4.3 Contra-indications

Hypersensitivity to the active substances or to other atropine like substances or to any of the excipients. Hypertrophic obstructive cardiomyopathy or tachyarrhythmia.

Berodual® metered aerosol (CFC), Duovent® metered aerosol (CFC)
Only for countries with soya lecithin as emulsifier:
BERODUAL/DUOVENT metered aerosol should not be taken in patients with a history of hypersensitivity to soya lecithin or related food products such as soybean and peanut.

4.4 Special warnings and precautions for use

Immediate hypersensitivity reactions may occur after administration of BERODUAL/DUOVENT, as demonstrated by rare cases of urticaria, angio-oedema, rash, bronchospasm and oropharyngeal oedema and anaphylaxis.
In the case of acute, rapidly worsening of dyspnoea the patient should be advised that a doctor should be consulted immediately.
In the following conditions BERODUAL/DUOVENT should only be used after careful risk/benefit assessment, especially when doses higher than recommended are used: in insufficiently controlled diabetes mellitus, recent myocardial infarction, severe organic heart or vascular disorders, hyperthyroidism and pheochromocytoma.
Cardiovascular effects may be seen with sympathicomimetic drugs, including BERODUAL/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 BERODUAL/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.
BERODUAL/DUOVENT, like other medicinal products containing anticholinergic active substances, should be used with caution in patients with prostatic hyperplasia or bladder-neck obstruction or predisposed to narrow-angle glaucoma.

BERODUAL® solution for inhalation and unit dose vials:

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.

BERODUAL® capsules for inhalation:

Since the inhaler device Inhalator Ingelheim and Inhalator M™ used for aerosolising the powder is breath actuated there should be no risk for the powder entering the eyes.

There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma and eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta2-agonist, has come into contact with the eyes. Thus patients must be instructed in the correct administration of BERODUAL/DUOVENT. Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival and corneal congestion may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop, treatment with miotic eye drops should be initiated and specialist advice should be sought immediately.

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

Prolonged use

In patients with bronchial asthma Berodual should be used only on an as-needed basis. In patients with and mild COPD, on demand treatment (symptom-oriented) may be preferable to regular use.

The addition or the increase of anti-inflammatory therapy to control airway inflammation and to prevent deterioration of disease control should be considered for patients with bronchial asthma and with steroid-responsive COPD.

In asthmatic patients, the use of increasing amounts of beta2-agonist containing medicinal products, such as BERODUAL/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 beta2-agonist containing medicinal products, beyond the recommended dose over extended periods of time. In this situation the patient's therapy plan, and in particular the adequacy of anti-inflammatory therapy with inhaled corticosteroids, should be reviewed to prevent potentially life-threatening deterioration of disease control.

Other sympathomimetic bronchodilators should only be used in combination with BERODUAL/DUOVENT under medical supervision.

Potentially serious hypokalemia may result from excessive beta2-agonist therapy.

The use of Berodual may lead to positive results with regard to fenoterol in tests for nonclinical substance abuse, e.g. in the context of athletic performance enhancement (doping).

Berodual® metered aerosol (HFA)

When using the new formulation of BERODUAL metered aerosol for the first time, some patients may notice that the taste is slightly different from that of the CFC-containing formulation. Patients should be made aware of this when changing from one formulation to the other. They should also be told that the formulations have been shown to be interchangeable for all practical purposes and that the difference in taste has no consequences in terms of the safety or the efficacy of the new formulation.

BERODUAL® solution for inhalation

This product contains the preservative benzalkonium chloride and the stabiliser disodium ededate dihydrate. When inhaled these components may cause bronchospasm in sensitive patients with hyper reactive airways.

Berodual® Inhalets®, capsules with inhalation powder

This product contains 38.8 mg of Glucose per maximum recommended daily dose.

4.5 Interaction with other medicaments and other forms of interaction

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

Hypokalemia induced by beta2-agonist may be increased by concomitant treatment with xanthine derivatives, corticosteroids and diuretics. This should be taken into account, particularly in patients with severe airway obstruction.

Hypokalemia may result in an increased susceptibility to arrhythmias in patients receiving digoxin. Additionally, hypoxia may aggravate the effects of hypokalemia on cardiac rhythm.

It is recommended that serum potassium levels be monitored in such situations.

Beta2-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.
A potentially serious reduction in bronchodilatation may occur during concurrent administration of beta-blockers.
Inhalation of halogenated hydrocarbon anaesthetics (e. g. halothane, trichloroethylene and enflurane) can increase the susceptibility on the cardiovascular effects of beta2-agonists.

Berodual® Respimat®
The risk of acute glaucoma may be increased when nebulised ipratropium bromide and beta2-agonists come into contact with the eyes simultaneously.

4.6 FERTILITY, PREGNANCY AND LACTATION

There are no sufficient data from the use of BERODUAL/DUOVENT in pregnant women. Animal studies do not indicate direct or indirect harmful effect with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women.

The potential of beta 2-agonists to inhibit uterine contraction should be taken into account.

Use of ß-2 sympathomimetics in the end of the pregnancy or in high doses may cause negative effects in the newborn baby (tremor, tachycardia, blood glucose fluctuations, hypokalaemia).

Preclinical studies have shown that fenoterol hydrobromide is excreted into breast milk. It is not known whether ipratropium is excreted into breast milk. But it is unlikely that ipratropium would reach the infant to an important extent, especially when taken by inhalation. Caution should be exercised when BERODUAL/DUOVENT is administered to nursing mothers.

Clinical data on fertility are not available for the combination of ipratropium bromide and fenoterol hydrobromide. Preclinical studies performed with the individual components ipratropium bromide and fenoterol hydrobromide showed no adverse effect on fertility.

4.7 Effects on Ability to Drive and Use Machines

Berodual® Respimat®
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, accomodation disorder, mydriasis and blurred vision during treatment with Berodual. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Many of the listed undesirable effects can be assigned to the anticholinergic and beta-adrenergic properties of Berodual. As with all inhalation therapy Berodual may show symptoms of local irritation. Adverse drug reactions were identified from data obtained in clinical trials and pharmacovigilance during post approval use of the drug.

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.

Adverse reactions have been ranked using the following convention:

Very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the vailable data)

Berodual® metered aerosol (HFA), Berodual® metered aerosol (CFC)
Berodual® solution for inhalation, Berodual® Inhalets®, Duovent® metered aerosol (CFC), Duovent® unit dose vials, Berodual Respimat

MedDRA SOC	CCDS term (MedDRA)	Frequency category according to EU SmPC guideline
Immune system disorders	Anaphylactic reaction	Rare*
	Hypersensitivity	Rare*
Metabolism and nutrition disorders	Hypokalemia	Rare*
Psychiatric disorders	Nervousness	Uncommon
	Agitation	Rare
	Mental disorder	Rare
Nervous system disorders	Headache	Uncommon
	Tremor	Uncommon
	Dizziness	Uncommon
	Hyperactivity	Not known
Eye disorders	Glaucoma	Rare*
	Intraocular pressure increased	Rare*
	Accommodation disorder	Rare*
	Mydriasis	Rare*
	Vision blurred	Rare*
	Eye pain	Rare*
	Corneal oedema	Rare*
	Conjunctival hyperaemia	Rare*
	Halo vision	Rare*
Cardiac disorders	Tachycardia, Heart rate increased	Uncommon
	Palpitations	Uncommon
	Arrhythmia	Rare
	Atrial fibrillation	Rare
	Supraventricular tachycardia	Rare*
	Myocardial ischaemia	Rare*
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Pharyngitis	Uncommon
	Dysphonia	Uncommon
	Bronchospasm	Rare
	Throat irritation	Rare
	Pharyngeal oedema	Rare

	Laryngospasm	Rare*
	Bronchospasm paradoxical	Rare*
	Dry throat	Rare*
Gastrointestinal disorders	Vomiting	Uncommon
	Nausea	Uncommon
	Dry mouth	Uncommon
	Stomatitis	Rare
	Glossitis	Rare
	Gastrointestinal motility disorder	Rare
	Diarrhoea	Rare
	Constipation	Rare*
	Oedema mouth	Rare*
Skin and subcutaneous tissue disorders	Urticaria	Rare
	Rash	Rare
	Pruritus	Rare
	Angioedema	Rare*
	Hyperhidrosis	Rare*
Musculoskeletal and connective tissue disorders	Muscular weakness	Rare
	Muscle spasms	Rare
	Myalgia	Rare
Renal and urinary disorders	Urinary retention	Rare
Investigations	Blood pressure systolic increased	Uncommon
	Blood pressure diastolic decreased	Rare

* Side effect has not been observed in any of the selected BERODUAL® clinical trials. The estimate is based on the upper limit of its 95% confidence interval, calculated from the totality of treated patients in accordance with the EU SmPC guideline [1] (3/4968 = 0.00060 which relates to “rare”).

4.9 Overdose

Symptoms

The effects of overdose are expected to be primarily related to fenoterol.
The expected symptoms with overdose are those of excessive ß-adrenergic stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, arrhythmias, and flushing.

Hypokalaemia may occur following overdose with fenoterol. Serum potassium levels should be monitored.

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

Therapy

Administration of sedatives, tranquilizers; in severe cases intensive therapy. Beta-receptor blockers, preferably beta1-selective, may be used as specific antidotes; however, a possible increase in bronchial obstruction must be taken into account and the dose should be adjusted carefully in patients suffering from bronchial asthma or COPD because of the risk of precipitating severe bronchospasm, which may be fatal.