anti-inflammatory therapy (e.g. inhaled corticosteroids) to control airway inflammation and to prevent deterioration of disease control.

The use of increasing amounts of $beta_2$-agonist containing products such as Duovent on a regular basis to control symptoms of bronchial obstruction may suggest declining disease control. If bronchial obstruction deteriorates it is inappropriate and possibly hazardous to simply increase the use of $beta_2$-agonist containing products such as Duovent, beyond the recommended dose over extended periods of time. In this situation, the patient's therapy plan, and in particular the adequacy of anti-inflammatory therapy with inhaled corticosteroids should be reviewed to prevent potentially life threatening deterioration of disease control.

Other sympathomimetic bronchodilators should only be used with Duovent under medical supervision.

In the following conditions Duovent should only be used after careful risk/benefit assessment, especially when doses higher than recommended are used: Insufficiently controlled diabetes mellitus, myocardial insufficiency, angina, cardiac dysrhythmias, hypertension recent myocardial infarction, hypertrophic subvalvular aortic stenosis, severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma.

Cardiovascular effects may be seen with sympathicomimetic drugs, including DUOVENT. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta-agonists. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving DUOVENT, should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be either respiratory or cardiac origin.

Potentially serious hypokalaemia may result from $beta_2$-agonist therapy.

Duovent should be used with caution in patients with prostatic hyperplasia or bladder neck obstruction or predisposed to or with narrow-angle glaucoma.

Users must be adequately instructed in the correct method of use of the nebuliser and the medication. Care should be taken to prevent the solution or mist from entering the eyes. It is recommended that the nebulised solution be administered via a mouth piece. 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.

There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic $beta_2$-agonist, was sprayed into the eyes.

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

Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.

Ipratropium bromide may cause reduced salivation leading to dry mouth.

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

4.5 Interaction with other medicinal products and other forms of interaction

Other beta-adrenergics and 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 (e.g. theophylline) may increase the adverse reactions.

ß-adrenergic blocking agents may antagonise fenoterol hydrobromide and potentially seriously reduce the bronchodilator effect if administered concurrently.

Beta-agonist induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, corticosteroids and diuretics. This should be taken into account particularly in patients with severe airway obstruction.

Hypokalaemia may result in an increased susceptibility to arrhythmias in patients receiving digoxin. Additionally, hypoxia may aggravate the effect of hypokalaemia on cardiac rhythm. It is recommended that serum potassium levels are monitored in such situations.

In those patients receiving sympathomimetic amines and monoamine oxidase inhibitors or tricyclic antidepressants, the product should be administered with care.

Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may increase the susceptibility to the cardiovascular effects of beta-agonists.

4.6 Fertility, pregnancy and lactation

This product should be used during pregnancy only if considered essential by the physician.

Beta-adrenergic agents have been shown to prolong pregnancy and inhibit labour. The inhibitory effect of fenoterol hydrobromide on uterine contraction should be taken into account.

Preclinical studies have shown that fenoterol hydrobromide is secreted in breast milk. It is not known whether ipratropium is excreted into breast milk. It is unlikely that ipratropium would reach the infant to an important extent, however caution should be exercised when DUOVENT is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

The following side effects have been reported. The frequencies given below are based on clinical trials involving 2009 patients who have been treated with fenoterol and ipratropium combinations.

Frequencies

Very common	≥ 1/10
Common	≥ 1/100 < 1/10
Uncommon	≥ 1/1,000 < 1/100
Rare	≥ 1/10,000 < 1/1000
Very rare	< 1/10,000
Not known	Cannot be estimated from the available data

Immune system disorders	
Anaphylactic reaction (1)	Rare (1)
Allergic type reactions	Rare
Angio-oedema of tongue, lips, and face	Not Known
Metabolism and nutrition disorders	
Hypokalaemia	Not Known
Psychiatric disorders	
Psychological alterations	Rare
Nervousness	Rare
Nervous System Disorders	
Headache	Rare
Dizziness	Rare
Fine Tremor	Rare
Eye Disorders	
Narrow angle Glaucoma (2)	Rare
Ocular accommodation disturbances	Not Known
Increased intraocular pressure(2)	Not Known
Eye pain(2)	Not Known
Mydriasis (2)	Not Known
Cardiac Disorders	
Tachycardia, increased heart rate	Uncommon
Arrhythmias	Uncommon
Atrial fibrillation	Rare
Palpitations	Rare
Supraventricular Tachycardia	Not known
Decrease in diastolic blood pressure	Not Known
Increase in systolic blood pressure	Not Known
Myocardial ischaemia	Not Known
Respiratory, Thoracic and Mediastinal Disorders	
Cough	Common (3)
Local Irritation	
-Pharyngitis	Common (3)
-Throat irritation	Rare (3)
Laryngospasm(1)	Rare (1)
Inhalation induced bronchospasm	Not Known
Gastro-intestinal Disorders	
Dryness of mouth	Uncommon
Nausea	Uncommon
Gastro-intestinal motility disturbances (4)	Uncommon
Skin and subcutaneous Disorders	
Skin reactions	Uncommon
Skin rash	Rare
Uticaria	Rare

Sweating	Not known

Musculosceletal and Connective Tissue Disorders

Myalgia	Rare
Muscle cramps	Rare
Weakness (muscle)	Not Known

Renal and Urinary Disorders

Urinary Retention	Rare

(1) Observed in trials with the mono-compound ipratropium bromide

(2) There have been isolated reports of ocular complications (i.e. mydriasis, increased intra-ocular pressure, narrow angle glaucoma, eye pain) when aerosolized ipratopium bromide either alone or in combination with an adrenergic $beta_2$-agonist was sprayed into the eyes – see section 4.4.

(3) verum frequency only for local side effects

(4) e.g. constipation, diarrhoea, vomiting

4.9 Overdose

Symptoms
The effects of overdosage are expected to be primarily related to fenoterol. The expected symptoms with overdosage are those of excessive beta-adrenergic-stimulation, the most prominent being tachycardia, palpitation, hypertension, hypotension, widening of the pulse pressure, anginal pain, arrhythmias, flushing, nausea, restlessness, dizziness, headache and tremor. Hypokalaemia may occur following overdosage with fenoterol. Serum potassium levels should be monitored.
Expected symptoms of overdosage with ipratropium bromide (such as dry mouth, visual accommodation disorder) are mild because the systemic availablility of inhaled ipratropium is very low.

Therapy
The administration of sedatives/tranquillisers may be necessary, however, should only be performed where resuscitation equipment is available due to the risk of respiratory depression. In severe cases intensive therapy in an appropriate unit may be necessary.

$Beta_1$-selective beta-adrenergic blocking agents should be chosen and blood pressure should be monitored. Should the administration of a beta-adrenergic blocking agent be considered necessary to counteract the effects of overdosage, its use in a patient liable to bronchospasm should be carefully monitored because of the risk of precipitating severe bronchospasm, which may be fatal.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

DUOVENT contains two active bronchodilating ingredients: ipratropium bromide, exhibiting an anticholinergic effect and feneterol hydrobromide a beta-adrenergic agent.

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In preclinical studies, it appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of cyclic guanosine monophosphate(cyclic GMP) caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle.

In controlled up to 90 day studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) significant improvements in pulmonary function (FEV_1 and $FEF_{25-75\%}$ increases of 15% or more) occurred within 15 minutes, reached a peak in 1-2 hours, and persisted in the majority of patients up to 6 hours.

In controlled up to 90 day studies in patients with bronchospasm associated with asthma, significant improvements in pulmonary function (FEV_1 increases of 15% or more) occurred in 40% of the patients.

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

Fenoterol hydrobromide is a direct acting sympathomimetic agent, selectively stimulating $beta_2$-receptors in the therapeutic dose range. The stimulation of $beta_1$-receptors comes into effect at a higher dose range. Occupation of $beta_2$-receptors activates adenyl cyclase via a stimulatory G_s-protein. The increase in cyclic AMP activates protein kinase A which then phosphorylates target proteins in smooth muscle cells. This in turn leads to the phosphorylation of myosin light chain kinase, inhibition of phosphoinositide hydrolysis, and the opening of large-conductance calcium-activated potassium channels.

Fenoterol relaxes bronchial and vascular smooth muscle and protects against bronchoconstricting stimuli such as histamine, methacholine, cold air, and allergen (early response). After acute administration the release of bronchoconstricting and proinflammatory mediators from mast cells is inhibited. Further, an increase in mucocillary clearance has been demonstrated after administration of higher doses of fenoterol.

Higher plasma concentrations, which are more frequently achieved with oral, or even more so, with intravenous administration inhibit uterine motility. Also at higher doses, metabolic effects are observed: Lipolysis, glycogenolysis, hyperglycemia and hypokalemia, the latter caused by increased K^+ uptake primarily in skeletal muscle. Beta-adrenergic effects on the heart such as increase in heart rate and contractility, are caused by the vascular effects of fenoterol, cardiac $beta_2$-receptor stimulation, and at supratherapeutic doses, by $beta_1$-receptor stimulation. As with other beta-adrenergic agents, QTc prolongations have been reported. For fenoterol these were discrete and observed at doses higher than recommended. The clinical significance has not been established. Tremor is a more frequently observed effect of beta-antagonists. Unlike the effects on the bronchial smooth muscle, the systemic effects of β-agonists are subject to the development of tolerance.

In clinical studies fenoterol was shown to be highly efficacious in manifest bronchospasm. It prevents bronchoconstriction following exposure to various stimuli such as exercise, cold air, and the early response following allergen exposure.

Concurrent use of these two active ingredients dilates the bronchi by affecting different pharmacological sites of action. The two active substances thus complement each other in their spasmolytic action on the bronchial muscles and allow a broad therapeutic use in the field of bronchopulmonary disorders associated with constriction of the respiratory tract. The complementary action is such that only a very low proportion of the β-adrenergic component is needed to obtain the desired effect, facilitating individual dosage suited to each patient with a minimum of adverse reactions.

In patients with asthma and with COPD studies with the metered aerosol have shown that DUOVENT is as efficacious as double the dose of fenoterol administered without ipratropium but is better tolerated in cumulative dose response studies. In adequately sized studies in patients with asthma or COPD better efficacy compared to its components ipratropium or fenoterol was demonstrated.

In acute asthma the combination of fenoterol and ipratropium is effective shortly after administration and has been shown to be more efficacious than each of its components.

5.2 Pharmacokinetic properties

About 16% of the dose are deposited in the respiratory tract following inhalation by metered aerosol. The remaining portion is being swallowed.

The active ingredients (fenoterol hydrobromide and ipratropium bromide) are absorbed very quickly from the respiratory tract. The peak plasma concentrations are reached only minutes after inhalation. There is no evidence that the pharmacokinetics of both ingredients in the combination differ from those of the monosubstance.

Fenoterol hydrobromide
The swallowed portion is mainly metabolised to sulfate conjugates. The absolute bioavailability following oral administration is low (approx. 1.5%). Following intravenous administration three phases were observed, whereby the terminal half-life was approximately 3 hours. Fenoterol and its conjugates are rapidly excreted renally (renal clearance: 267 ml/min). About 40% of the drug is bound to plasma proteins. In its non-metabolised state, fenoterol hydrobromide can slowly pass through the placenta and enter the maternal milk.

Ipratropium bromide
The absolute bioavailability after oral administration is low (approx. 2%). Following intravenous administration a rapid biphasic decline in plasma is noted for ipratropium. The terminal half-life was about 1.6 hours. The total clearance of the active ingredient is 2.3 L/min. Approximately 40% of the clearance is renal (0.9 L/min) and 60% non-renal i.e. mainly hepato-metabolic. The main metabolites found in urine bind poorly to the muscarinic receptor. Forty-six percent of the active ingredient are excreted renally after intravenous administration, 4.4% - 13.1% after inhalation from a metered dose inhaler are excreted as unchanged compound in urine. The drug is minimally (less than 20%) bound to plasma proteins. The ipratropium ion does not cross the blood-brain barrier. It is not known if the placental barrier is crossed.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

As the product contains no preservative, a fresh vial should be used for each dose and the vial should be opened immediately before administration. Any solution left in the vial should be discarded.

6.4 Special precautions for storage

Store below 25°C. Keep the vials in the outer carton.

6.5 Nature and contents of container

Low density polyethylene (LDPE) vials formed in strips of 10 packed into cartons containing 20 or 60 vials. Each vial contains 4 ml of solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Limited
Ellesfield Avenue
Bracknell, Berkshire
RG12 8YS
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 7/34/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th December 1993

Date of last renewal: 2nd October 2007

10 DATE OF REVISION OF THE TEXT

May 2011