SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FORMAXA AXAHALER 12 micrograms/dose, inhalation powder, hard capsule.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One hard capsule (metered dose) contains 12 micrograms of formoterol fumarate dihydrate. The dose delivered through the mouthpiece is 9 micrograms formoterol fumarate dihydrate.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule.

Colorless hard capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Formoterol is indicated as add on therapy to maintenance treatment with inhaled corticosteroids, for the relief of broncho-obstructive symptoms and prevention of exercise-induced symptoms, in patients with asthma when adequate treatment with corticosteroids is not sufficient. Formoterol is also indicated for the relief of broncho-obstructive symptoms in patients with chronic obstructive pulmonary disease (COPD).

It is recommended that therapy be started by physicians who specialize in pulmonology or pediatrics.

4.2 Posology and method of administration

For use only in adults and adolescents.

For inhalation use.

Use of doses above those normally required by the individual patient on more than 2 days per week, is a sign of suboptimal disease control and maintenance treatment should be reassessed.

Asthma:

In asthma, Formoterol can be used once or twice daily ("regular dosage") and as "relief medication" to relieve acute broncho-obstructive symptoms.

Regular dosage: 1 inhalation once or twice daily. Some patients may need 2 inhalations once or twice daily.

Prevention of exercise-induced bronchoconstriction: 1 inhalation before exercise.

The daily dose for regular use should not exceed 4 inhalations, however occasionally up to a maximum of 6 inhalations may be allowed within a 24-hour period.

No more than 3 inhalations should be taken on any single occasion.

COPD:

Regular dosage: 1 inhalation once or twice daily.

The daily dose for regular use should not exceed 2 inhalations.

If required, additional inhalations above those prescribed for regular therapy may be used for relief of symptoms, up to a maximum total daily dose of 4 inhalations (regular plus as required). More than 2 inhalations should not be taken on any single occasion.

If FORMAXA is replacing some other formoterol inhalers, it must be taken into account that the dose of active substance which the patient is receiving may change. Therefore, the dose may need adjustment.

Special patient groups:

No adjustment of dose should be required in the elderly, or in patients with renal or hepatic impairment at the recommended normal doses. (See section 4.4.).

Children:

FORMAXA is not recommended for children under the age of 12 years.

Use of the device:

FORMAXA is inspiratory flow driven which means that, when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

A package leaflet is included in the package with instructions for use included for the inhaler.

To ensure appropriate administration of the medicinal product, the physician or the nursing staff should advise the patient in the use of the inhaler.

It is important for the patient to know that the hypromellose capsule may break when punctured in the capsule chamber, and small pieces of hypromellose may reach the mouth and pharynx at inhalation. This can be minimized by avoiding pushing the puncture buttons more often than once.

4.3 Contraindications

Hypersensitivity to formoterol or to lactose-monohydrate (which contains small amounts of milk proteins).

4.4 Special warnings and precautions for use

FORMAXA is not a medicinal product that is essentially similar to other inhalers containing formoterol. Patients should not be switched from another formoterol inhaler preparation to FORMAXA without close medical supervision.

Formaxa should only be used in patients requiring long-term regular bronchodilator therapy and not as an alternative to short acting β2-agonists in the event of an acute attack. In the event of an acute attack, a β2-agonists with a short duration of action should be used.

Frequent need of medication for the prevention of exercise-induced bronchoconstriction (EIB) can be a sign of suboptimal asthma control, and warrants a reassessment of the asthma therapy and an evaluation of compliance. If the patient needs prophylactic treatment for EIB several times every week despite adequate maintenance treatment (e.g. corticosteroids and long-acting β2-agonists), the total asthma management should be reassessed by a specialist.

Anti-inflammatory therapy.

Asthma patients who require regular therapy with a beta2-agonists, should also receive regular and adequate doses of inhaled anti-inflammatory agents (e.g. corticosteroids and/or children with sodium chromoglicate) or oral corticosteroids. When FORMAXA is prescribed, patients should be evaluated for the adequacy of the anti-inflammatory therapy they receive. The patient should be advised to continue taking anti-inflammatory therapy unchanged after the introduction of FORMAXA even when the symptoms improve. If the symptoms do not improve, or, if the dosage of FORMAXA needed to control the symptoms increases, it is in general an indication of worsening of the treated condition, and requires a reconsideration of the asthma medication.

Co-existing clinical conditions:

In conjunction with the following clinical conditions, special monitoring of the patient is needed, with special consideration of dosage limits.

Caution should be observed when treating patients with thyrotoxicosis, phaneochromocytoma, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischemic heart disease, tachyarrhythmia, or severe heart failure.

Caution should be observed when treating patients with prolongation of the QTc-interval (> 0.44 sec). Formoterol itself may induce prolongation of the QTc-interval

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Due to the hyperglycemic effect of beta2-agonist, it is recommended that the blood glucose levels must be specially monitored (with extra testing).

Hypokalemia:

Beta2-agonist therapy may cause severe hypokalemia. Special caution is recommended when treating severe asthma, because concomitant hypoxia and medication (see section 4.5), may increase risk of hypokalemia. Monitoring serum potassium levels is recommended in these cases.

The potential of paradoxal bronchospasm must be taken into account in conjunction with FORMAXA therapy. If this occurs, exposure to FORMAXA must be discontinued immediately, and replaced with an alternative therapy.

4.5 Interaction with other medicinal products and other forms of interaction.

Concomitant use of medicinal products such as erythromycin, quinidine, disopyramide, procainamide, phentiazine, antihistamines, and tricyclic antidepressants with FORMAXA and other beta2-agonists may be associated with QT-interval prolongation, and an increased risk of ventricular arrhythmias.

Concomitant use of other sympathomimetic agents may potentiate the undesirable effects of FORMAXA.

FORMAXA should be used with caution in patients on MAO-inhibitors or tricyclic antidepressants, since the action of beta2-agonists on the cardiovascular system may be potentiated.

Concomitant treatment of xanthine derivatives, steroids, and diuretics may potentiate a possible hypokalemic effect of beta2-agonists. Hypokalemia may increase the risk of arrhythmias in patients treated with digitalis (see section 4.4).

Beta-blockers may weaken or antagonise the effect of FORMAXA. Therefore, FORMAXA should not be used concomitantly with beta-blockers (including eye drops), unless there are compelling reasons for their use.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

4.6 Pregnancy and lactation

Clinical experience in pregnant women is limited. During pregnancy, FORMAXA should until further experience is available, only be used after special consideration, especially during the first three months and shortly before delivery.

It is known whether formoterol passes into human breast milk. FORMAXA should therefore not be given to mothers who are breast feeding their infants. In rats, small amounts of formoterol have been detected in maternal milk.

4.7 Effects on ability to drive and use machines

FORMAXA has no or negligible influence on the ability to drive and use machines

4.8 Undesirable effects

Categorization by prevalence:

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)

Musculoskeletal, connective tissue and bone disorders:

Common: tremor.

Uncommon: muscle cramps, myalgia.

Cardiac disorders:

Common: palpitations, tachycardia.

Uncommon: arrhythmias.

Rare: atrial fibrillation, supraventricular tachycardia, extra systoles.

Very rare (including isolated cases): angina pectoris, prolongation of QTc-interval, variations in the blood pressure (decrease or increase).

Metabolism and nutrition disorders:

Rare: hypokalaemia.

Very rare (including. isolated cases): hyperglycaemia.

Treatment with β2-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Skin and subcutaneous disorders:

Rare: exanthema, urticaria, pruritus.

Very rare (including. isolated cases): hypersensitivity reactions, angioneurotic oedema.
Nervous system disorders:
Common: headache.
Uncommon: exitedness, dizziness, anxiety, nervousness, insomnia, agitation, restlessness.
Respiratory tract:
Uncommon: aggravated bronchospasm.
Gastrointestinal disorders.
Rare: nausea.
Local irritation:
Uncommon: irritation in the mouth and pharynx.
Rare: taste disorders.
Isolated cases:
Rare: Hypersensitivity reactions, such as severe hypotension urticaria, angioedema, pruritus or exanthema, peripheral edema.
Lactose monohydrate contains small amounts of milk proteins and can therefore cause allergic reactions.

4.9 Overdose

There is no clinical experience in the management of overdose.
Symptoms of formoterol overdosage may include typical effects of beta2-agonists, such as nausea, vomiting, headache, tremor, somnolence, palpitation, tachycardia, ventricular arrhythmia, metabolic acidosis, hypokalemia, and hyperglycaemia.
Treatment of overdose: Supportive therapy of vital functions, symptomatic therapy. In serious cases the patient should be hospitalised.
Use of cardioselective beta-blockers should be considered. However, they should be used very cautiously because beta-blockers may trigger bronchospasms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Selective beta-2-receptor agonist
ATC code:
R03AC13

The active ingredient in FORMAXA, formoterol, is an effective beta2-agonist, which has a selective effect on beta2-receptors of smooth muscles. It has a strong bronchodilating effect starting within 1 to 3 minutes, and which is still significant 12 hours after the inhalation. In therapeutic doses, the cardiovascular effects are insignificant, and occur infrequently.

Formoterol blocks the release of histamine and leukotrienes from passively sensitized pulmonary mast cells. In animal studies formoterol has been found to have some anti-inflammatory effects, such as an inhibitory effect on edema and clustering of inflammatory cells.
In humans the medicinal product inhibits bronchoconstriction caused by allergens, exercise, cold air, histamine, or methacholine.

5.2 Pharmacokinetic properties

Absorption: It is likely that approx. 90% of the inhaled dose is swallowed and absorbed from the gastro-intestinal tract. Thus, pharmacokinetics of the oral dose is mostly true for the inhaled dose as well.
Oral formoterol fumarate dihydrate is well absorbed from the gastro-intestinal tract up to doses of 300 micrograms. The peak level of the unchanged substance is reached in 0.5 to 1 hour. At least sixty-five percent of an oral dose of 80 micrograms is absorbed.
The pharmacokinetics of formoterol is linear in the studied dosage ranges (20 - 300 micrograms orally). Repeated oral administration (40 - 160 micrograms/day) is not cumulative.
Plasma levels of the active substance following inhaled therapeutic formoterol doses are so low that they were not detectable using past measuring techniques. Measurements of its excretion into the urine indicate rapid absorption of formoterol. The excretion rate peaks in 1 - 2 hours for inhaled doses of 12 to 96 micrograms.
Cumulative excretion of formoterol in the urine has shown that the amount of absorbed formoterol increases in relation to the dose, both at doses of 12 to 24 micrograms of inhalation powder, and at doses of 12 to 96 micrograms of two inhalation aerosols of different composition.

Distribution: Sixty-one to sixty-four percent of formoterol binds to plasma protein (34% mainly to albumin). Formoterol plasma levels resulting from therapeutic doses do not saturate the binding sites.
Metabolism: Formoterol is mainly eliminated via direct glucuronization. Glucuronization via O-methylation is another route.
Elimination: Elimination of formoterol from the circulation appears to be multiphased; the apparent half-life depends on the observed time-interval. The half-life of elimination has been determined as 2 - 3 hours based on measured plasma or blood levels 6, 8, or 12 hours after oral administration. The half-life has been calculated as 5 hours based on measured excretion rates into the urine of varying from 3 to 16 hours.
Formoterol and its metabolites are totally eliminated; 2/3 of the oral dose is excreted into the urine, and 1/3 into the feces. After inhalation, on average, approx. 6 to 9 percent of the dose is excreted unchanged into the urine. The renal clearance of formoterol is 150 mL/min.

5.3 Preclinical safety data

The effects of formoterol seen in toxicity studies in rats and dogs were mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These effects are known pharmacological manifestations seen after the administration of high doses of β2-agonists.

A somewhat reduced fertility in male rats was observed at high systemic exposure to formoterol.

No genotoxic effects of formoterol have been observed in in-vitro or in vivo tests. In rats and mice a slight increase in the incidence of benign uterine leiomyomas has been observed. This effect is looked upon as a class-effect observed in rodents after long exposure to high doses of β2-agonists.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (which contains milk proteins), lactose anhydrous.

Shell *of the capsule*: hypromellose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package, in order to protect from moisture.

6.5 Nature and contents of container

HDPE tablet container closed with a polypropylene screwcap which contains desiccant (silica gel).

Packages of 60 hard capsules + inhaler. The inhaler is made of plastic parts.

6.6. Instructions for Use and Handling

No special requirements (see section 4.2 (mode of administration)).

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

07.08.2005