

Berodual® N Metered Aerosol

Composition
1 metered dose (puff) contains:
8(8)-3α-hydroxy-8-(prop-1-yl-1H,5αH-tropanium
bromide (α)-tropate monohydrate (= ipratropium bromide)
anhydrous 21 mg
1-(3,5-dihydroxy-phenyl)-2-[[1-(4-hydroxy-benzyl)
-ethyl]-amino]-ethanol hydrobromide (= fenoterol
hydrobromide) 50 mg
Excipients:
1,1,1,2-Tetrafluoroethane (HFA 134a), citric acid anhy-
drous, water purified, ethanol absolute

Pharmacological properties
Pharmaco-therapeutic group: Adrenergics in combination
with anticholinergics for obstructive airway diseases
ATC code: R03AL01
BERODUAL contains two active bronchodilating ingredi-
ents: ipratropium bromide, exhibiting an anticholinergic
effect and fenoterol hydrobromide a beta-adrenergic
agent.
Ipratropium bromide is a quaternary ammonium com-
pound with anticholinergic (parasympatholytic) prop-
erties. In preclinical studies, it inhibits vagally mediated
reflexes by antagonising the action of acetylcholine, the
transmitter agent released from the vagus nerve. Anticho-
linergics prevent the increase in intracellular concentra-
tion of Ca++ which is caused by interaction of acetylcho-
line with the muscarinic receptor on bronchial smooth
muscle. Ca++ release is mediated by a 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 sys-
temic one.

Non-clinical and clinical evidence suggest no deleterious
effect of ipratropium bromide on airway mucous secre-
tion, mucociliary clearance or gas exchange.
Fenoterol hydrobromide is a direct acting sympathomi-
metic agent, selectively stimulating beta2-receptors in the
therapeutic dose range. The stimulation of beta2-receptors
leads into effect at a higher dose rang. Occupation of
beta2-receptors activates adenylyl cyclase via a stimulatory
Gs-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
allergens (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, glyco-
genolysis, 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 beta2-receptor stimulation,
and at supratherapeutic doses, by beta2-receptor stimula-
tion. As with other beta-adrenergic agents, QTc prolunga-
tions have been reported. For fenoterol, QTc prolongation
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 mus-
cle, the systemic effects on skeletal muscle of beta-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 broncho-
pulmonary disorders associated with constriction of the
respiratory tract. The complementary action is such that
only a very low proportion of the beta-adrenergic component
is needed to obtain the desired effect, facilitating individ-
ual dosage suited to each patient with a minimum of
adverse reactions.

Clinical efficacy and safety
In patients with asthma and COPD, better efficacy com-
pared to its components ipratropium or fenoterol was
demonstrated. Two studies (one with asth- ma patients, one
with COPD patients) have shown that BERODUAL is as
efficacious as double the dose of fenoterol administered
without ipratropium but was better tolerated in cumula-
tive dose response studies.
In acute bronchoconstriction BERODUAL 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
bronchodilatation are therefore not related to the pharma-
cokinetics of the active constituents of the preparation.
Following inhalation 10 to 39% of a dose is generally
deposited in lungs, depending on the formulation, inhala-
tion 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 sim-
ilar amount of the dose is deposited in the respiratory tract
following inhalation by metered aerosol with HFA. In par-
ticular after inhalation of the aqueous solution via the
RESPIMAT inhaler, a more than 2-fold higher lung deposi-
tion 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-substances.

Fenoterol hydrobromide
The swallowed portion is mainly metabolised to sulphate
conjugates. The absolute bioavailability following oral
administration is low (approx. 1.5%).
After intravenous administration, free fenoterol and con-
jugated fenoterol are approximately to 25% and 27% of the
administered dose in the cumulative 24-hour urine. After
inhalation via BERODUAL metered dose inhaler approxi-
mately 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%.

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. In this 3-compartment model the
apparent volume of distribution of fenoterol at steady state
is estimated at 189 L (± 2.7 L/kg).
About 40 % of the drug are bound to plasma proteins.
Preclinical studies with rats revealed that fenoterol and its
metabolites do not cross the blood-brain barrier.Fenoterol
has a total clearance of 1.8 L/min and a renal clearance of
0.27 L/min.

In an excretion balance study cumulative renal excretion
(2 days) of drug-related radioactivity (including parent com-
pound and all metabolites) accounted for 65% of dose after
intravenous administration and total radioactivity excreted
in faeces was 14.8% of dose. 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
Cumulative renal excretion (0-24 hrs) of ipratropium (parent
compound) is approximated to 46% of an intravenously
administered dose, below 1% of an oral dose and approxi-
mately 3 to 13% of an inhaled dose via BERODUAL metered
dose inhaler. Based on these data, the total systemic bio-
availability 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, or only slightly, contribute to systemic exposure.
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 (Vss) is approximately 176 L (± 24 L/kg).
The drug is minimally (less than 20%) bound to plasma pro-
teins. Preclinical studies with rats and dogs, revealed that
the quaternary amine ipratropium does not cross the
blood-brain barrier.

The half-life of the terminal elimination phase is approxi-
mately 1.6 hours. Ipratropium has a total clearance of
2.3 L/min and a renal clearance of 0.9 L/min. After intrave-
nous administration approximately 60% of a dose is metabo-
lised, the major portion probably in the liver by oxidation.
In an excretion balance study cumulative renal excretion
(6 days) of drug-related radioactivity (including parent com-
pound and all metabolites) accounted for 72.1% after intra-
venous administration, 9.3% after oral administration and
3.2% after inhalation. Total radioactivity excreted via the
faeces was 6.3% following intravenous application, 88.5%
following oral dosing and 69.4% after inhalation. Regarding
the excretion of drug-related radioactivity after intravenous
administration, the main excretion occurs via the kidneys.

The half-life for elimination of drug-related radioactivity
(parent compound and metabolites) is 3.6 hours. Binding of
the main urinary metabolites to the muscarinic receptor is
negligible and the metabolites have to be regarded as
ineffective.

Indications
Treat and prevent bronchospasm diseases including bron-
chial asthma, obstructive bronchitis, chronic bronchitis,
emphysema and pulmonary bronchial disorder accompa-
nied with bronchospasm.

Dosage and administration
The product should be used by physician prescription.
The dosage should be adapted to the individual require-
ments. The following dosages are recommended for adults
and children > 6 years:
Acute asthma episodes
2 actuations are sufficient for prompt symptom relief in
many cases. In more severe cases, if breathing has not
noticeably improved after 5 minutes, two further actuations
may be taken.

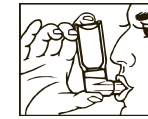
If an attack has not been relieved by 4 actuations, further
actuations may be required.
In these cases, patients should be advised to consult the
doctor or the nearest hospital immediately.

Intermittent and long-term treatment (in asthma)
BERODUAL metered dose aerosol should be used only on an
as-needed basis).
1 - 2 actuations for each administration, up to a maximum
of 8 actuations per day (average 1-2 actuations 3 times
daily).

In children BERODUAL metered dose aerosol should only be
used on medical advice and under the supervision of an
adult.
Patients should be instructed in the correct administration
of the metered aerosol to ensure successful therapy (see
Instructions for use).

Before first time use of the metered dose aerosol the follow-
ing rule should be observed:
Remove protective cap and depress the valve twice
Before each use of the metered dose aerosol the following
rule should be observed:

1. Remove protective cap.
(If the inhaler has not been used for more than three days
the valve has to be actuated once)
2. Breathe out deeply.
3. Hold the inhaler as shown in fig. 1, and close lips around
the mouthpiece.
The arrow and the base of the container should be point-
ing upwards.



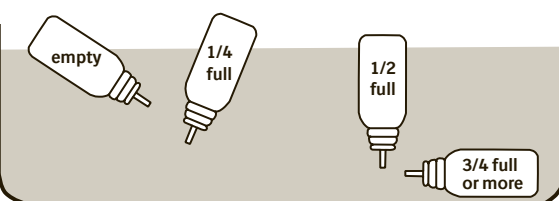
(Fig. 1)

4. Breathe in as deeply as possible, pressing the base of the
canister firmly at the same time, this releases one metered dose. Hold the
breath for a few seconds, then remove the mouthpiece
from the mouth and breathe out.
The same action should be repeated for a second
inhalation.
5. Replace the protective cap after use.

The container is not transparent. It is therefore not possible
to see when it is empty. The inhaler will deliver 200 or if
available 300 doses. While there have all been used the
canister may still appear to contain a small amount of fluid.
The inhaler should, however, be replaced because you may
not get the right amount of treatment.

The approximate amount of treatment in your inhaler can be
checked as follows:

- Shaking the canister will show if there is any remaining
fluid.
- Alternatively remove the canister from the plastic mouth-
piece and put it into a container of water. The contents of
the canister can be estimated by observing its position in
the water.



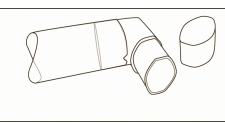
(Fig. 2)

Clean your inhaler at least once a week.
It is important to keep the mouthpiece of your inhaler clean
and ensure that medicine does not build up and block the
spray.
For cleaning, first take off the dust cap and remove
the mouthpiece from the inhaler. Rinse with water and
through the inhaler until no medication build-up
and/or dirt is visible.



(Fig. 3)

After cleaning shake out the inhaler and let it air-dry without
using any heating system. Once the mouthpiece is dry,
replace the canister and the dust cap.



(Fig. 4)

WARNING:
The plastic mouthpiece has been specially designed for use
with BERODUAL metered dose aerosol to ensure that you
always get the right amount of the medicine. The mouth-
piece must never be used with any other metered dose
aerosol nor must the BERODUAL metered dose aerosol be
used with any mouthpiece other than the one supplied with
the product.

The container is under pressure and should by no account
be opened by force or exposed to temperatures above 50°C.

Contraindications
BERODUAL is contraindicated in patients with known
hypersensitivity to fenoterol hydrobromide or atropine-like
substances or to any of the excipients of the product.
BERODUAL is also contraindicated in patients with hyper-
trophic obstructive cardiomyopathy and tachyarrhythmia.

Special warnings and precautions
Hypersensitivity
Immediate hypersensitivity reactions may occur after
administration of BERODUAL, as demonstrated by rare
cases of urticaria, angio-oedema, rash, bronchospasm,
oropharyngeal oedema and anaphylaxis.
Paradoxical bronchospasm
As with other inhaled medicines BERODUAL may result in
paradoxical bronchospasm that may be life-threatening. If
paradoxical bronchospasm occurs BERODUAL should be
discontinued immediately and alternative therapy
substituted.

Ocular complications
BERODUAL should be used with caution in patients predis-
posed to narrow-angle glaucoma.

In children 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 beta2-
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 conjunc-
tival 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 administra-
tion of BERODUAL.

Care must be taken not to allow the product to enter the
eyes.

Systemic effects
In the following conditions BERODUAL should only be used
after careful risk/benefit assessment, especially when doses
higher than recommended are used:
Insufficiently controlled diabetes mellitus, recent myocar-
dial infarction, severe organic heart or vascular disorders,
hyperthyroidism, pheochromocytoma, or with pre-
existing urinary outflow tract obstruction (e.g. prostatic
hyperplasia or bladder-neck obstruction).

Cardiovascular effects
Cardiovascular effects may be seen with sympathomi-
metic drugs, including BERODUAL. 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, 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 beta2-
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 (difficulty
in breathing) patients should be advised to consult a doctor
should be consulted immediately.

Prolonged use
- In patients with bronchial asthma BERODUAL 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 deteriora-
tion of disease control should be considered for patients
with bronchial asthma and with steroid-responsive COPD.

The use of increasing amounts of beta2-agonists containing
products such as BERODUAL 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 products such as
BERODUAL 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 BERODUAL under medical supervision (see sec-
tion Interactions).

Doping warning
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).

Interactions
The chronic co-administration of BERODUAL with other
anticholinergic drugs has not been studied. Therefore, the
chronic co-administration of BERODUAL with other anti-
cholinergic drugs is not recommended.
Other beta-adrenergics and anticholinergics and xanthine
derivatives (such as theophylline) may enhance the bron-
chodilatory 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 beta2-agonist may be increased by
concomitant treatment with xanthine derivatives, corti-
costeroids, 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 car-
diac rhythm. It is recommended that serum potassium levels
are 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.

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
Preclinical data, combined with available experience in
humans have shown no evidence of ill adverse effects in
pregnancy of fenoterol or ipratropium. Nonetheless, the
usual precautions regarding the use of drugs during preg-
nancy, 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 hydrobro-
mide 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 BERODUAL is administered to
a nursing woman.

Fertility
Clinical data on fertility are neither available for the combi-
nation of ipratropium bromide and fenoterol hydrobromide
nor for each of the two components of the combination.
Non-clinical studies performed with the individual compo-
nents ipratropium bromide and fenoterol hydrobromide
showed no adverse effect on fertility (see section
Toxicology).

Effects on ability to drive and use machines
No studies on the effect on the ability to drive and use
machines have been performed.
However, patients should be advised that they may experi-
ence undesirable effects such as dizziness, tremor, accomo-
dation disorder, mydriasis and blurred vision during treat-
ment 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.

Side 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.

Immune system disorders
• anaphylactic reaction
• hypersensitivity
Metabolism and nutritional disorders
• hypokalaemia
Psychiatric disorders
• nervousness
• agitation
Mental disorder
Nervous system disorders
• headache
• tremor
Cardiac disorders
• tachycardia, heart rate increased
• palpitations
Arrhythmia
• atrial fibrillation
• supraventricular tachycardia
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

Availability
Metered aerosol: pack of 100 ml below in steel can,
10 ml metered aerosol = 200 puffs

Store in a safe place out of the reach of children!

MD, by
Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Stasse 173
55216 Ingelheim am Rhein
Germany

20140055

Overdose
Symptoms
The effects of overdose are expected to be primarily related
to fenoterol.
The expected symptoms with overdose are those of exces-
sive beta-adrenergic-stimulation, the most prominent being
tachycardia, palpitation, tremor, hypertension, hypotension,
widening of the pulse pressure, angular 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
BERODUAL.
Expected symptoms of overdose with ipratropium bromide
(such as dry mouth, visual accommodation disorder) are
mild because the systemic availability of inhaled ipratro-
pium is very low.

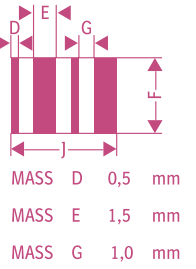
Therapy
Treatment with BERODUAL should be discontinued. Acid
base and electrolyte monitoring should be considered.
Administration of sedatives, tranquilisers, in severe cases
intensive care treatment.
Beta-receptor blockers, preferably beta1-selective, are suit-
able as specific antidotes; however, a 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 precipitat-
ing severe bronchospasm, which may be fatal.

Toxicology
Single-dose toxicity studies with the combination ipratro-
pium bromide and fenoterol hydrobromide in a ratio of
1/2.5 (ipratropium bromide/fenoterol hydrobromide) in
mice and rats after oral, intravenous and inhalation admin-
istration revealed a low level of acute toxicity. In compari-
son to the individual components, the LD50 values of the
combination were determined more by the ipratropium
bromide component than by fenoterol hydrobromide with-
out any indication of potentiation.
Repeat-dose toxicity studies with the combination ipratro-
pium bromide and fenoterol hydrobromide were performed
in rats (oral, inhalation) and dogs (intravenous, inhalation)
for up to 13 weeks. Only minor toxic effects at concentra-
tions up to several hundred times greater than that recom-
mended in man were observed. Left ventricular myocardial
scars were seen in only in one animal from the highest treat-
ment group (84µg/kg/day) of the 4-week intravenous study in
dogs. The 13-week oral study in rats and the 13-week inha-

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Example
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