PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

FACET® TURBUHALER® 320:9 µg/dose (Inhaler)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose contains as active constituents:

Budesonide 320 micrograms and formoterol fumarate dihydrate 9 micrograms.

Formoterol fumarate dihydrate is hereafter referred to as 'formoterol'.

Contains sugar: lactose monohydrate 491 µg per dose

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhaler:

The colour of the turning grip is red. On the turning grip a Braille code is embossed. The colour of the cover is white. Inside the cover 5 fins are present. The figure 60 is visible in the dose-indicator window. The mouthpiece has 4 bars, and can be rotated.

Contents:

The contents are white to off-white, predominantly in the form of rounded granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma:

FACET TURBUHALER 320:9 µg/dose is indicated in the treatment of asthma in adolescents and adults needing inhaled corticosteroids where continued use of a high dose combination (inhaled corticosteroid and long-acting beta-2-agonist) is appropriate.

COPD:

FACET TURBUHALER 320:9 µg/dose is indicated in 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 FACET TURBUHALER 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.

FACET TURBUHALER is taken as regular maintenance treatment. Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times. Increasing use of rapid-acting bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the therapy.

Patient	***Dosage***	***Recommendation***

Asthma in adults:		
Adults (18 years and older):	1 inhalation twice daily.	In some cases, a maximum of up to 2 inhalations twice daily may be required as a maintenance dose or temporarily during worsening of asthma.
Adolescents (12-17 years):	1 inhalation twice daily.	During worsening of asthma, the dose may temporarily be increased to a maximum of 2 inhalations twice daily.
COPD:		
Adults (18 years and older):	1 inhalation twice daily	Maximum daily dose: 2 inhalations

Efficacy and safety have not been studied in children for FACET TURBUHALER 320:9 µg/dose.

FACET TURBUHALER 320:9 µg/dose should be used as FACET maintenance therapy only. Lower strengths are available for the FACET maintenance and reliever therapy regimen.

General information:

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

Special Populations

There are no special dosing requirements for elderly patients.

There are no data available for use of FACET TURBUHALER 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.

Instructions for correct use of TURBUHALER:

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

Note: It is important to instruct the patient:

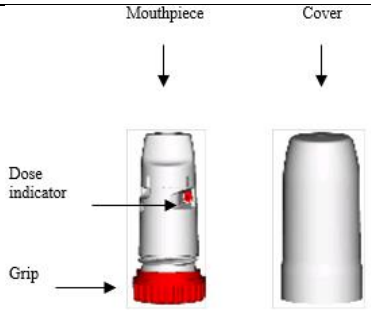
- To carefully read the instructions for use included below in this professional information, which is packed together with each inhaler.
- To breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs.
- Never to breathe out through the mouthpiece.
- To replace the cover of the FACET TURBUHALER 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 medication when using TURBUHALER due to the small amount of medicine dispensed.

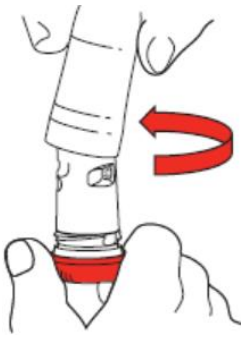
Method of administration

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

Turbuhaler (Fig. 1) is a multidose inhaler from which very small amounts of powder (which you will not taste or feel) are administered. When you breathe in through the	

Turbuhaler the powder is delivered to your lungs. It is therefore important that you **inhale forcefully and deeply** through the mouthpiece	 **Fig.1**

How to use Facet Turbuhaler

To administer one dose, simply follow the instructions below. Unscrew and lift off the cover (Fig. 2).	 **Fig. 2**

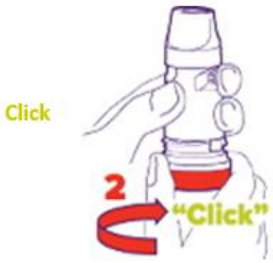
TWIST, CLICK AND INHALE

1. TWIST

Hold the inhaler upright with the red grip downwards and **twist** the grip as far as it will go in one direction. Do not hold the mouthpiece when you turn the grip (Fig. 3).	 **Fig. 3**

2. CLICK

Then **twist the grip as far as it will go in the opposite**	

direction (Fig. 4). A **click** will tell you that your dose is loaded. *Perform the procedure twice if you are using the Turbuhaler for the first time.* **Breathe out**. Do **not** breathe out **through** the mouthpiece.	 **Fig. 4**

3. INHALE

Place the mouthpiece gently between your teeth, close your lips and **inhale forcefully and deeply through the device**. Do not chew or bite hard on the mouthpiece. Remove the inhaler from your mouth, before breathing out. If more than one dose has been prescribed, repeat steps 1-3.	 **Fig. 5**

REMEMBER YOU WILL NOT TASTE OR FEEL THE POWDER.

Replace the cover (by screwing it back on tightly) after use.

Rinse your mouth with water after the daily maintenance dose. Do not swallow.

Cleaning:

Wipe the outside of the mouthpiece regularly (once a week) with a dry tissue. **Do not use water or other liquids when cleaning the mouthpiece.**

IMPORTANT INFORMATION TO NOTE!

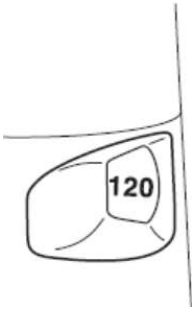
Don't be concerned if you click your Turbuhaler more than once. The dose counter will continue moving, however it can only give you one dose at a time.

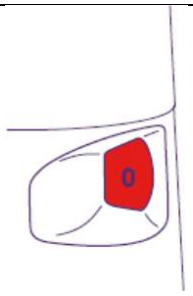
Do not try to remove the mouthpiece since it is fixed to the Turbuhaler.
The mouthpiece can be rotated, but do not twist it unnecessarily.

As the amount of powder dispensed is very small, you may not be able to taste it after inhalation. However, you can still be confident that you have inhaled the dose if you have followed the instructions.

The rattling sound heard if you shake the inhaler is not produced by the medication but by the drying agent.

How will I know when to replace my inhaler?

The dose indicator (Fig.6) tells you approximately how many doses are left in the inhaler, starting with either 60 or 120 when full. The indicator is marked in intervals of 10 doses. Therefore, it does not show the loading of each individual dose. You should be reassured that Turbuhaler delivers the dose even if you may not notice a movement in the dose indicator.	 **Fig. 6**

For the last 20 doses, the background of the indicator is red. When the zero reaches the middle of the window (Fig. 7), it is time for you to discard the inhaler. Please note that even when the dose indicator registers zero, it is still possible to turn the grip. The red grip will still twist and click even when your Turbuhaler is empty. However, the indicator stops moving and the zero remains in the window.	 **Fig. 7**

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

Treatment with FACET TURBUHALER 320:9 µg/dose should not be initiated to treat a severe exacerbation.

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

If patients find the treatment ineffective, or exceed the prescribed dose of FACET TURBUHALER, 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.

Medical practitioners should closely follow the growth of children and adolescents taking long-term corticosteroids by any route, and weigh the benefits of the corticosteroid therapy against the possible risk of growth suppression.

Particular care is needed in patients who are transferred from systemic to inhaled glucocorticosteroids, since they may remain at risk of impaired adrenal function for a considerable time. Patients who have required 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 surgery and infection or conditions associated with severe electrolyte loss or severe stress. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

In recommended doses FACET TURBUHALER 320:9 µg/dose supplies less than normal physiological amounts of glucocorticosteroid systemically and does NOT provide the mineralocorticosteroid activity that is necessary for coping with these emergencies.

FACET TURBUHALER 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.

FACET TURBUHALER contains lactose (< 1 mg/inhalation). This amount may cause problems in lactose intolerant people.

COPD population:

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

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

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, 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

The safety of FACET TURBUHALER in pregnant and lactating women has not been established. Corticosteroids are teratogenic in animals.

Pregnancy

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.

Breastfeeding

Safety in breastfeeding has not been demonstrated. A clinical pharmacology study has shown that inhaled budesonide is excreted in breast milk.

Fertility

There are no animal studies on the effect of the budesonide/formoterol combination on fertility.

4.7 Effects on ability to drive and use machines

FACET TURBUHALER is not expected to adversely affect the ability to drive or use machines.

4.8 Undesirable effects

a) Summary of the safety profile

Since FACET TURBUHALER contains both budesonide and formoterol, the same type and intensity of undesirable effects as reported for these substances may occur. The most common medicine related adverse reactions are pharmacologically predictable side effects of beta-2-

agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment.

b) Tabulated summary of adverse reactions

Adverse reactions which have been associated with budesonide or formoterol are given below in Table 1:

Table 1: Adverse reactions by frequency and system organ class (SOC):

Frequency	**System Organ Class**	**Event**
Common 1 % to 10 %	*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,
Uncommon 0,1 % to 1 %	*Cardiac disorders:*	Tachycardia
	Gastrointestinal disorders:	Nausea
	Musculoskeletal and connective tissue disorders:	Muscle cramps
	Nervous system disorders:	Dizziness
	Psychiatric disorders:	Agitation, restlessness, nervousness, sleep

		disturbances
Rare 0,01 % to 0,1 %	*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
Very rare < 0,01 %	*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

4.9 Overdose

An overdose of formoterol would likely lead to effects that are typical for beta-2-adrenergic agonists: tremor, headache, palpitations, and tachycardia. Hypotension, metabolic acidosis, hypokalaemia and hyperglycaemia may also occur. Supportive and symptomatic treatment may be indicated. A dose of 90 micrograms administered during 3 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 may appear.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.5.1 Corticosteroids and analogues

Mechanisms of action and pharmacodynamic effects:

FACET TURBUHALER contains budesonide and formoterol, which have different modes of action. The respective mechanisms of action of both medicines are discussed below.

Budesonide:

Budesonide is a glucocorticosteroid with a local anti-inflammatory effect in the airways. The exact mechanisms of action of corticosteroids in asthma are not fully understood.

Formoterol:

Formoterol is a selective beta-2-adrenergic agonist that produces relaxation of bronchial smooth muscle. The bronchodilating effect sets in within 1-3 minutes after inhalation, and lasts up to 12 hours after a single dose.

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 TURBUHALER 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 TURBUHALER 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 litres/kg for formoterol and 3 litres/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-hydroxybudesonide and 16-alpha-hydroxyprednisolone, 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 eliminated by metabolism in the liver followed by renal excretion. After inhalation, 8-13 % of the delivered dose of formoterol is excreted unmetabolised in the urine. Formoterol has a high systemic clearance (approximately 1,4 litres/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 excreted 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 i.v. 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 and patients with renal failure is unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (which may contain milk protein residue).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

Store with cover tightened.

6.5 Nature and contents of container

FACET TURBUHALER is a multidose inspiratory flow driven, dry powder inhaler. The inhaler is made of plastic parts. Each inhaler contains 60 doses.

6.6 Special precautions for disposal and other handling

No special requirements. Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2, Northdowns Office Park

17 Georgian Crescent West

Bryanston, Johannesburg, 2191

South Africa

8 REGISTRATION NUMBER

45/21.5.1/0259

9 DATE OF FIRST AUTHORISATION

12 May 2020

10 DATE OF REVISION OF THE TEXT

19 July 2022