SCHEDULING STATUS

S4

1. NAME OF MEDICINE:

HALECORD 100/6 [INHALATION POWDER, PRE-DISPENSED 100/6 mcg]

HALECORD 200/6 [INHALATION POWDER, PRE-DISPENSED 200/6 mcg]

HALECORD 400/12 [INHALATION POWDER, 400/12 mcg]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

HALECORD 100/6 [INHALATION POWDER, PRE-DISPENSED 100/6 mcg]

100/6 microgram: Each single dose blister strip contains 100 micrograms of budesonide and 6 micrograms of formoterol fumarate dihydrate, which corresponds to an inhaled dose of 97 micrograms budesonide and 5.5 micrograms formoterol fumarate dihydrate

HALECORD 200/6 [INHALATION POWDER, PRE-DISPENSED 200/6 mcg]

200/6 microgram: Each single dose blister strip contains 200 micrograms of budesonide and 6 micrograms of formoterol fumarate dihydrate, which corresponds to an inhaled dose of 194 micrograms budesonide and 5.5 micrograms formoterol fumarate dihydrate.

HALECORD 400/12 [INHALATION POWDER, PRE-DISPENSED 400/12 mcg]

400/12 microgram: Each single dose blister strip contains 400 micrograms of budesonide and 12 micrograms of formoterol fumarate dihydrate, which corresponds to an inhaled dose of 380 micrograms budesonide and 11 micrograms formoterol fumarate dihydrate.

HALECORD Contains: sugar

100/6 mcg: lactose monohydrate 12.394 mg.

200/6 mcg: lactose monohydrate 12.294 mg

400/12 mcg: lactose monohydrate 12.088 mg

For the full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM:

Inhalation powder.

Pre-dispensed white powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

<u>Asthma</u>

HALECORD 100/6 is indicated in the treatment of asthma in adolescents and adults where use of a combination (inhaled corticosteroid and long-acting beta-2-agonist) is appropriate.

HALECORD 200/6 is indicated in the treatment of asthma in adolescents and adults to achieve overall asthma control, including the prevention and relief of symptoms as well as the reduction of the risk of exacerbations.

HALECORD is suitable for any asthma severity, where the use of inhaled corticosteroids is appropriate and where a long-acting beta-2-agonist is appropriate.

Chronic obstructive pulmonary disease (COPD)

HALECORD 200/6 is indicated for the regular treatment of patients with moderate to severe chronic obstructive pulmonary disease (COPD), with frequent symptoms and a history of exacerbations.

4.2 Posology and method of administration

Posology

The dosage of **HALECORD** should be individualised according to disease severity. When control has been achieved, the dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

HALECORD can be used according to different treatment approaches for asthma:

a) **HALECORD** anti-inflammatory reliever therapy.

b) **HALECORD** anti-inflammatory reliever plus maintenance therapy.

As an alternative, **HALECORD** can be used in a fixed dose therapy:

c) **HALECORD** maintenance therapy.

*a) **HALECORD** anti-inflammatory reliever therapy (patients with mild disease):*

HALECORD 200/6:

HALECORD is taken as needed for the relief of asthma symptoms when they occur, and to prevent allergen- or exercise-induced bronchoconstriction (or to prevent symptoms in those circumstances recognised by the patient to precipitate an asthma attack). The formoterol component in **HALECORD** provides fast onset of effect (within 1-3 minutes) with long-acting (at least 12 hours after a single dose) bronchodilation in reversible airways obstruction. Patients should be advised to always have **HALECORD** available for relief of symptoms.

Clinical studies have demonstrated that **HALECORD** anti-inflammatory reliever therapy provides significant reductions in severe exacerbations and was statistically superior on daily asthma symptom control compared to a short-acting beta-2-agonist therapy alone.

Recommended doses:

Medical Practitioner should discuss allergen exposure and exercise patterns with the patients and take these into consideration when recommending the dose frequency.

Adults and adolescents (12 years and older):

HALECORD 200/6:

Patients should take 1 inhalation as needed in response to symptoms and for the prevention of allergen or exercise-induced bronchoconstriction to control asthma. 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 normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. Patients using more than 8 inhalations daily should be reassessed for alternative explanations of persisting symptoms.

*b) **HALECORD** Anti-inflammatory and Reliever Plus Maintenance Therapy*:

HALECORD 100/6 or **HALECORD 200/6**:

When maintenance treatment with a combination of inhaled corticosteroid and long acting beta-2-agonist is required, **HALECORD** is taken as anti-inflammatory reliever therapy and in addition, patients take a daily maintenance dose of **HALECORD**. The as needed inhalations provide both rapid relief of symptoms and improved overall asthma control. Patients should be advised to have **HALECORD** available for relief of symptoms at all times. A separate inhaler for relief of symptoms is not required.

Clinical studies have demonstrated that **HALECORD** anti-inflammatory reliever plus maintenance therapy provides clinically meaningful reductions in severe exacerbations while maintaining symptom control, compared to **HALECORD** maintenance therapy with a separate short-acting bronchodilator.

Recommended doses:

Adults and adolescents (12 years and older):

HALECORD 100/6:

The recommended maintenance dose is 2 inhalations per day, given either as 1 inhalation in the morning and evening or as 2 inhalations in either the morning or the 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 reassessment of asthma therapy should be considered in patients using an increasing number of **HALECORD** inhalations for symptom relief without achieving improved asthma control within 3 days.

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 temporarily.

If the patient experiences deteriorating symptoms after taking the appropriate maintenance therapy and additional as needed inhalations, the patient should be reassessed for alternative explanations of persisting symptoms.

HALECORD 200/6:

Medical practitioner should discuss allergen exposure and exercise patterns with the patients and take these into consideration when recommending the dose frequency.

Patients should take 1 inhalation as needed in response to symptoms and for the prevention of allergen- or exercise induced bronchoconstriction to control asthma. 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.

Patients also take the recommended maintenance dose, which is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or the evening. For some patients, a maintenance dose of 2 inhalations twice daily may be appropriate.

A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. A reassessment of asthma therapy should be considered in patients using an increasing number of

HALECORD inhalations for symptom relief without achieving improved asthma control within 3 days.

If the patient experiences deteriorating symptoms after taking the appropriate maintenance therapy and additional as needed inhalations, the patient should be reassessed for alternative explanations of persisting symptoms.

*c) **HALECORD** Maintenance Therapy (fixed dose):*

HALECORD 100/6 or H**ALECORD 200/6**:

When maintenance treatment with a combination of inhaled corticosteroid and long-acting beta-2-agonist is required, **HALECORD** is taken as a fixed daily dose treatment, with a separate short-acting bronchodilator for relief of symptoms.

Patients should be advised to have their separate short acting bronchodilator available for relief of symptoms at all times.

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

Recommended doses: Adults

(18 years and older):

HALECORD 100/6 or **HALECORD 200/6**:

1-2 inhalations twice daily. In some cases, a maximum of up to 4 inhalations twice daily may be required as a maintenance dose or temporarily during worsening of asthma.

Adolescents (12-17 years):

HALECORD 100/6 or **HALECORD 200/6**:

1-2 inhalations twice daily. During worsening of asthma, the dose may temporarily be increased to a maximum of 4 inhalations twice daily.

When control has been achieved, the dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

COPD

Adults (18 years and older):

HALECORD 200/6:

2 inhalations twice daily.

Maximum daily dose: 4 inhalations.

General information:

If patients take **HALECORD** as a maintenance therapy, they should be instructed that, for optimal benefit, **HALECORD** must be used even when they are asymptomatic.

Special Populations:

The patients should be instructed that, for optimal benefit, **HALECORD** must be used even when they are asymptomatic.

There are no special dosing requirements for elderly patients.

There are no data available for use of **HALECORD** 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 diseases.

Method of administration

Instructions for correct use of **HALECORD*:***

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

It is important to instruct the patient:

●To carefully read the instructions for use included at the end of the package insert, which

is packed together with each 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 **HALECORD** after use.

●To rinse the mouth out with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush.

The patient may not taste or feel any medicine when using **HALECORD** due to the small amount of medicine dispensed.

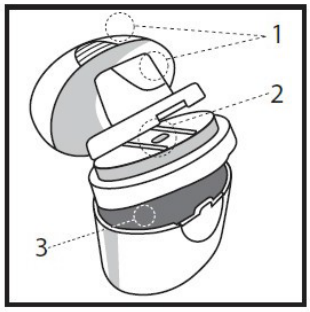
INSTRUCTIONS FOR USE/HANDLING BY PATIENT:

Please read the complete instructions carefully before you start to take your medicine.

HALECORD device is comprised of 3 parts:

- The mouthpiece and its cap (1).
- The surface (2) on which the blister strip is placed (medicine supporting surface).
- The storage case (3) which houses the blister strips.

The three parts are connected to each other and can be independently opened.



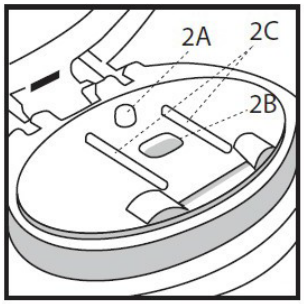
Clinical query: 02/06/2023

The drug supporting surface contains:

- An attachment point (2A) where the blister strip is attached.

- A cavity (2B) which accommodates the blister of the strip.

- Two strip guides (2C) which firmly secure the blister strip in the correct position on the medicine supporting surface.

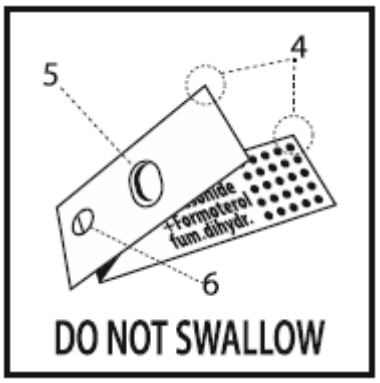


The blister strip consists of:

- Two aluminium sheets (4).

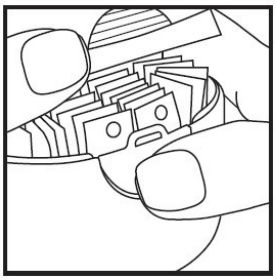
- A blister (5), containing the medicine.

- A hole (6).



A. Preparing the device

Open the storage case by pressing as in the figure, take a strip and close the storage case again.



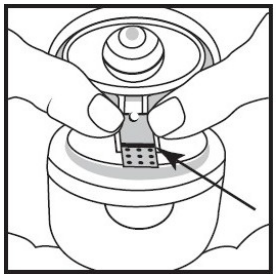
Uncover the mouthpiece completely by applying light pressure on the striped area.

Unlock and push the mouthpiece backwards so as to reveal the medicine supporting surface.

Hold the blister strip with its shiny surface upwards, so as to see the blue line, as shown by the arrow in the figure. The labelled surface of the strip should face downwards.

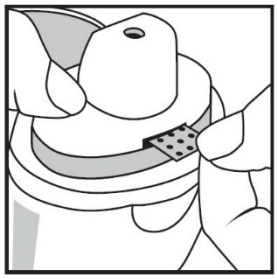
Place the hole of the strip on the attachment point of the medicine supporting surface. By applying light pressure make sure that the strip is securely attached on the attachment point.

The blister of the strip will fit in the cavity of the medicine supporting surface and the guides will secure the strip in the correct position.



Close the mouthpiece and pull away horizontally the embossed protruding end of the strip to be detached.

The dose is now ready to be inhaled.



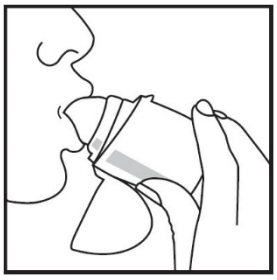
B. Inhalation of the dose

Hold the device away from your mouth. Exhale completely. Be careful not to exhale on the mouthpiece of the device. Bring **HALECORD** to your mouth and place your lips tightly around the mouthpiece.

Breathe in slowly and deeply through your mouth (and not through your nose) until your lungs are full.

Hold in your breath approximately 5 seconds or as long as you comfortably can and at the same time remove the device from your mouth.

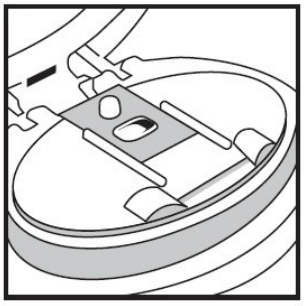
Exhale and continue to breathe normally.



Open the mouthpiece.

You will notice that you have inhaled all the powder and that the blister of the strip is empty.

Remove the empty strip, and proceed to step C.



C. Cleaning the device

Following each use, wipe the mouthpiece and the medicine supporting surface with a dry cloth or dry paper tissue. Do not use water to clean the device.

Close the mouthpiece and its cap.

4.3 Contraindications

- Hypersensitivity to budesonide, formoterol or to inhaled lactose.
- Children below the age of 12 years, as safety and efficacy have not been demonstrated

4.4 Special warnings and precautions for use

Dosing advice

Treatment with **HALECORD** should not be initiated to treat a severe exacerbation.

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

Deterioration of disease

If patients find the treatment ineffective, or exceed the highest recommended dose of **HALECORD**, medical attention must be sought. Sudden and progressive deterioration in control of asthma or 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. For treatment of severe exacerbations, a combination product of inhaled corticosteroid and long-acting beta-2-agonist alone is not sufficient.

Transfer from oral therapy:

Particular care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time. Patients, who have required high dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids, may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

In recommended doses **HALECORD** supplies less than normal physiological amounts of glucocorticosteroid systemically and does NOT provide the mineralocorticosteroid activity that is necessary for coping with these emergencies.

Excipients:

Contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not use **HALECORD.**

Caution with special diseases:

HALECORD should be administered with caution in patients with severe cardiovascular disorders (including heart rhythm abnormalities), diabetes mellitus, untreated hypokalaemia or thyrotoxicosis.

High doses of beta-2-agonists can lower serum potassium by inducing a redistribution of potassium from the extracellular to the intracellular compartment, via stimulation of Na+/K+-ATPase in muscle cells. The clinical importance of this effect is uncertain.

COPD Population:

Clinical studies and meta-analyses indicate that maintenance treatment of COPD with inhaled corticosteroids may lead to an increased risk of pneumonia.

Healthcare professionals should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

Paediatric population:

HALECORD is not indicated in children under 12 years of age.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

The metabolism of budesonide is primarily mediated by the enzyme CYP3A4. Inhibitors of this enzyme, e.g. ketoconazole, may therefore increase systemic exposure to budesonide.

This is of limited clinical importance for short-term (1-2 weeks) treatment with ketoconazole but should be taken into consideration during long-term treatment with ketoconazole.

Pharmacodynamic interactions

Beta-adrenergic blockers (including eye drops) can weaken or inhibit the effect of formoterol. Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular dysrhythmias.

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

4.6 Fertility, pregnancy, and lactation

Pregnancy

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

There are no adequate data from use of formoterol (as in **HALECORD)** in pregnant women. In animal reproductive studies formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels (see Preclinical safety data).

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 Preclinical safety data). 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, **HALECORD** 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.

<u>Lactation</u>

Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol (as in **HALECORD)** passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk.

Administration of **HALECORD** 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.

4.7 Effects on the ability to drive and use machines

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

4.8 Undesirable effects

Since **HALECORD** 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 medicine 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 by frequency and system organ class (SOC)

Frequency	**System Organ Class**	**Event**
Frequent	*Cardiac disorders:*	Palpitations
	Infections and infestations:	Candida infections in oropharynx, Pneumonia (in COPD patients)
	Nervous system disorders:	Headache, tremor
	Respiratory, thoracic and mediastinal disorders:	Irritation in the throat, coughing, hoarseness
Less frequent	*Cardiac disorders:*	Tachycardia
	Gastrointestinal disorders:	Nausea
	Musculoskeletal and connective tissue disorders:	Muscle cramps
	Nervous system disorders:	Dizziness
	Psychiatric disorders:	Agitation, restlessness, nervousness, sleep disturbances
Less frequent	*Cardiac disorders:*	Cardiac dysrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Immune system disorders:	Immediate and delayed hypersensitivity reactions, e.g. dermatitis, exanthema, urticaria, pruritus, angioedema and anaphylactic reaction.

	Respiratory, thoracic and mediastinal disorders:	Bronchospasm
	Skin and subcutaneous tissue disorders:	Skin bruising
Less frequent	*Cardiac disorders:*	Angina pectoris
	Endocrine disorders:	Signs or symptoms of systemic gluco-corticosteroid effects, e.g. hypofunction of the adrenal gland
	Metabolism and nutrition disorders:	Hyperglycaemia
	Psychiatric disorders:	Depression, behavioural disturbances

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Paediatric population

Not indicated.

4.9 Overdose

An overdose of formoterol (as in **HALECORD**) 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

A 21.5.1. Pharmacotherapeutic group: Corticosteroids and analogues

Mechanisms of action and pharmacodynamic effects

HALECORD 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.

Mechanism of action of each active substance is displayed below:

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

Budesonide/Formoterol Combination

Asthma

5.2 Pharmacokinetic properties

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

Pharmacokinetic parameters: for the combination there was a higher exposure to budesonide compared to the administration of budesonide and formoterol as monoproducts.

Absorption:

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 inhaler ranged from 32-44 % of the delivered dose. The systemic bioavailability is approximately 49 % of the delivered dose.

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 inhaler ranged from 28-49 % of the delivered dose. The systemic availability is about 61 % of the delivered dose.

Distribution and metabolism:

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, i.e. 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 unmetabolized 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 litres/minute) and the plasma elimination half-life after IV dosing averages 4 hours.

Budesonide has a systemic clearance of approximately 0,5 litres/min in 4-6 year(s) old asthmatic children. Per kilogram body weight, children have a clearance which is approximately 50 % greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2,3 hours in asthmatic children.
The pharmacokinetics of formoterol in children has not been studied.
The pharmacokinetics of budesonide or formoterol in elderly 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 Pre-clinical 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

Lactose monohydrate (contains milk proteins).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below or below 30 °C

6.5 Nature and contents of container

Budesonide and formoterol fumarate dihydrate 100/6 mcg:

A white plastic inhalation device, containing 60 alu-alu single dose blister strips and a spare canister containing 60 alu-alu blisters, are packed in a carton box together with the instruction leaflet (BT x 120 doses: 1 device x 60 doses + 1 canister x 60 doses)

Budesonide and formoterol fumarate dihydrate 200/6 mcg:

A white plastic inhalation device, containing 60 alu-alu single dose blister strips and spare plastic canister containing 60 alu-alu single dose blister strips packed in a carton box together with the instruction leaflet (BT x 120 doses:1 device x 60 doses + 1 canister x 60 doses).

Budesonide & formoterol fumarate dehydrate 400/12 mcg:

A white plastic inhalation device, containing 60 alu-alu dose blister strips, packed in a carton box together with the instruction leaflet (BT x 60 doses: 1 device x 60 doses).

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicine or waste material should be returned to the pharmacy for destruction or it must be disposed of in accordance with local requirements for medical waste destruction.

7. Holder of certificate of registration

Innovata Pharmaceuticals

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. Registration numbers

TBI

9. Date of first authorization/Renewal of the authorization

TBI

10. Date of revision of the text

TBI

REFERENCES:

Ref 1: Symbicord Turbuhaler 80/4,5 microgram/dose.

Date of publication: 25 January 2022

Marketing authorisation holder; AstraZeneca Pharmaceuticals (Pty) Ltd, Building 2, Northdowns Office Park, 17 Georgian Crescent West, Bryanston, Johannesburg, 2191

Ref 2: Symbicort Turbohaler 200micrograms/6 micrograms/inhalation, inhalation powder. SmPC

Date of first authorisation: 15th May 2001

Date of last renewal: 19th February 2010

Date of revision of the text: 20th August 2019

Marketing authorisation holder; AstraZeneca UK Limited, 600 Capability Green, Luton, LU1 3LU, UK.