Duovent®

Boehringer Ingelheim

COMPOSITION

DUOVENT® nebuliser solution in unit dose vials (UDVs)

1 unit dose vial (= 4 ml solution for inhalation) contains

(8r)-3α-hydroxy-8-isopropyl-1αH,5αH-tropanium bromide (±)-tropate monohydrate
(= ipratropium bromide) corresponding to 500 mcg ipratropium bromide anhydrous 522mcg

1-(3,5-dihydroxy-phenyl)-2-[[1-(4-hydroxy-benzyl)-ethyl]-amino]-ethanol hydrobromide
(= fenoterol hydrobromide) 1250mcg

Excipients: sodium chloride, hydrochloric acid, water purified

DESCRIPTION

Clear, colourless or almost colourless liquid, free from suspended particles and filled into polyethylene unit dose vials

PHARMACOLOGICAL PROPERTIES

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

ATC code: R03AL01

Mode of action

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

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In non-clinical studies, it inhibits vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of Ca++ which is caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Ca++ release is mediated by the second messenger system consisting of IP3 (inositol triphosphate) and DAG (diacylglycerol).

The bronchodilatation following inhalation of ipratropium bromide is primarily a local, site-specific effect, not a systemic one.

Non-clinical 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 hydrobromide 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 pro-inflammatory mediators from mast cells is inhibited. Further, an increase in mucociliary clearance has been demonstrated after administration of doses of fenoterol (0.6 mg).

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, hyperglycaemia and hypokalaemia, the latter caused by increased K^+-uptake primarily into 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 metered dose inhalers these were discrete and observed at doses higher than recommended. However, systemic exposure after administration with nebulisers (nebuliser solution, nebuliser solution in unit dose vials) might be higher than with recommended MDI doses. The clinical significance has not been established. Tremor is a more frequently observed effect of beta-agonists. Unlike the effects on the bronchial smooth muscle, the systemic effects on skeletal muscle of ß-agonists are subject to the development of tolerance.

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 ß-adrenergic component is needed to obtain the desired effect, facilitating individual dosage suited to each patient with a minimum of adverse reactions.

Clinical trials

Clinical efficacy and safety

In patients with asthma and COPD, better efficacy compared to its components ipratropium or fenoterol was demonstrated. Two studies (one with asthma patients, one with COPD patients) have shown that DUOVENT® is as efficacious as double the dose of fenoterol administered without ipratropium but was better tolerated in cumulative dose response studies.

In acute bronchoconstriction DUOVENT® is effective shortly after administration and is therefore also suitable for treating acute episodes of bronchospasm.

Pharmacokinetics

The therapeutic effect of the combination ipratropium bromide and fenoterol hydrobromide is produced by a local action in the airway. The pharmacodynamics of the bronchodilation are therefore not related to the pharmacokinetics of the active constituents of the preparation.

Following inhalation 10 to 30% of a dose is generally deposited in lungs, depending on the formulation, inhalation technique and device, while the remainder of the delivered dose is deposited in the mouthpiece, mouth and the upper part of the respiratory tract (oropharynx). A similar amount of the dose is deposited in the respiratory tract following inhalation by metered aerosol with HFA 134a propellant. In particular after inhalation of the aqueous solution via the RESPIMAT inhaler, a more than 2-fold higher lung deposition is experimentally observed as compared to the metered aerosol inhaler. The oropharyngeal deposition is correspondingly decreased and is significantly lower for the RESPIMAT inhaler as compared to the metered aerosol inhaler. The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes). The amount of the active substance deposited in the oropharynx is slowly swallowed and passes the gastrointestinal tract. Therefore the systemic exposure is a function of both oral and lung bioavailability.

There is no evidence that the pharmacokinetics of both ingredients in the combination differ from those of the mono-substance.

Fenoterol hydrobromide

Absorption

The absolute bioavailability following oral administration is low (approx. 1.5%).

The absolute bioavailability of fenoterol following inhalation is 18.7%. Absorption from the lung follows a biphasic course. 30% of the fenoterol hydrobromide dose is rapidly absorbed with a half-life of 11 minutes and 70% is slowly absorbed with a half-life of 120 minutes.

Distribution

Fenoterol distributes widely throughout the body. About 40% of the drug are bound to plasma proteins. In this 3-compartment model the apparent volume distribution of fenoterol at steady state (Vdss) is approximately 189 L (≈ 2.7 L/kg)

Non-clinical studies with rats revealed that fenoterol and its metabolites do not cross the blood-brain barrier.

Biotransformation
Fenoterol undergoes extensive metabolism by conjugation to glucuronides and sulphates in humans. Following oral administration, fenoterol is metabolised predominantly by sulphation. This metabolic inactivation of the parent compound starts already in the intestinal wall.

Elimination
After inhalation via BERODUAL® metered dose inhaler approximately 1% of an inhaled dose is excreted as free fenoterol in the 24-hour urine. Based on these data, the total systemic bioavailability of inhaled doses of fenoterol hydrobromide is estimated at 7%. Fenoterol has a total clearance of 1.8 L/min and a renal clearance of 0.27 L/min.

Kinetic parameters describing the disposition of fenoterol were calculated from plasma concentrations after i.v. administration. Following intravenous administration, plasma concentration-time profiles can be described by a 3-compartment model, whereby the terminal half-life is approximately 3 hours.

Following oral administration, total radioactivity excreted in urine was approximately 39% of dose and total radioactivity excreted in faeces was 40.2% of dose within 48 hours.

Ipratropium bromide
Absorption
Cumulative renal excretion (0-24 hrs) of ipratropium (parent compound) is below 1% of an oral dose and approximately 3 to 13% of an inhaled dose via BERODUAL® metered dose inhaler. Based on these data, the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 28% respectively. Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.

Distribution
Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after i.v. administration. A rapid biphasic decline in plasma concentrations is observed. The apparent volume of distribution at steady-state (Vdss) is approximately 176 L (≈ 2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Non-clinical studies with rats and dogs, revealed that the quarternary amine ipratropium does not cross the blood-brain barrier.
Binding of the main urinary metabolites to the muscarinic receptor is negligible and the metabolites have to be regarded as ineffective.

Biotransformation
After intravenous administration approximately 60% of a dose is metabolised, the major portion probably in the liver by oxidation.

Elimination
The half-life of the terminal elimination phase is approximately 1.6 hours. Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min.
In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 88.5% following oral dosing and 69.4% after inhalation.

INDICATIONS
DUOVENT® is a bronchodilator for the prevention and treatment of symptoms in chronic obstructive airway disorders with reversible airflow limitation such as bronchial asthma and especially chronic bronchitis with or without emphysema. Concomitant anti-inflammatory therapy should be considered for patients with bronchial asthma and steroid responsive chronic obstructive pulmonary disease (COPD).

DOSAGE AND ADMINISTRATION
Treatment should be initiated and administered under medical supervision, e.g. in the hospital setting. Home based treatment can be recommended in exceptional cases (severe symptoms or experienced patients requiring higher

doses) when a low dose rapid acting beta-agonist bronchodilator such as BERODUAL® metered dose inhaler has been insufficient in providing relief after consultation with an experienced physician.

It can also be recommended in patients who are in need for nebuliser treatment for other reasons e.g. handling issues of MDI or requirement of higher doses in experienced patients.

The treatment with the nebuliser solution in UDVs should always be started with the lowest recommended dose (1 UDV). In very severe cases, two unit dose vials may be required for symptom relief. The dosage should be adapted to the individual requirements and tailored according to the severity of the acute episode. Administration should be stopped when sufficient symptom relief is achieved.

The following dosages are recommended for adults (including elderly patients) and adolescents > 12 years:

Acute episodes of bronchospasm

1 unit dose vial is sufficient for prompt symptom relief in most cases, typically the hospital-based treatment of moderate to severe asthma attacks or the home- and hospital-based treatment of patients with moderate to severe COPD.

In very severe cases, two unit dose vials may be required for symptom relief.

These should be administered under medical supervision.

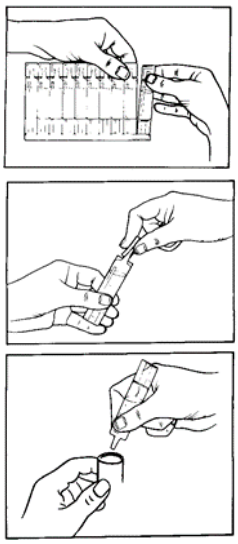
Children ≤ 12 years:
Because of insufficient information the general use in children ≤12 years of age is not recommended.

INSTRUCTIONS FOR USE
This solution is ready for use and requires no dilution.

The unit dose vials are intended only for inhalation with suitable nebulising devices and must not be taken orally or administered parenterally.

DUOVENT® nebuliser solution can be administered using a range of commercially available nebulising devices. The lung and systemic drug exposure is dependent on the nebuliser used and may be higher than with BERODUAL® metered dose inhaler depending on the efficiency of the device.

Where wall oxygen is available the solution is best administered at a flow rate of 6 - 8 litres per minute.
The instructions provided by the manufacturer of the nebulising device for proper care, maintenance and cleaning of the equipment should be followed.



1. Prepare the nebuliser for filling, according to the instructions provided by the manufacturer or physician.
2. Tear one unit dose vial from the strip.
3. Open the unit dose vial by firmly twisting the top.
4. Squeeze the content of the unit dose vial into the nebuliser reservoir.
5. Assemble the nebuliser and use as directed.
6. After use throw away any solution left in the reservoir and clean the nebuliser, following the manufacturer's instructions.

Since the unit dose vials contain no preservative, it is important that the contents are used soon after opening and that a fresh vial is used for each administration to avoid microbial contamination. Partly used, opened or damaged unit dose vials should be discarded.

CONTRAINDICATIONS

DUOVENT® is contraindicated in patients with known hypersensitivity to fenoterol hydrobromide or atropine-like substances or to any of the excipients of the product. DUOVENT® is also contraindicated in patients with hypertrophic obstructive cardiomyopathy and tachyarrhythmia.

SPECIAL WARNINGS AND PRECAUTIONS

Hypersensitivity

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

Paradoxical bronchospasm

As with other inhaled medicines DUOVENT®, may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs DUOVENT®, should be discontinued immediately and substituted with an alternative therapy.

Ocular complications

DUOVENT® should be used with caution in patients predisposed to narrow-angle glaucoma.

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

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

Thus patients must be instructed in the correct administration of DUOVENT®. Care must be taken not to allow the product to enter the eyes.

It is recommended that the nebulised solution is 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.

Systemic effects

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, recent myocardial infarction, severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma, or with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-neck obstruction).

Cardiovascular effects
Cardiovascular effects may be seen with sympathomimetic 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 of either respiratory or cardiac origin.

Hypokalaemia
Potentially serious hypokalaemia may result from beta$_2$-agonist therapy (see also section Overdose).

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

Dyspnoea
In the case of acute, rapidly worsening dyspnoea, a physician should be consult immediately.

Prolonged use
- In patients with bronchial asthma DUOVENT® should be used only on an as-needed basis. In patients with mild COPD on demand (symptom-oriented) treatment may be preferable to regular use.
- The addition or the increase of anti-inflammatory therapy to control airway inflammation and to prevent deterioration of disease control should be considered for patients with bronchial asthma and with steroid-responsive COPD.

The use of increasing amounts of beta$_2$-agonists 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.

Concomitant use with other sympathomimetic bronchodilators
Other sympathomimetic bronchodilators should only be used with DUOVENT® under medical supervision (see section Interactions).

Doping warning
The use of DUOVENT® may lead to positive results with regard to fenoterol in tests for non-clinical substance abuse, e.g. in the context of athletic performance enhancement (doping).

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

Other beta-adrenergics, anticholinergics and xanthine derivatives (such as theophylline) may enhance the bronchodilatatory effect. The concurrent administration of other beta-mimetics, systemically available anticholinergics and xanthine derivatives (e.g. theophylline) may increase the adverse reactions.

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

Hypokalaemia induced by beta$_2$-agonists 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 effects of hypokalaemia on cardiac rhythm. It is recommended that serum potassium levels are monitored in such situations.

$Beta_2$-agonist containing medicinal products should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta-adrenergic agonists may be enhanced.

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

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Non-clinical data, combined with available experience in humans have shown no evidence of adverse effects in pregnancy of fenoterol or ipratropium. Nonetheless, the usual precautions regarding the use of drugs during pregnancy, especially during the first trimester, should be exercised.
The inhibitory effect of fenoterol on uterine contraction should be taken into account.

Lactation

Non-clinical studies have shown that fenoterol hydrobromide**,** is excreted into breast milk. It is unknown whether ipratropium is excreted into breast milk. But it is unlikely that ipratropium would reach the infant to an important extent, especially when taken by aerosol. However, caution should be exercised when DUOVENT® is administered to a nursing woman.

Fertility

Clinical data on fertility are neither available for the combination of ipratropium bromide and fenoterol hydrobromide nor for each of the two components of the combination. Non-clinical studies performed with the individual components ipratropium bromide and fenoterol hydrobromide showed no adverse effect on fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that they may experience undesirable effects such as dizziness, tremor, accommodation disorder, mydriasis and blurred vision during treatment with DUOVENT®. Therefore, caution should be recommended when driving a car or operating machinery.

SIDE EFFECTS

Summary of the safety profile

Many of the listed undesirable effects can be assigned to the anticholinergic and beta-adrenergic properties of DUOVENT®. As with all inhalation therapy DUOVENT® may show symptoms of local irritation.

The most frequent side effects reported in clinical trials were cough, dry mouth, headache, tremor, pharyngitis, nausea, dizziness, dysphonia, tachycardia, palpitations, vomiting, blood pressure systolic increased and nervousness.

Summary of adverse reactions

The following adverse reactions have been reported during use of DUOVENT® in clinical trials and during the post-marketing experience.

Immune system disorders

- anaphylactic reaction
- hypersensitivity

Metabolism and nutritional disorders

- hypokalemia

Psychiatric disorders

- nervousness
- agitation
- mental disorder

Nervous system disorders

- headache
- tremor
- dizziness

Eye disorders

- glaucoma
- intraocular pressure increased
- accommodation disorder
- mydriasis
- vision blurred
- eye pain
- corneal oedema
- conjunctival hyperaemia
- halo vision

Cardiac disorders

- tachycardia, heart rate increased
- palpitations
- arrhythmia
- atrial fibrillation
- supraventricular tachycardia
- myocardial ischaemia

Respiratory, thoracic and mediastinal disorders

- cough
- pharyngitis
- dysphonia
- bronchospasm
- throat irritation
- pharyngeal oedema
- laryngospasm
- bronchospasm paradoxical
- dry throat

Gastrointestinal disorders

- vomiting
- nausea
- dry mouth
- stomatitis
- glossitis
- gastrointestinal motility disorder
- diarrhoea
- constipation
- oedema mouth

Skin and subcutaneous tissue disorders

- urticaria
- rash
- pruritus
- angioedema
- hyperhidrosis

Musculoskeletal and connective tissue disorders

- muscular weakness
- muscle spasms
- myalgia

Renal and urinary disorders

- urinary retention

Investigations

- blood pressure systolic increased
- blood pressure diastolic decreased

OVERDOSE

Symptoms

The effects of overdose are expected to be primarily related to fenoterol.
The expected symptoms with overdose are those of excessive beta-adrenergic-stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, arrhythmias, and flushing. Metabolic acidosis and hypokalaemia have also been observed with fenoterol when applied in doses higher than recommended for the approved indications of DUOVENT®.

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

Therapy

Treatment with DUOVENT® should be discontinued. Acid base and electrolyte monitoring should be considered. Administration of sedatives and in severe cases intensive care treatment may be needed.
Beta-receptor blockers, preferably $beta_1$-selective, are suitable as specific antidotes; however, a possible increase in bronchial obstruction must be taken into account and the dose should be adjusted carefully in patients suffering from bronchial asthma or COPD because of the risk of precipitating severe bronchospasm, which may be fatal.

AVAILABILITY

Box of 60's

STORAGE CONDITION

Store below 30^0C.

Please refer to the packaging for information on shelf-life.

MANUFACTURED BY

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Amiens Cedex 2, France
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

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