

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gardette, 160 micrograms/4.5 micrograms/actuation pressurised inhalation, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (ex-actuator) contains: budesonide 160 micrograms/actuation and formoterol fumarate dihydrate 4.5 micrograms/actuation.

This is equivalent to a metered dose containing budesonide 200 micrograms/actuation and formoterol fumarate dihydrate 6 micrograms/actuation.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, suspension.

White suspension in an aluminium canister fitted into a red actuator with a grey dust cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic Obstructive Pulmonary Disease (COPD)

Gardette is indicated in adults, aged 18 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: Inhalation use.

COPD

Recommended dose:

Adults: 2 actuations twice daily.

General information

Special patient groups:

There are no special dosing requirements for elderly patients. There are no data available for use of Gardette 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.

Paediatric Population:

There is no relevant use of Gardette 160 micrograms /4.5 micrograms in children 11 years of age and under or in adolescents 12 to 17 years of age in the symptomatic treatment of COPD.

Instructions for the correct use of Gardette

On actuation of Gardette, a volume of the suspension is expelled from the canister at high velocity. When the patient inhales through the mouthpiece at the same time as actuating the inhaler, the substance will follow the inspired air into the airways.

Use of a spacer device (e.g. **AeroChamber Plus Flow Vu or AeroChamber Plus**) with Gardette (pressurised inhalation, suspension) is usually recommended, specially in patients who have, or are likely to have, difficulties to coordinate actuation with inhalation (see section 5.2).

Note: Patients should be instructed on the correct use and care of their inhaler and spacer, and their inhalation technique checked to ensure optimum delivery of inhaled drugs to the lungs. 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 inhaler.
- If a spacer is to be used, carefully read the instructions for use in the instruction leaflet, which is packed with each spacer device.
- If the drying agent, which is inside the wrapper, has leaked out of its packet, do not use the inhaler.
- Shake the inhaler well for at least 5 seconds prior to each use to mix its contents properly.
- Prime the inhaler by actuating it twice into the air when the inhaler is new, has not been used for more than one week or if it has been dropped.
- Remove the mouthpiece cover.
- Hold the inhaler upright.
- Place the mouthpiece in the mouth. While breathing in slowly and deeply, press the device firmly to release the medication. Continue to breathe in and hold the breath for approximately 10 seconds or as long as is comfortable. Inhaling at the same time as actuating the inhaler ensures that active substances reach the lungs.
- Shake the inhaler again and repeat.
- Replace the mouthpiece cover after use.
- Rinse the mouth with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush.
- Clean the mouthpiece of the inhaler regularly, at least once a week with a clean dry cloth.
- Do not put the inhaler into water.

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

Dosing advice

Patients should be advised to have their rescue inhaler available at all times.

Patients should be reminded to take their Gardette maintenance dose as prescribed, even when asymptomatic.

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 dose.

It is recommended that treatment with Gardette is not stopped without supervision by a physician.

Deterioration of disease

If patients find the treatment ineffective, medical attention must be sought. Sudden and progressive deterioration in control of COPD 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.

Transfer from oral therapy

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 Gardette 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.

During transfer from oral therapy to Gardette, 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.

Interactions with other medicinal products

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.

Caution with special diseases

Gardette 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.

Potentially serious hypokalaemia may result from high doses of β_2 adrenoceptor agonists. Concomitant treatment of β_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 β_2 adrenoceptor agonist. It is recommended that serum potassium levels are monitored during these circumstances.

As for all β_2 adrenoceptor agonists, additional blood glucose controls should be considered in diabetic patients.

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

Systemic effects

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).

Potential effects on bone density should be considered particularly in patients on high doses for prolonged periods that have coexisting risk factors for osteoporosis. 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 Gardette at higher doses is available.

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.

Adrenal function

Treatment with supplementary systemic steroids should not be stopped abruptly.

The 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.

Paradoxical bronchospasm

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 Gardette 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).

COPD population

There are no clinical study data on Gardette available in COPD patients with a pre-bronchodilator $FEV_1 > 50\%$ predicted normal and with a post-bronchodilator $FEV_1 < 70\%$ predicted normal (see section 5.1).

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patient with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

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 (see section 4.4).

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. Gardette 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 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

For Gardette or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-foetal development study in the rat showed no evidence of any additional effect from the combination.

There are no adequate data from use of formoterol in pregnant women. In animal studies, formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels (see section 5.3).

Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies, glucocorticosteroids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended doses.

Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.

During pregnancy, Gardette should only be used when the benefits outweigh the potential risks.

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 Gardette 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

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

4.8 Undesirable effects

Since Gardette 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 β_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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ 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 Pneumonia (in COPD patients)
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, dysphonia including 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 dose will minimise the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroid.

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. Gardette 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.

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

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 of formoterol 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 Gardette 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

Gardette contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of COPD exacerbations.

Budesonide

Budesonide is a glucocorticosteroid which when inhaled has a dose-dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer COPD 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 β_2 -adrenoceptor agonist which when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with airway obstruction. The bronchodilating effect is dose dependant, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

Clinical efficacy and safety

The efficacy and safety of Gardette 160 micrograms /4.5 micrograms in the symptomatic treatment of patients with COPD has been evaluated in two 12-month studies (Studies 001 and 003) and one 6-month study (Study 002). Gardette 160 micrograms /4.5 micrograms, 2 inhalations twice daily, was compared with the corresponding dose of formoterol fumarate dihydrate (4.5 μ g, 2 inhalations twice daily) in Studies 001, 002 and 003 and the corresponding dose of budesonide (160 μ g, 2 inhalations twice daily) in Study 002.

The primary endpoints were pre-dose FEV₁ and 1-hour post dose FEV₁ (Study 001 and 002) and COPD exacerbations (Study 003). A total of 4887 patients with moderate to severe COPD were randomised into the 3 trials of which 1178 were on Gardette 160 micrograms /4.5 micrograms. The inclusion criteria for all three studies was pre-bronchodilator FEV₁ <50% predicted normal. Median post-bronchodilator FEV₁ at screening in the trials was 39% predicted normal.

In Studies 001 and 002, Gardette 160 micrograms /4.5 micrograms was superior to placebo for post-dose FEV₁ (180 mL and 170 mL mean increase, respectively) and pre-dose (through) FEV₁ (90 mL and 80 mL mean increase, respectively).

In Studies 001 and 002, Gardette 160 micrograms /4.5 micrograms was also superior to formoterol for post-dose FEV₁ (30 mL and 40 mL mean increase, respectively) and pre-dose (through) FEV₁ (40 mL and 40 mL mean increase, respectively).

In the 12-month study (001), Gardette 160 micrograms /4.5 micrograms resulted in statistically significant and clinically meaningful reductions in severe exacerbations (defined as a worsening of COPD requiring oral steroid use and/or hospitalisation), with a 37% reduction in exacerbation rate ($p < 0.001$) compared with placebo and a 25% reduction in exacerbation rate ($p = 0.004$) compared with formoterol. Gardette significantly reduced the risk of first severe exacerbation by 34% compared to placebo ($p < 0.001$) and by 23% compared to formoterol ($p = 0.015$).

Gardette 160 micrograms /4.5 micrograms also significantly reduced breathlessness, daily rescue medication use, night-time awakenings and improved health-related quality of life (as measured by St. George's Respiratory Questionnaire total score) compared with placebo in both studies.

Serial FEV₁ measures over 12 hours were obtained in subsets of patients in both Studies 001 and 002. The median time to onset of bronchodilation (>15% improvement in FEV₁) was seen at 5 minutes in patients receiving Gardette 160 micrograms /4.5 micrograms. Maximal improvement in FEV₁ occurred at approximately 2 hours post-dose and post-dose bronchodilator effect was generally maintained over 12 hours.

In a second 12-month study (003), Gardette 160 micrograms /4.5 micrograms resulted in statistically significant reductions in the severe exacerbations compared with formoterol, with a 35% reduction in number of exacerbations ($P < 0.001$) and a 21% reduction in the risk of first exacerbation ($p = 0.026$).

The treatment was well tolerated. Evaluation of safety in the 3 trials revealed a safety profile for Gardette that was consistent with the established profiles for Gardette Turbuhaler and the inhaled budesonide and formoterol monoproducts.

Paediatric population

There is no relevant use of Gardette 160 micrograms /4.5 micrograms in children or adolescents in the symptomatic treatment of COPD.

5.2 Pharmacokinetic properties

Absorption

Following administration of Gardette (pressurised inhalation, suspension) 160 micrograms /4.5 micrograms (two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentration of budesonide generally increased in proportion to dose. The accumulation index for the group that received two inhalations twice daily was 1.32 for budesonide and 1.77 for formoterol.

In a single-dose study, 12 inhalations of Gardette (pressurised inhalation, suspension) 80 micrograms /4.5 micrograms (total dose 960/54 µg) were administered to patients with COPD. Mean budesonide peak plasma concentration of 3.3 nmol/L occurred at 30 minutes following dosing whilst mean peak formoterol plasma concentration of 167 pmol/L was rapidly achieved at 15 minutes after dosing.

In a single-dose study, 8 inhalations of Gardette (pressurised inhalation, suspension) 160 micrograms /4.5 micrograms (total dose 1280/36 µg) and Gardette Turbuhaler 160 micrograms /4.5 micrograms (total dose 1280/36 µg) were administered to healthy volunteers. Gardette (pressurised inhalation, suspension) delivered a comparable amount of active drug to the systemic circulation as Gardette Turbuhaler. The AUC for the budesonide component in Gardette (pressurised inhalation, suspension) was 90% of the Turbuhaler comparator. The AUC for the formoterol component in Gardette (pressurised inhalation, suspension) was 116% of the Turbuhaler comparator.

The systemic exposure to budesonide and formoterol from Gardette (pressurised inhalation, suspension) 160 micrograms /4.5 micrograms with and without the **AeroChamber Plus Flow Vu** spacer device was evaluated in a study conducted in healthy volunteers.

The total systemic exposure of Gardette (pressurised inhalation, suspension) administered through the **AeroChamber Plus Flow Vu** spacer was increased compared to no spacer, with mean AUC being 68% and 77% higher for budesonide and formoterol, respectively. However, the highest increases in exposure with spacer were observed in subjects showing low exposure without spacer (most probably due to poor inhalation technique).

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

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 deformedylated 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 budesonide or formoterol in patients with renal failure is 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.

Pre-clinical data on the CFC-free propellant HFA 227 reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Apaflurane (HFA 227)

Povidone

Macrogol 1000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life for Gardette as packaged for sale is 2 years. The shelf life after first opening is 3 months.

6.4 Special precautions for storage

For best results, this medicine should be at room temperature before use. Do not refrigerate or freeze. Protect from frost and direct sunlight.

Replace the mouthpiece cover firmly and snap into position after use.

As with most inhaled medicinal products in pressurised containers, the therapeutic effect of this medicinal product decreases when the container is cold. This medicine should be at room temperature before use. The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister. The canister should not be broken, punctured or burnt, even when it seems empty.

6.5 Nature and contents of container

A pressurised container comprising an internally coated aluminium can, sealed with a metering valve and attached to a dose indicator. The can is fitted into a red plastic actuator incorporating a white plastic mouthpiece and integrated grey plastic dust cap. Each inhaler delivers 120 actuations of budesonide/formoterol fumarate dihydrate 160/4.5 micrograms after initial priming. Each inhaler is individually wrapped in a foil laminate pouch containing a desiccant.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

For Sweden (RMS):

AstraZeneca AB
151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2021-02-19