SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

{Trade name} 200 micrograms/6 micrograms per inhalation inhalation powder.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose of 10 mg inhalation powder contains:
200 micrograms of beclometasone dipropionate anhydrous and 6 micrograms of formoterol fumarate dihydrate.
This is equivalent to a delivered dose (the dose leaving the mouthpiece) of 158.8 micrograms of beclometasone dipropionate anhydrous and 4.9 micrograms of formoterol fumarate dihydrate.

Excipient with known effect:
Each metered dose contains 9.8 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder.

The multidose inhaler contains a white or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

{Trade name} is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting $beta_2$-agonist) is appropriate:
- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting $beta_2$-agonist or
- patients already adequately controlled on both inhaled corticosteroids and long-acting $beta_2$-agonists.

{Trade name} is indicated in adults.

Note: there are no relevant clinical data on the use of {Trade name} for the treatment of acute asthma attacks.

4.2 Posology and method of administration

Posology

{Trade name} is not intended for the initial management of asthma. The dosage of {Trade name} is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the dose is adjusted. If an

individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of beta$_2$-agonists and/or corticosteroids by individual inhalers should be prescribed.

Because of its extrafine particle size distribution, dose adjustment is required when patients are transferred to {Trade name} inhalation powder from a formulation with a non-extrafine particle size distribution. When switching patients from previous treatments, it should be considered that the recommended total daily dose of beclometasone dipropionate for {Trade name} is lower than that for current beclometasone dipropionate-containing non-extrafine products and should be adjusted to the needs of the individual patient.

Dose recommendations for adults 18 years and above
Two inhalations twice daily.
The maximum daily dose is 4 inhalations daily.

Patients should be regularly reassessed by a doctor, so that the dosage of {Trade name} remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When control of symptoms is maintained with the lowest recommended dosage, then the next step-down could include the inhaled corticosteroid alone.
A lower strength of the beclometasone dipropionate component in the same Nexthaler device is available for step-down treatment ({Trade name} 100/6 micrograms).
Patients should be advised to take {Trade name} every day even when asymptomatic.

Special populations
There is no need to adjust the dose in elderly patients.
There are no data available for use of {Trade name} in patients with hepatic or renal impairment (see section 5.2).

Paediatric population
{Trade name} 200/6 micrograms should not be used in children and adolescents below 18 years.

Method of administration
{Trade name} is for inhalation use.

Nexthaler is a breath-operated inhaler. Moderate and severe asthmatic patients were shown to be able to produce sufficient inspiratory flow to trigger inhalation release from Nexthaler (see section 5.1). The delivery of {Trade name} with Nexthaler is flow-independent in the range of inspiratory flow that this patient population can achieve through the inhaler.

Correct use of the Nexthaler inhaler is essential in order for the treatment to be successful. The patient should be advised to read the Patient Information Leaflet carefully and follow the instructions for use as given in the leaflet. For instructions for use, see below

The number of inhalations shown in the window on the shell does not decrease on closing the cover if the patient has not inhaled through the inhaler.

The patient should be instructed to only open the inhaler's cover when needed. In the event that the patient has opened the inhaler but not inhaled, and the cover is closed, the metered dose is moved back to the powder reservoir within the inhaler; the following metered dose can be safely inhaled.

Patients should rinse their mouth or gargle with water or brush their teeth after inhaling (see section 4.4).

INSTRUCTIONS FOR USE OF NEXTHALER INHALER

A. Contents of the Package

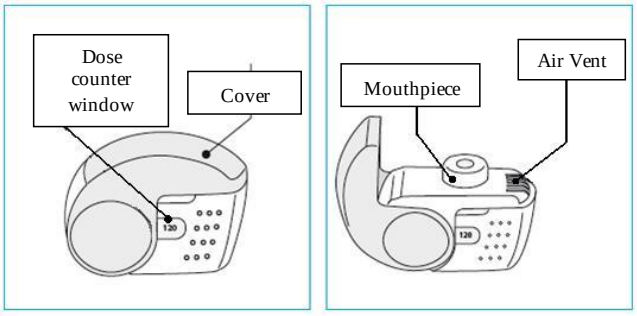
For information on the contents of the pack, see section 6.5.

If the package contents are not the same as described in section 6.5, return your inhaler to the person who supplied it and get a new one.

B. General Warnings & Precautions

- **Do not** remove the inhaler from the sachet if you do not intend to use it immediately.
- Only use your inhaler as indicated.
- Keep the cover closed until you need to take an inhalation from your inhaler.
- When you are not using your inhaler keep it in a clean and dry place.
- **Do not** attempt to take your Nexthaler inhaler apart for any reason.

C. Key features of your Nexthaler inhaler



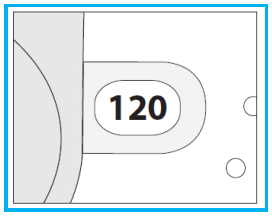
Taking a dose from your Nexthaler inhaler requires just three simple steps: Open, Inhale, Close.

D. Before using a new Nexthaler inhaler

1. **Open the sachet and take out your inhaler.**
   - **Do not** use your inhaler if the sachet is not sealed or it is damaged – return it to the person who supplied it and get a new one.
   - Use the label on the box to write down the date you open the sachet.
2. **Inspect your inhaler.**

- If your inhaler looks broken or damaged, return it to the person who supplied it and get a new one.

3. **Check the Dose Counter Window. If your inhaler is brand new you will see "120" in the Dose Counter Window.**
   - **Do not** use a new inhaler if the number shown is less than "120" – return it to the person who supplied it and get a new one.

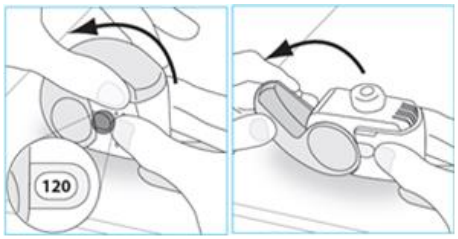


E. How to use your Nexthaler inhaler

- If you are not sure you are receiving your dose correctly contact your pharmacist or doctor.
- If you are not sure the dose counter has gone down by one after inhalation, wait until your next scheduled dose and take this as normal. Do not take an extra dose.

E1. Open

1. **Hold your inhaler firmly in the upright position.**
2. **Check the number of inhalations left: any number between "1" and "120" shows that there are inhalations left.**
   - If the Dose Counter Window shows "0" there are no inhalations left – dispose of your inhaler and get a new one.
3. **Open the cover fully.**

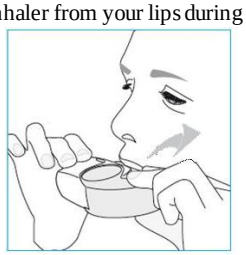


4. **Before inhaling breathe out as far as is comfortable.**
   - **Do not** breathe out through your inhaler.

E.2. Inhale

Whenever possible, stand or sit in an upright position when inhaling.

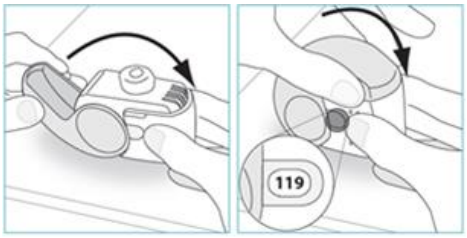
1. **Lift your inhaler up, bring it to your mouth and place your lips around the mouthpiece.**
   - **Do not** cover the air vent when holding your inhaler.
   - **Do not** inhale through the air vent.
2. **Take a forceful and deep breath through your mouth.**
   - You may notice a taste when you take your inhalation.
   - You may hear or feel a click when you take your inhalation.
   - **Do not** inhale through your nose.
   - **Do not** remove your inhaler from your lips during the inhalation.



3. **Remove your inhaler from your mouth.**
4. **Hold your breath for 5 to 10 seconds or as long as is comfortable.**
5. **Breathe out slowly.**
   - **Do not** breathe out through your inhaler.

E.3. Close

1. **Move your inhaler back to the upright position and close the cover fully.**
2. **Check that the dose counter has gone down by one.**



3. **If you need to take another dose, repeat steps E.1 to E.3.**

F. Cleaning

- Normally, it is not necessary to clean your inhaler.
- If necessary you may clean your inhaler after use with a dry cloth or tissue.
    - **Do not** clean your inhaler with water or other liquids. Keep it dry.

G. Storage and Disposal

For information on storage conditions and disposal instructions, see sections 6.4 and 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

It is recommended that the dose is tapered when the treatment is discontinued; treatment should not be stopped abruptly.

The management of asthma should normally follow a stepwise programme and patient response should be monitored clinically and by lung function tests.
If patients find the treatment ineffective medical attention must be sought. Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy. Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment. Consideration should be given to the need for increased treatment with corticosteroids, either inhaled or oral therapy, or antibiotic treatment if an infection is suspected.
Patients should not be initiated on {Trade name} during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma. Serious asthma-related adverse events and exacerbations may occur during treatment with {Trade name}. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on {Trade name}.
As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing, cough and shortness of breath after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. {Trade name} should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

{Trade name} is not intended for the initial management of asthma.

For treatment of acute asthma attacks patients should be advised to have their short-acting bronchodilator available at all times.

Patients should be reminded to take {Trade name} daily as prescribed even when asymptomatic.
Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of {Trade name}. Regular review of patients as treatment is stepped down is important. The lowest effective dose of {Trade name} should be used (see section 4.2).

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important therefore that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children and adolescents aged less than 16 years inhaling higher than recommended doses of beclometasone dipropionate may be at particular risk. Situations which could potentially trigger acute adrenal crisis, include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Patients transferring from oral to inhaled corticosteroids may remain at risk of impaired adrenal reserve for a considerable time. Patients who have required high dose emergency corticosteroid therapy in the past or have received prolonged treatment with high doses of inhaled corticosteroids may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures.

{Trade name} should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

{Trade name} should be used with caution (which may include monitoring) in patients with cardiac arrhythmias, especially third degree atrioventricular block and tachyarrhythmias, idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, ischaemic heart disease, severe heart failure, severe arterial hypertension and aneurysm.

Caution should also be observed when treating patients with known or suspected prolongation of the QTc interval, either congenital or drug induced (QTc > 0.44 seconds). Formoterol itself may induce prolongation of the QTc interval.

Caution is also required when {Trade name} is used by patients with thyrotoxicosis, diabetes mellitus, phaeochromocytoma and untreated hypokalaemia.

Potentially serious hypokalaemia may result from beta$_2$-agonist therapy. Particular caution is advised in severe asthma as this effect may be potentiated by hypoxia. Hypokalaemia may also be potentiated by concomitant treatment with other drugs which can induce hypokalaemia, such as xanthine derivatives, steroids and diuretics (see section 4.5). Caution is also recommended in unstable asthma when a number of "rescue" bronchodilators may be used. It is recommended that serum potassium levels are monitored in such situations.

The inhalation of formoterol may cause a rise in blood glucose levels. Therefore blood glucose should be closely monitored in patients with diabetes.

If anaesthesia with halogenated anaesthetics is planned, it should be ensured that {Trade name} is not administered for at least 12 hours before the start of anaesthesia as there is a risk of cardiac arrhythmias.

Patients should be advised to rinse the mouth or gargle with water or brush the teeth after inhaling the prescribed dose to minimise the risk of oropharyngeal fungal infections and dysphonia.

The medicinal product contains lactose. Lactose contains small amounts of milk proteins, which may cause allergic reactions. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes.

Beclomethasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents.

Pharmacodynamic interactions
Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. {Trade name} should therefore not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons.
The use of other beta-adrenergic drugs may have potentially additive effects, therefore caution is required when theophylline or other beta-adrenerigic drugs are prescribed concomitantly with formoterol.
Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, certain antihistamines (e.g. terfenadine), monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.

In addition L-dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards $beta_2$-sympathomimetics.
Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.
There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of beta$_2$-agonists (see section 4.4). Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

4.6 Fertility, pregnancy and lactation

~~***Fertility***~~
~~There are no data in humans. In animal studies in rats, the presence of beclometasone dipropionate at high doses in the combination was associated with reduced female fertility and embryotoxicity (see section 5.3).~~

Pregnancy
There are no relevant clinical data on the use of {Trade name} in pregnant women. Animal studies using beclometasone dipropionate and formoterol combination showed evidence of toxicity to reproduction and to the fetuses after high systemic exposure (see section 5.3). High doses of corticosteroids administered to pregnant animals are known to cause abnormalities of fetal development including cleft palate and intra-uterine growth retardation. Because of the tocolytic actions of beta$_2$-sympathomimetic agents particular care should be exercised in the run up to delivery. Formoterol should not be recommended for use during pregnancy and particularly at the end of pregnancy or during labour unless there is no other (safer) established alternative.
Administration of {Trade name} during pregnancy should only be considered if the expected benefits outweigh the potential risks.

~~***Lactation (***~~***Breast-feeding***~~***)***~~
There are no relevant clinical data on the use of {Trade name} during lactation in humans.
Although no data from animal experiments are available, it is reasonable to assume that beclometasone dipropionate is secreted in milk, like other corticosteroids.
While it is not known whether formoterol passes into human breast milk, it has been detected in the milk of lactating animals.
Administration of {Trade name} to women who are breast-feeding should be considered if the expected benefits outweigh the potential risks. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from {Trade name} therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data in humans. In animal studies in rats, the presence of beclometasone dipropionate at high doses in the combination was associated with reduced female fertility and embryotoxicity (see section 5.3).

4.7 Effects on ability to drive and use machines
{Trade name} has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
The most common adverse reaction is tremor. In a 12-week clinical trial with {Trade name} 100/6 micrograms, tremor was seen only with the highest dose regimen (400/24 micrograms daily), appeared

Formatiert: Einzug: Links: 0 cm

most frequently at the beginning of treatment and was mild in intensity. No patient was withdrawn from the trial as a result of tremor.

Clinical Trials Experience in asthma patients
The safety of {Trade name} 100/6 micrograms was assessed in active- and placebo-controlled clinical trials in which 719 patients aged 12 and older with asthma of varying severity were exposed to the drug. The incidence of adverse reactions in the table below relates to asthmatic patients aged 12 years and older and is based upon the safety findings of two pivotal clinical trials where {Trade name} 100/6 micrograms was administered at the doses recommended in this SmPC for a period of 8-12 weeks. No psychiatric disorders were observed in the clinical trials with {Trade name} 100/6 micrograms but they are included in the table as a potential class-effect of inhaled corticosteroids.

Undesirable effects which have been associated with beclometasone dipropionate and formoterol administered as a fixed combination ({Trade name}) are given below, listed by system organ class. Frequencies are defined as: 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) and very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	**Adverse Reaction**	**Frequency**
Infections and infestations	Nasopharyngitis	Uncommon
	Oral candidiasis	Uncommon
Metabolism and nutrition disorders	Hypertriglyceridaemia	Uncommon
Psychiatric disorders	Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)	Frequency not known
Eye disorders	Vision, blurred (see also section 4.4)	Frequency not known
Nervous system disorders	Tremor	Common
	Headache	Uncommon
Cardiac disorders	Tachycardia	Uncommon
	Sinus bradycardia	Uncommon

	Angina pectoris	Uncommon
	Myocardial ischaemia	Uncommon
Respiratory, thoracic and mediastinal disorders	Throat irritation, exacerbation of asthma	Uncommon
	Dyspnoea	Uncommon
	Oropharyngeal pain	Uncommon
	Dysphonia	Uncommon
	Cough	Uncommon
Gastrointestinal disorders	Nausea	Uncommon
General disorders and administration site conditions	Fatigue	Uncommon
	Irritability	Uncommon
Investigations	Electrocardiogram QT prolonged	Uncommon
	Cortisol free urine decreased	Uncommon
	Blood cortisol decreased	Uncommon
	Blood potassium increased	Uncommon
	Blood glucose increased	Uncommon
	Electrocardiogram poor r-wave progression	Uncommon

Among the observed adverse reactions those typically associated with formoterol are: tremor, headache, tachycardia, sinus bradycardia, angina pectoris, myocardial ischaemia, QT prolongation.

Among the observed adverse reactions those typically associated with beclometasone dipropionate are: nasopharyngitis, oral candidiasis, dysphonia, throat irritation, irritability, cortisol free urine decreased, blood cortisol decreased, blood glucose increased.

Additional adverse reactions not observed in the clinical experience with {Trade name} but typically associated with the inhaled administration of beclometasone dipropionate are other oral fungal infections. Taste disturbances have occasionally been reported during inhaled corticosteroid therapy.

See section 4.4 for measures to minimize the occurrence of oral fungal infections, oral candidiasis and dysphonia.

Systemic effects of inhaled corticosteroids (e.g. beclometasone dipropionate) may occur particularly when administered at high doses prescribed for prolonged periods, these may include Cushing's Syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma (see also section 4.4).

Additional adverse reactions not observed in the clinical experience with therapeutic doses of {Trade name} 100/6 micrograms but typically associated with the administration of beta$_2$-agonist such as formoterol are palpitations, atrial fibrillation, ventricular extrasystoles, tachyarrhythmia, potentially serious hypokalaemia and increase/decrease of blood pressure. Insomnia, dizziness, restlessness, and anxiety have occasionally been reported during inhaled formoterol therapy. Formoterol may also induce muscle cramps, myalgia.

Hypersensitivity reactions including rashes, urticaria, pruritus and erythema and oedema of the eye, face, lips and throat (angioedema) have been reported.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing, cough and shortness of breath after dosing (see also section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest recommended dose of {Trade name} in a single administration is 2 inhalations. Four cumulative inhalations of {Trade name} (total beclometasone dipropionate 800 micrograms, formoterol 24 micrograms given as a single dose) have been studied in asthmatic patients. The cumulative treatment did not cause abnormal, clinically relevant effect on vital signs and neither serious nor severe adverse reactions were observed (see also section 4.8).

For the pressurised inhalation solution formulation, inhaled doses of up to twelve cumulative actuations of 100/6 micrograms each (total beclometasone dipropionate 1200 micrograms, formoterol 72 micrograms) have been studied in asthmatic patients. The cumulative treatments did not cause abnormal effect on vital signs and neither serious nor severe adverse events were observed.

Excessive doses of formoterol may lead to effects that are typical of beta$_2$-adrenergic agonists: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, prolongation of QTc interval, metabolic acidosis, hypokalaemia, hyperglycaemia.

In case of overdose of formoterol, supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardioselective beta-adrenergic blockers may be considered, but only subject to extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm. Serum potassium should be monitored.

Acute inhalation of beclometasone dipropionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function recovers in a few days, as verified by plasma cortisol measurements. In these patients treatment should be continued at a dose sufficient to control asthma.

Chronic overdose of inhaled beclometasone dipropionate: risk of adrenal suppression (see section 4.4.). Monitoring of adrenal reserve may be necessary. Treatment should be continued at a dose sufficient to control asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases; Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics.
ATC code: R03AK08.

Mechanisms of action and pharmacodynamic effects
{Trade name} contains beclometasone dipropionate and formoterol in a dry powder formulation resulting in an extrafine aerosol with an average mass median aerodynamic diameter (MMAD) of 1.4-1.7 micrometers and co-deposition of the two components. The aerosol particles of {Trade name} are on average much smaller than the particles delivered in non-extrafine formulations.

A radio-labelled drug deposition study in asthmatic adults with {Trade name} 100/6 micrograms has demonstrated that a high proportion of the drug (estimated 42% of the nominal dose) is deposited in the lung, with a homogenous deposition through the airways. These delivery characteristics support the use of a low corticosteroid dose with enhanced local pharmacodynamic effects, which were shown to be equivalent to the corresponding pressurised inhalation solution.

The two actives of {Trade name} have different modes of action. In common with other inhaled corticosteroids and beta$_2$-agonist combinations, additive effects are seen in respect of reduction in asthma exacerbations.

Beclometasone dipropionate
Beclometasone dipropionate given by inhalation at recommended doses has a glucocorticoid antiinflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically.

Formoterol
Formoterol is a selective beta$_2$-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after dose administration.

Clinical experience

The efficacy of the two components of {Trade name} inhalation powder has been assessed for the lower strength (100 micrograms/6 micrograms) in three separate studies in comparison with the 100 micrograms/6 micrograms pressurised inhalation solution formulation in moderate to severe patients with persistent asthma. Overall, the efficacy of the two inhalers is expected to be equivalent in clinical practice at both 1 and 2 inhalations bid.

In one study the primary objective was the efficacy evaluation of the inhaled corticosteroid component measured on bronchodilation (pre-dose FEV_1). A clinically significant improvement in pre-dose FEV_1 was seen in 696 patients with moderate to severe symptomatic asthma at the end of a 3 months treatment period in comparison with baseline values, with 1 inhalation bid and 2 inhalations bid of both formulations. A mean increase of at least 250 mL was observed. There was no clinically relevant difference in pre-dose FEV_1 between {Trade name} inhalation powder and the pressurised inhalation solution at either dosage. A significant dose-response was observed for morning PEF. Statistical significance for the dose-response in pre-dose FEV_1 was not reached. Measurements of control of asthma such as morning and evening asthma symptoms scores and percentage of days without symptoms improved significantly from baseline through to the end of the treatment period, particularly for the two high doses of both formulations.

In the second study the primary aim was the efficacy evaluation on the long-acting $beta_2$-agonist component of {Trade name}. In this study bronchodilation at the onset and up to 12 hrs after single doses administration was measured by serial spirometric evaluations of FEV_1 (FEV_1 AUC over at least 80% of formoterol duration of action). Compared with placebo, {Trade name}, one inhalation and four inhalations of both actives significantly improved the FEV_1 AUC_{0-12}. Both doses of {Trade name} inhalation powder were non-inferior to the corresponding dose of the pressurised inhalation solution formulation. A statistically significant dose-response was found with both formulations between the low and high dose.

In the third study, after a 4-week run-in period with beclometasone dipropionate/formoterol pressurised inhalation solution fixed combination, 1 inhalation bid, 755 controlled asthmatic patients were randomised to 8 weeks of treatment with the same inhaler, with {Trade name} inhalation powder or with beclometasone dipropionate 100 micrograms per dose inhalation powder, all given at 1 inhalation bid. The primary objective was the change from baseline over the entire treatment period in mean morning expiratory flow (PEF). After 8 weeks of treatment there was no difference in the primary endpoint between the two combination inhalers, both being significantly better than beclometasone dipropionate monotherapy. No differences were found between the two combination inhalers in measures of symptoms such as the asthma control questionnaire score and the number of rescue-free days.

An open-label placebo study was conducted to verify that the inspiratory flow which could be generated through the Nexthaler inhaler is not influenced by patient's age, disease and disease severity, and therefore the activation and drug delivery from the device could be achieved in all patients. The primary endpoint was the percentage of patients in each age and disease group able to activate the inhaler. Eighty-nine patients, in the age range 5-84 years, including moderate and severe asthmatics (FEV_1 > 60% and ≤ 60% predicted, respectively), and moderate and severe COPD patients (FEV_1 ≥ 50% and < 50% predicted, respectively) participated in the trial. All patients, irrespective of age, disease and disease severity, were able to generate sufficient inspiratory flow to activate the Nexthaler inhaler.

In a double blind, randomised, 5-way crossover, placebo controlled study in 60 partially controlled or uncontrolled adult asthmatic patients with two different single doses (1 or 4 inhalations) of {Trade name} 100 micrograms/6 micrograms and {Trade name} 200 micrograms/6 micrograms, or placebo, the bronchodilator effect (FEV_1 AUC_{0-12h} normalised by time) was investigated. The adjusted mean difference (95% CI) for {Trade name} 200 micrograms /6 micrograms vs {Trade name} 100 micrograms/6 micrograms was 0.029 (-0.018; 0.076) L for the lower formoterol dose level (1 inhalation – 6 µg) and 0.027 (-0.020; 0.073) L for the higher formoterol dose level (4 inhalations – 24 µg). The results showed that the lower limits of the two-sided 95% CIs for the adjusted mean difference between treatments were well above the pre-specified non-inferiority limit (-0.12 L) thus demonstrating the predefined non-inferiority (0.12 L) of {Trade name} 200 micrograms/6 micrograms compared to the lower strength in terms of FEV_1 AUC_{0-12h} normalised by time at both formoterol dose levels (6 and 24 micrograms).

5.2 Pharmacokinetic properties

Beclometasone dipropionate
Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity that is hydrolysed via esterase enzymes to an active metabolite beclometasone-17-monopropionate which has a more potent topical anti-inflammatory activity compared with the pro-drug beclometasone dipropionate.

Absorption, distribution and biotransformation
Inhaled beclometasone dipropionate is rapidly absorbed through the lungs; prior to absorption there is extensive conversion to its active metabolite beclometasone-17-monopropionate via esterase enzymes that are found in most tissues. The systemic availability of the active metabolite arises from lung and from gastrointestinal absorption of the swallowed dose. The bioavailability of swallowed beclometasone dipropionate is negligible however, pre-systemic conversion to beclometasone-17-monopropionate results in part of the dose being absorbed as the active metabolite.
There is an approximately linear increase in systemic exposure with increasing inhaled dose.
The absolute bioavailability following inhalation from a pressurised metered dose inhaler is approximately 2% and 62% of the nominal dose for unchanged beclometasone dipropionate and beclometasone-17-monopropionate respectively.
Following intravenous dosing, the disposition of beclometasone dipropionate and its active metabolite are characterised by high plasma clearance (150 and 120 L/h respectively), with a small volume of distribution at steady state for beclometasone dipropionate (20L) and larger tissue distribution for its active metabolite (424L). Metabolic disposition of beclometasone dipropionate mainly (82%) results in its active metabolite beclometasone-17-monopropionate.
Plasma protein binding is moderately high (87%).

Elimination
Faecal excretion is the major route of beclometasone dipropionate elimination mainly as polar metabolites. The renal excretion of beclometasone dipropionate and its metabolites is negligible. The terminal elimination half-lives are 0.5 h and 2.7 h for beclometasone dipropionate and beclometasone-17-monopropionate respectively.

Special populations
The pharmacokinetics of beclometasone dipropionate in patients with **renal or hepatic impairment** has not been studied; however, as beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes present in intestinal fluid, serum, lungs and liver, to originate the more polar

products beclometasone-21-monopropionate, beclometasone-17-monopropionate and beclometasone, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of beclometasone dipropionate.
As beclometasone dipropionate or its metabolites were not traced in the urine, an increase in systemic exposure is not envisaged in patients with renal impairment.

Linearity/non-linearity
A clinical pharmacology study was conducted to evaluate the lung bioavailability and total systemic exposure of the two components across two different dose strengths of the inhalation powder ({Trade name} 100/6 micrograms and {Trade name} 200/6 micrograms). These parameters were assessed after a single dose (4 inhalations) of each formulation, both with and without activated charcoal block. The study had an open-label, 6-way cross-over, single-dose design. A total of 30 adult asthmatic patients with an $FEV_1 \geq 70\%$ of the predicted values were enrolled and treated with low daily doses of inhaled corticosteroids (e.g., budesonide or equivalent ≤400 µg/day) or low dose of inhaled corticosteroids/long-acting β_2-agonists fixed combinations. The lung bioavailability of B17MP (active metabolite of beclometasone dipropionate) and the total systemic exposure of B17MP were dose-proportional between the 200/6 and the approved 100/6 strength in both study conditions (with and without activated charcoal). Formoterol bioequivalence in terms of lung bioavailability and total systemic exposure was not fully demonstrated in this study as the lower 90% CI of C_{max} and AUC_t were below the 80% lower bioequivalence limit when the two dose strengths were compared. This reduced systemic exposure (which amounts to 20-14% in C_{max} and AUC_t) does not raise concerns in terms of safety since no differences in systemic effects (including glucose, potassium and cardiovascular parameters) have been observed thus showing that {Trade name} 200/6 micrograms is at least as safe as {Trade name} 100/6 micrograms. In terms of lung deposition the difference was 20% and 22% for C_{max} and AUC_t respectively. The equivalent efficacy in terms of bronchodilation of the two dose strengths (100/6 micrograms and 200/6 micrograms) has been demonstrated in a specific pharmacodynamics study (see section 5.1).

Formoterol

Absorption and distribution
Following inhalation, formoterol is absorbed both from the lung and from the gastrointestinal tract. The fraction of an inhaled dose that is swallowed after administration with a metered dose inhaler (MDI) may range between 60% and 90%. At least 65% of the fraction that is swallowed is absorbed from the gastrointestinal tract. Peak plasma concentrations of unchanged drug occur within 0.5 to 1 hours after oral administration. Plasma protein binding of formoterol is 61-64% with 34% bound to albumin. There was no saturation of binding in the concentration range attained with therapeutic doses. The elimination half-life determined after oral administration is 2-3 hours. Absorption of formoterol is linear following inhalation of 12 to 96 µg of formoterol fumarate.

Biotransformation
Formoterol is widely metabolised and the prominent pathway involves direct conjugation at the phenolic hydroxyl group. Glucuronide acid conjugate is inactive. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Cytochrome P450 isoenzymes CYP2D6, CYP2C19 and CYP2C9 are involved in the O-demethylation of formoterol. Liver appears to be the primary site of metabolism. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

Elimination
The cumulative urinary excretion of formoterol after single inhalation from a dry powder inhaler increased linearly in the 12 – 96 µg dose range. On average, 8% and 25% of the dose was excreted as unchanged and total formoterol, respectively. Based on plasma concentrations measured following inhalation of a single 120 µg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively. The relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.
After oral administration (40 to 80 µg), 6% to 10% of the dose was recovered in urine as unchanged drug in healthy subjects; up to 8% of the dose was recovered as the glucuronide.
A total 67% of an oral dose of formoterol is excreted in urine (mainly as metabolites) and the remainder in the faeces. The renal clearance of formoterol is 150 ml/min.

Special populations
Hepatic/Renal impairment: the pharmacokinetics of formoterol has not been studied in patients with hepatic or renal impairment; however, as formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

Clinical experience
The systemic exposure to beclometasone dipropionate and formoterol in the combination has been compared to the single components. There was no evidence of pharmacokinetic or pharmacodynamic (systemic) interactions between beclometasone dipropionate and formoterol.

5.3 Preclinical safety data

Non-clinical data of the individual components of {Trade name} reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. The toxicity profile of the combination reflected that of single components with no increase in toxicity or unexpected findings.

Reproduction studies in rats showed dose-dependent effects. The presence of beclometasone dipropionate at high doses was associated with reduced female fertility, decrease in the number of implantations and embryofetal toxicity. High doses of corticosteroids to pregnant animals are known to cause abnormalities of fetal development including cleft palate and intra-uterine growth retardation, and it is likely that the effects seen with the beclometasone dipropionate/formoterol combination were due to beclometasone dipropionate. These effects were noted only with high systemic exposure to the active metabolite beclometasone-17-monopropionate (more than 200 fold the expected plasma levels in patients). Additionally, increased duration of gestation and parturition, an effect attributable to the known tocolytic effects of beta$_2$-sympathomimetics, was seen in animal studies. These effects were noted when maternal plasma formoterol levels were below the levels expected in patients treated with {Trade name}.

Genotoxicity studies performed with a beclometasone dipropionate/formoterol combination do not indicate mutagenic potential. No carcinogenicity studies have been performed with the proposed combination. However animal data reported for the individual constituents do not suggest any potential risk of carcinogenicity in man.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (may contain small amounts of milk proteins)
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After first opening the sachet, the medicinal product should be used within 6 months.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.
Only remove the inhaler from its foil package immediately before first use.

Before first opening the sachet:
This medicinal product does not require any special temperature storage conditions.

After first opening the sachet:
Do not store above 25°C.

6.5 Nature and contents of container

Each carton contains 1, 2 or 3 Nexthaler inhalers which provide 120 inhalations each. Each inhaler is contained in a heat sealed protective sachet (foil package) made of PET/Al/PE (Polyethylene Terephtalate/Aluminium/ Polyethylene) or PA/Al/PE (Polyamide/Aluminium/Polyethylene).
Not all pack sizes may be marketed.

{Trade name} is a multi-dose inhalation device. The device consists of a casework comprising a lower shell with window to display number of inhalations left and an integral cover. When opened, the cover, which also drives the dose counter mechanism, reveals a mouthpiece through which the powder is inhaled. The lower shell and mouthpiece are made from acrylonitrile butadiene styrene and the cover is made from polypropylene.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[to be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[to be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

<[to be completed nationally]>