SUMMARY PRODUCT CHAARACTERISTICS

1. Name of the medicinal product

Forb 100 HFA Inhalation.

Forb 200 HFA Inhalation.

Forb 400 HFA Inhalation.

2. Qualitative and quantitative composition

Each metered dose contains: budesonide 100 micrograms/inhalation and formoterol fumarate dihydrate 6 micrograms/inhalation.

Each metered dose contains: budesonide 200 micrograms/inhalation and formoterol fumarate dihydrate 6 micrograms/inhalation.

Each metered dose contains: budesonide 400 micrograms/inhalation and formoterol fumarate dihydrate 6 micrograms/inhalation.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Inhalation powder.

4. Clinical particulars

4.1 Therapeutic indications

1. Forb 100

- Forb 100 is indicated in adults, adolescents, and children aged 6 years and older.
- Forb 100 is indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β_2 adrenoceptor agonist) is appropriate:
- Patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β_2 adrenoceptor agonists **or**
- Patients already adequately controlled on both inhaled corticosteroids and long-acting β_2 adrenoceptor agonists.

Note: Forb (100 micrograms/6 micrograms/inhalation) is not appropriate in patients with severe asthma.

2. Forb 200

Asthma

Forb 200 is indicated in adults and adolescents (12 years and older) for the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate:

- Patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists **or**

- Patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists.

Chronic Obstructive Pulmonary Disease (COPD)

Forb 200 is indicated in adults, aged 18 years and older, for the symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV1) <70% predicted normal (post bronchodilator) and an exacerbation history despite regular bronchodilator therapy (see also section 4.4).

3. Forb 400

Asthma

Forb 400 is indicated in adults, and adolescents aged 12 - 17 years, for the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate:

- Patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists **or**

- Patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists.

Chronic Obstructive Pulmonary Disease (COPD)

Forb 400 is indicated in adults, aged 18 years and older, for the symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV1) <70% predicted normal (post bronchodilator) and an exacerbation history despite regular bronchodilator therapy (see also section 4.4).

4.2 Posology and method of administration

Route of administration: For inhalation use

Posology

i. Forb 100/200

Forb is not intended for the initial management of asthma. The dosage of the components of Forb 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 maintenance dose is adjusted. If an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of β_2 adrenoceptor agonists and/or corticosteroids by individual inhalers should be prescribed.

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Patients should be regularly reassessed by their prescriber/health care provider so that the dosage of Forb remains optimal. When long-term control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

For Forb there are two treatment approaches:

A. Forb maintenance therapy: Forb is taken as regular maintenance treatment with a separate rapid-acting bronchodilator as rescue.

B. Forb maintenance and reliever therapy: Forb is taken as regular maintenance treatment and as needed in response to symptoms.

A. Forb maintenance therapy

Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Recommended doses:

Adults (18 years and older): 1-2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily.

Adolescents (12 – 17 years): 1-2 inhalations twice daily.

Children (6 years and older): 2 inhalations twice daily.

In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include Forb given once daily, when in the opinion of the

prescriber, a long-acting bronchodilator in combination with an inhaled corticosteroid would be required to maintain control.

Increasing use of a separate rapid acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

Children under 6 years: As only limited data are available, Forb is not recommended for children younger than 6 years.

B. Forb maintenance and reliever therapy

Patients take a daily maintenance dose of Forb and in addition take Forb as needed in response to symptoms. Patients should be advised to always have Forb available for rescue use.

Forb maintenance and reliever therapy should especially be considered for patients with:

• Inadequate asthma control and in frequent need of reliever medication

• Asthma exacerbations in the past requiring medical intervention

Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of Forb as-needed inhalations.

Recommended doses:

Adults and adolescents (12 years and older): The recommended maintenance dose is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion.

A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice. They should be reassessed and their maintenance therapy should be reconsidered.

Children under 12 years: Forb maintenance and reliever therapy is not recommended for children.

ii. Frob 200

A. Forb maintenance therapy

Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Recommended doses:

Adults (18 years and older): 1-2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily.

Adolescents (12 – 17 years): 1-2 inhalations twice daily.

In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include Forb given once daily, when in the opinion of the prescriber, a long-acting bronchodilator in combination with an inhaled corticosteroid would be required to maintain control.

Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

Children (6 years and older): A lower strength (100 micrograms/6 micrograms/inhalation) is available for children 6-11 years.

Children under 6 years: As only limited data are available, Forb is not recommended for children younger than 6 years.

B. Forb maintenance and reliever therapy

Patients take a daily maintenance dose of Forb and in addition take Forb as needed in response to symptoms. Patients should be advised to always have Forb available for rescue use.

Forb maintenance and reliever therapy should especially be considered for patients with:

• Inadequate asthma control and in frequent need of reliever medication

• Asthma exacerbations in the past requiring medical intervention

Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of Forb as-needed inhalations.

Recommended doses:

Adults and adolescents (12 years and older): The recommended maintenance dose is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening. For some patients a maintenance dose of 2 inhalations twice daily may be appropriate. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion.

A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice. They should be reassessed and their maintenance therapy should be reconsidered.

Children under 12 years: Forb maintenance and reliever therapy is not recommended for children.

COPD

Recommended doses:

Adults: 2 inhalations twice daily

iii. Forb 400

Asthma

Recommended doses:

Adults (18 years and older): 1 inhalation twice daily. Some patients may require up to a maximum of 2 inhalations twice daily.

Adolescents (12-17 years): 1 inhalation twice daily.

Patients should be regularly reassessed by their prescriber/health care provider, so that the dosage of Forb remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When long-term control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include Forb given once daily, when in the opinion of the prescriber, a long-acting bronchodilator would be required to maintain control.

Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

Children (6 years and older): A lower strength (100 micrograms/6 micrograms/inhalation) is available for children 6 - 11 years.

Children under 6 years: As only limited data are available, Forb is not recommended for children younger than 6 years.

Forb 400/6 should be used as Forb maintenance therapy only. Lower strengths are available for the Forb maintenance and reliever therapy regimen (200 micrograms/6 micrograms/inhalation and 100 micrograms/6 micrograms/inhalation).

COPD

Recommended doses:

Adults: 1 inhalation twice daily

General information

Special patient groups:

There are no special dosing requirements for elderly patients. There are no data available for use of Forb in patients with hepatic or renal impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

Method of administration

Note: It is important to instruct the patient

• To carefully read the instructions for use in the patient information leaflet which is packed together with each Forb inhaler.

• To breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs.

• Never to breathe out through the mouthpiece.

• To replace the cover of the Forb after use to rinse their mouth out with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

The patient may not taste or feel any medication when using Forb due to the small amount of drug dispensed.

4.3 Contraindications

Hypersensitivity to the active substances or to the excipient 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 and should not be stopped abruptly.

If patients find the treatment ineffective, or exceed the highest recommended dose of Forb, medical attention must be sought (see section 4.2). Sudden and progressive deterioration in control of asthma is potentially life threatening and the patient should undergo urgent medical assessment. In this situation consideration should be given to the need for increased therapy with corticosteroids e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present.

Patients should be advised to have their rescue inhaler available at all times, either Forb (for patients using Forb as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for patients using Forb as maintenance therapy only).

Patients should be reminded to take their Forb maintenance dose as prescribed, even when asymptomatic. The prophylactic use of Forb, e.g. before exercise, has not been studied. The reliever inhalations of Forb should be taken in response to asthma symptoms but are not intended for regular prophylactic use, e.g. before exercise. For such use, a separate rapid-acting bronchodilator should be considered.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Forb. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Forb should be used (see section 4.2).

Patients should not be initiated on Forb 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 Forb. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of Forb.

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath after dosing. If the patient experiences paradoxical bronchospasm Forb should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway (see section 4.8).

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment 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 and glaucoma, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see section 4.8).

Long-term studies with inhaled budesonide in children at mean daily doses of 400 micrograms (metered dose) or in adults at daily doses of 800 micrograms (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of Forb at higher doses is available.

If there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy, care should be taken when transferring patients to Forb therapy.

The benefits of inhaled budesonide therapy would normally minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Recovery may take a considerable amount of time after cessation of oral steroid therapy and hence oral steroid-dependent patients transferred to inhaled budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances HPA axis function should be monitored regularly.

Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore, additional systemic corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Rapid reduction in the dose of steroids can induce acute adrenal crisis. Symptoms and signs which might be seen in acute adrenal crisis may be somewhat vague but may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, seizures, hypotension and hypoglycaemia.

Treatment with supplementary systemic steroids or inhaled budesonide should not be stopped abruptly.

During transfer from oral therapy to Forb, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these conditions. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.

To minimise the risk of oropharyngeal candida infection (see section 4.8), the patient should be instructed to rinse their mouth out with water after inhaling the maintenance dose. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

Concomitant treatment with itraconazole, ritonavir or other potent CYP3A4 inhibitors should be avoided (see section 4.5). If this is not possible the time interval between administration of the interacting drugs should be as long as possible. In patients using potent CYP3A4 inhibitors, Forb maintenance and reliever therapy is not recommended.

Forb should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval.

The need for, and dose of inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

Potentially serious hypokalaemia may result from high doses of β_2 adrenoceptor agonists. Concomitant treatment of $\beta_2$adrenoceptor agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the $\beta_2$adrenoceptor agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the

likelihood for hypokalaemia is increased. It is recommended that serum potassium levels are monitored during these circumstances.

As for all $\beta_2$adrenoceptor agonists, additional blood glucose controls should be considered in diabetic patients.

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.

Paediatric population

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained, if possible. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and budesonide should be as long as possible (section 4.4). In patients using potent CYP3A4 inhibitors, Forb maintenance and reliever therapy is not recommended.

The potent CYP3A4 inhibitor ketoconazole, 200 mg once daily, increased plasma levels of concomitantly orally administered budesonide (single dose of 3 mg) on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average

increased only three-fold showing that separation of the administration times can reduce the increase in plasma levels. Limited data about this interaction for high-dose inhaled budesonide indicates that marked increase in plasma levels (on average four fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 μg).

Pharmacodynamic interactions

Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. Forb should therefore not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons.

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine) 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 β_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 use of other beta-adrenergic drugs or anticholinergic drugs can have a potentially additive bronchodilating effect.

Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Hypokalaemia may result from beta$_2$-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics (see section 4.4).

Budesonide and formoterol have not been observed to interact with any other drugs used in the treatment of asthma.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

During pregnancy, Forb should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.

Breastfeeding

Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of Forb to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Fertility

There is no data available on the potential effect of budesonide on fertility. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Since Forb contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side effects of $\beta_2$adrenoceptor agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment.

Adverse reactions, which have been associated with budesonide or formoterol, are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1000) and very rare (< 1/10 000).

Table 1

SOC	Frequency	Adverse Drug reaction
Infections and infestations	Common	Candida infections in the oropharynx
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, e.g. exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction
Endocrine disorders	Very rare	Cushing's syndrome, adrenal suppression, growth retardation, decrease in bone mineral density
Metabolism and nutrition disorders	Rare	Hypokalaemia
	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Aggression, psychomotor hyperactivity, anxiety, sleep disorders
	Very rare	Depression, behavioural changes (predominantly in children)
Nervous system disorders	Common	Headache, tremor
	Uncommon	Dizziness
	Very rare	Taste disturbances
Eye disorders	Uncommon	Vision blurred (see also section 4.4)
	Very rare	Cataract and glaucoma
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris. Prolongation of QTc-interval
Vascular disorders	Very rare	Variations in blood pressure
Respiratory, thoracic and mediastinal disorders	Common	Mild irritation in the throat, coughing, hoarseness

	Rare	Bronchospasm
Gastrointestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps

Candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each maintenance dose will minimise the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroid. If oropharyngeal thrush occurs, patients should also rinse their mouth out with water after the as-needed inhalations.

As with other inhalation therapy, paradoxical bronchospasm may occur very rarely, affecting less than 1 in 10,000 people, with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Forb should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary (see section 4.4).

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 and glaucoma. Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur. Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure and individual sensitivity.

Treatment with β_2 adrenoceptor agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Paediatric population

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored (see section 4.4).

4.9 Overdose

An overdose of formoterol would likely lead to effects that are typical for β_2 adrenoceptor agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment may be indicated. A dose of 90 micrograms administered during three hours in patients with acute bronchial obstruction raised no safety concerns.

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may appear.

If Forb therapy has to be withdrawn due to overdose of the formoterol component of the drug, provision of appropriate inhaled corticosteroid therapy must be considered.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases: Adrenergics, Inhalants.

ATC-code: R03AK07

Mechanisms of action and Pharmacodynamic effects

Forb contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma exacerbations. The specific properties of budesonide and formoterol allow the combination to be used either as maintenance and reliever therapy, or as maintenance treatment of asthma.

Budesonide

Budesonide is a glucocorticosteroid which when inhaled has a dose-dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer asthma exacerbations. Inhaled budesonide has less severe adverse effects than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown.

Formoterol

Formoterol is a selective $\beta_2$adrenoceptor agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction.

The bronchodilating effect is dose-dependent, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

5.2 Pharmacokinetic properties

Absorption

The fixed-dose combination of budesonide and formoterol, and the corresponding monoproducts have been shown to be bioequivalent with regard to systemic exposure of budesonide and formoterol, respectively. In spite of this, a small increase in cortisol suppression was seen after administration of the fixed-dose combination compared to the monoproducts. The difference is considered not to have an impact on clinical safety.

There was no evidence of pharmacokinetic interactions between budesonide and formoterol.

Pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and formoterol as monoproducts or as the fixed-dose combination. For budesonide, AUC was slightly higher, rate of absorption more rapid and maximal plasma concentration higher after administration of the fixed combination. For formoterol, maximal plasma concentration was similar after administration of the fixed combination. Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation. In studies, mean lung deposition of budesonide after inhalation via the powder inhaler ranged from 32% to 44% of the delivered dose. The systemic bioavailability is approximately 49% of the delivered dose. In children 6-16 years of age the lung deposition falls in the same range as in adults for the same given dose. The resulting plasma concentrations were not determined.

Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. In studies the mean lung deposition of formoterol after inhalation via the powder inhaler ranged from 28% to 49% of the delivered dose. The systemic bioavailability is about 61% of the delivered dose.

Distribution and biotransformation

Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 l/kg for formoterol and 3 l/kg for budesonide. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an

extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-hydroxy-budesonide and 16-alfa-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.

Elimination

The major part of a dose of formoterol is transformed by liver metabolism followed by renal elimination. After inhalation, 8% to 13% of the delivered dose of formoterol is excreted unmetabolised in the urine. Formoterol has a high systemic clearance (approximately 1.4 l/min) and the terminal elimination half-life averages 17 hours.

Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are eliminated in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 l/min) and the plasma elimination half-life after i.v. dosing averages 4 hours.

The pharmacokinetics of formoterol in children have not been studied. The pharmacokinetics of budesonide and formoterol in patients with renal failure are unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

Linearity/non-linearity

Systemic exposure for both budesonide and formoterol correlates in a linear fashion to administered dose.

5.3 Preclinical safety data

The toxicity observed in animal studies with budesonide and formoterol, given in combination or separately, were effects associated with exaggerated pharmacological activity.

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant in humans at the recommended doses. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure and implantation losses as well as decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use. However, these animal experimental results do not seem to be relevant in humans

6. Pharmaceutical particulars

6.1 List of excipients

Ethanol

Sorbitan Trioleate

Propellant HFA 134a (1,1,1,2 Tetrafluoroethane)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage:

Store in dry place below 30^0C. Do not freeze.

6.5 Nature and contents of container

One aluminium canister containing metered doses along with adaptor packed in carton along with pack insert.

6.6 Special precautions for disposal and other handling:

No special requirements