1.3.1.1 PROFFESIONAL INFORMATION (APPROVED)

SCHEDULING STATUS: **S 4**

1. NAME OF THE MEDICINE

Vannair® 80:4,5 (Inhaler)

Vannair® 160:4,5 (Inhaler)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VANNAIR® 80:4,5:

Each single actuation contains as active constituents:

Budesonide 80 µg and formoterol fumarate dihydrate 4,5 µg (hereafter referred to as formoterol).

VANNAIR® 160:4,5:

Each single actuation contains as active constituents:

Budesonide 160 µg and formoterol 4,5 µg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

The canister contains a white to off-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma:

VANNAIR 80:4,5 & 160:4,5:

VANNAIR is indicated in the treatment of asthma in adults and children 6 years and older where continued use of a combination (inhaled corticosteroid and long-acting beta-2-agonist) is appropriate.

COPD:

VANNAIR 160:4,5:

VANNAIR 160:4,5 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

The dosage of VANNAIR 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. VANNAIR 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 a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

Patient	***Dosage***	***Recommendation***
Asthma in adults and adolescents: ***VANNAIR 80:4,5 or 160:4,5:***		
Adults (18 years and older):	2 inhalations twice daily	In some cases, up to a maximum of 4 inhalations twice daily may be required as maintenance dose or temporarily during worsening of asthma.
Adolescents (12-17 years):	2 inhalations twice daily	During worsening of asthma the dose may temporarily be increased to a maximum of 4 inhalations twice daily.
Asthma in children: ***VANNAIR 80:4,5:***		
Children (6-11 years):	2 inhalations twice daily	Maximum daily dose: 4 inhalations
COPD: ***VANNAIR 160:4,5:***		
Adults (18 years and older):	2 inhalations twice daily	Maximum daily dose: 4 inhalations

General information:

The patients should be instructed that, for optimal benefit VANNAIR 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 VANNAIR 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 VANNAIR inhaler:

On actuation of VANNAIR, 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.

Note: 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.
- Shake the inhaler gently 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 1 week or if it has been dropped.
- Place the mouthpiece in the mouth. While breathing 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.
- Shake the inhaler again and repeat.

- Rinse the mouth with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush.
- Clean the mouthpiece of the inhaler regularly, at least once a week with a dry clean cloth.
- Do not put the inhaler into water.
- The VANNAIR inhaler must not be taken apart. The VANNAIR canister must only be used with the VANNAIR actuator and, the VANNAIR actuator must not be used with any other inhalation product.

4.3 Contraindications

Hypersensitivity (allergy) to budesonide, formoterol or any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

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

It is recommended that the dose be tapered when long-term treatment is

discontinued and should not be stopped abruptly.

If the patient finds the treatment ineffective, or exceeds the prescribed dose of VANNAIR, 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.

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

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

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 VANNAIR supplies less than normal physiological amounts of glucocorticosteroid systematically and does NOT provide the mineral corticosteroid activity that is necessary for coping with these emergencies.

VANNAIR 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 re-distribution 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.

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 VANNAIR in pregnant and lactating women has not been established.

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated summary of adverse reactions

Since VANNAIR 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 disappear within a few days of treatment.

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 glucocorticosteroid 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 µg 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

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

ATC-code: R03AK07

Mechanism of action and pharmacodynamic effects:

VANNAIR 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 slightly higher exposure to formoterol compared to the administration of formoterol as a monoproduct.

Absorption:

Inhaled budesonide is rapidly absorbed, and the maximum plasma concentration is reached within 30 minutes after inhalation. In studies, meanlung deposition of budesonide after inhalation via 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 inhaler ranged from 28-49 % of the delivered dose.

The systemic bioavailability is approximately 61 % of the delivered dose.

In children the plasma concentration and lung deposition fall in the same range as in adults.

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/min) and the plasma elimination half-life after i.v. dosing averages 4 hours.

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 the elderly and in patients with renal failure is unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Apaflurane (HFA 227), macrogol (polyethylene glycol) 1000 and povidone K25.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 30 °C.

Keep out of reach of children.

The canister should not be broken, punctured or burnt, even when apparently empty. The canister contains a pressurised liquid. Do not expose to temperatures above 50 °C.

6.5. Nature and contents of container

VANNAIR consists of a canister, actuation counter, shield component and actuator. The actuation counter is attached to the base of the canister, then fitted into a plastic actuator with a white mouthpiece and a grey dust cap.

VANNAIR is a pressurised container, comprising an internally coated aluminium canister, sealed with a metering valve and fitted into a plastic actuator. Each inhaler is individually wrapped in a foil laminate pouch containing a desiccant.

Each inhaler delivers 120 actuations of budesonide/formoterol fumarate dihydrate micronised 80/4,5 or 160/4,5 µg after initial priming.

6.6. Special precautions for disposal and other handling

No special requirements.

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 NUMBERS

VANNAIR 80:4,5: A39/21.5.1/0506

VANNAIR 160:4,5: A39/21.5.1/0507

9. DATE OF FIRST AUTHORISATION

08th February 2008

10. DATE OF REVISION OF THE TEXT

16 October 2020

INSTRUCTIONS FOR USE/HANDLING:

Please read all the following instructions carefully before using your inhaler.

Information about your VANNAIR inhaler:

- Your doctor, nurse or pharmacist should instruct you on the correct use of your inhaler.
- Your inhaler will already be assembled when you first receive it. Please do not you're your inhaler apart. If it becomes loose, then place it back and continue to use it as instructed.
- Before starting to use your VANNAIR inhaler, remove it from the foil wrapper. Throw away the wrapper as well as the drying agent, which is inside the wrapper. If the drying agent has leaked out of its packet, do not use the inhaler.
- After you have taken the inhaler out of its foil wrapper, you should use it within 3 months. Write the use by date (3 months from opening the wrapper) on the inhaler carton to remind you when to stop using the inhaler.
- PLEASE NOTE: The VANNAIR inhaler must not be taken apart. The VANNAIR canister must only be used with the VANNAIR actuator and, the VANNAIR actuator must not be used with any other inhalation product.
- The parts of your inhaler are shown in the picture (Figure 1).

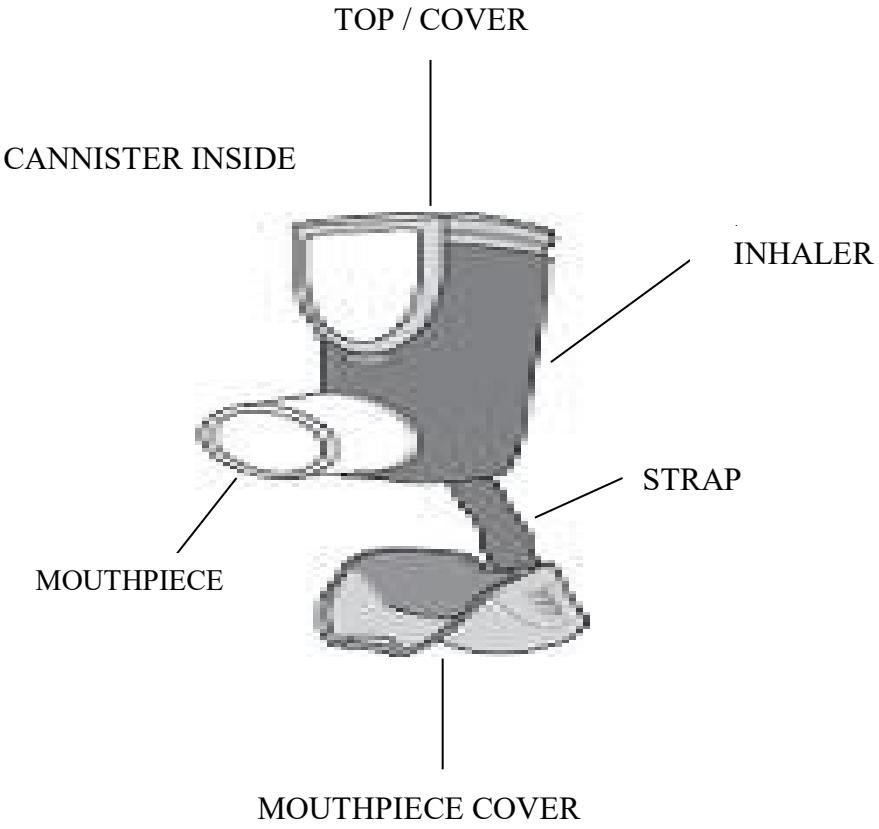

Figure 1

Preparing your VANNAIR inhaler:

You need to prepare your inhaler for use in the following situations:

- If you are using your new VANNAIR inhaler for the first time.
- If you have not used it for more than 7 days.
- If it has been dropped.

To prepare your inhaler for use, follow the instructions below:

1. Shake the inhaler well to mix the contents of the aerosol canister.
2. Remove the mouthpiece cover by pressing lightly on the bumps on the side. The strap on the mouthpiece cover will stay attached to the inhaler.
3. Hold the inhaler upright. Then press the counter (on the top of the inhaler) to release a puff into the air. You can use 1 or both hands, as shown in the pictures (Figure 2 and 3).

Figure 2

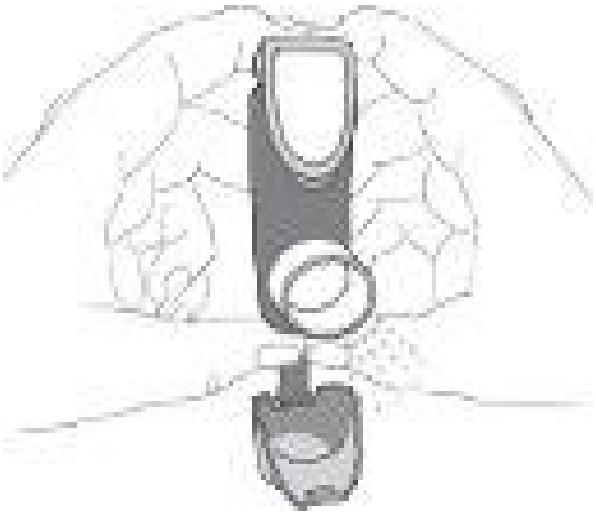

Figure 3

4. Release your finger(s) from the counter.
5. Wait for 10 seconds, shake well and then repeat steps 3 and 4.
6. Your inhaler is now ready for use.

How to take an inhalation:

Each time you need to take an inhalation, follow the instructions below:

1. Shake the inhaler well to mix the contents of the aerosol canister.
2. Remove the mouthpiece cover by pressing lightly on the bumps on the side. Check that the mouthpiece is not blocked.
3. Hold your inhaler upright in front of your mouth, using your thumb(s) at the base of the inhaler and your index finger(s) on the top. Breathe out gently.
4. Place the mouthpiece gently between your teeth. Close your lips (Figure 4).
5. Start to breathe in slowly and deeply through your mouth. Press the counter (on the top of the inhaler) firmly to release a puff. Keep breathing in for a short while after pressing the counter.

Figure 4

6. Continue to breathe in and hold your breath for approximately 10 seconds, or for as long as it is comfortable.
7. Before you breathe out, release your finger from the counter and remove the inhaler from your mouth. Keep the inhaler upright.
8. To take another inhalation, shake the inhaler well for 5 seconds and repeat steps 3 to 7.
9. Replace the mouthpiece cover. Always store your VANNAIR inhaler so that it stands upright on its red plastic base.
10. Rinse your mouth with water after your daily morning and or/evening doses and spit it out.

Cleaning your VANNAIR inhaler:

Your inhaler mouthpiece will need to be cleaned regularly, at least once a week and to do this you will need to:

1. Remove the mouthpiece.
2. Wipe the inside and outside of the mouthpiece opening with a clean, dry cloth.
3. Replace the mouthpiece cover.
4. Do not put the inhaler in water.
5. Do not try to take the inhaler apart.

How will I know when to replace my VANNAIR inhaler?

READING THE COUNTER:

- The arrow on the counter on the top of the inhaler points to the number of inhalations (puffs) remaining in your inhaler.
- The counter will count down towards zero (‘0’) each time you release a puff of medicine (either when preparing your inhaler for use or when taking the medicine).

- When the arrow on the counter enters the yellow area, this means that there are about 20 puffs left.

- It is very important that you note the number of inhalations (puffs) remaining in your VANNAIR inhaler by reading the counter. Discard VANNAIR after the counter reaches zero ('0'), indicating that you have used the number of inhalations on the product label and box. Your inhaler may not feel empty and it may continue to operate, but you will not get the right amount of medicine if you keep using it.

REMEMBER:

VANNAIR has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

AstraZeneca Logo

Ref: Vannair 80:4,5 and 160:4,5 – EPI (29-09-2020)

CDS: June 2020