NEW ZEALAND DATA SHEET

1. PRODUCT NAME

VANNAIR® 100/6, metered aerosol inhaler
VANNAIR® 200/6, metered aerosol inhaler

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VANNAIR is a pressurised metered dose inhaler, comprising an internally coated aluminium can, sealed with a metering valve and fitted into a plastic actuator.

VANNAIR 100/6

VANNAIR 100/6 pMDI delivers the same amount of budesonide and formoterol as Symbicort Turbuhaler® 100/6.

Each delivered dose (the dose that leaves the mouthpiece) of VANNAIR 100/6 pMDI contains as active constituents: budesonide 80 micrograms/inhalation and formoterol fumarate dihydrate 4.5 micrograms/inhalation.

Each inhaler contains 120 inhalations.

VANNAIR 200/6

VANNAIR 200/6 pMDI delivers the same amount of budesonide and formoterol as Symbicort Turbuhaler 200/6.

Each delivered dose (the dose that leaves the mouthpiece) of VANNAIR 200/6 pMDI contains as active constituents: budesonide 160 micrograms/inhalation and formoterol fumarate dihydrate 4.5 micrograms/inhalation.

Each inhaler contains 120 inhalations.

Formoterol fumarate dihydrate is hereafter referred to as formoterol.

3. PHARMACEUTICAL FORM

Metered aerosol inhaler

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4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Asthma

VANNAIR pMDI is indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting beta-2-agonist) is appropriate. This includes:

- Patients who are not adequately controlled with inhaled corticosteroid therapy and "as needed" inhaled short-acting beta-2 adrenoceptor agonists.
- Patients who are already adequately controlled on regular separate long acting beta-agonist and inhaled corticosteroid therapies.

Chronic obstructive pulmonary disease (COPD)

VANNAIR 200/6 pMDI is indicated for the symptomatic treatment of moderate to severe COPD (pre-bronchodilator FEV_1 ≤50% predicted normal) in adults with frequent symptoms despite long-acting bronchodilator use, and a history of recurrent exacerbations. VANNAIR is not indicated for the initiation of bronchodilator therapy in COPD.

4.2 DOSE AND METHOD OF ADMINISTRATION

The dosage of VANNAIR pMDI 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.

Asthma

The patients should be instructed that VANNAIR pMDI must be used even when asymptomatic for optimal benefit.

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

Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants reassessment of the asthma therapy.

<u>Adults and adolescents (12 years and older):</u>

VANNAIR 100/6:	2 inhalations once or twice daily. Maximum daily maintenance dose: 4 inhalations
VANNAIR 200/6:	2 inhalations once or twice daily. Maximum daily maintenance dose: 4 inhalations

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

Children (6-11 years)

VANNAIR 100/6: 2 inhalations twice daily.
Maximum daily dose: 4 inhalations

Children under 6 years of age:

The use of VANNAIR is not recommended in children under six years of age.

COPD

Adults

Two inhalations of VANNAIR 200/6 twice daily. The maximum recommended daily dose is 4 inhalations (corresponding to 800 µg budesonide / 24 µg formoterol).

Special Populations

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 pMDI

On actuation of VANNAIR pMDI, 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 in the patient information leaflet 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 or has not been used for more than one week or if it has been dropped.
- 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.
- shake the inhaler again and repeat.
- 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 (allergy) to budesonide, formoterol or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Dosing and discontinuation

The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

Therapy with VANNAIR should not be initiated during a severe exacerbation or if patients have significantly worsening or acutely deteriorating asthma.

The lowest effective dose of VANNAIR should be used.

Patients should be reminded to take their VANNAIR maintenance dose as prescribed, even when asymptomatic. They should also be advised to have their rescue inhaler available at all times.

VANNAIR should not be taken in response to asthma symptoms. For such use, a separate rapid-acting bronchodilator should be considered.

If the patient finds the treatment ineffective or exceeds the prescribed dose of VANNAIR pMDI, the patient should be reviewed by a physician.

Once asthma symptoms are controlled, consideration may be given to stepping down treatment with VANNAIR. Regular review of patients as treatment is stepped down is important.

When long-term treatment with VANNAIR is to be discontinued, the dose should be tapered. Treatment should not be stopped abruptly.

Deterioration of asthma control

Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control.

Sudden and progressive deterioration in control of asthma is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids, e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present.

Patients should be advised to seek medical attention if sudden deterioration of their asthma occurs, or if they find that short-acting relief bronchodilator treatment becomes less effective.

Asthma exacerbations

Serious asthma-related adverse events and exacerbations may occur during treatment with VANNAIR. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after inhalation of VANNAIR.

VANNAIR must not be initiated or the dose increased during an asthma exacerbation.

Potential systemic effects of inhaled corticosteroids

VANNAIR contains an inhaled corticosteroid (budesonide).

VANNAIR should not be used to initiate treatment with inhaled corticosteroids in patients being transferred from oral steroids.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. However, 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). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

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.

Therefore it is important that the patient is reviewed regularly and the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

HPA axis suppression and adrenal insufficiency

Dose-dependent HPA axis suppression (as indicated by 24 hour urinary and/or plasma cortisol AUC) has been observed with inhaled budesonide, although the physiological circadian rhythms of plasma cortisol were preserved. This indicates that the HPA axis suppression represents a physiological adaptation in response to inhaled budesonide, not necessarily adrenal insufficiency. The lowest dose that results in clinically relevant adrenal insufficiency has not been established. Very rare cases of clinically relevant adrenal dysfunction have been reported in patients using inhaled budesonide at recommended doses.

Clinically important disturbances of the HPA axis and/or adrenal insufficiency induced by severe stress (e.g. trauma, surgery, infection in particular gastroenteritis or other conditions associated with severe electrolyte loss) may be related to inhaled budesonide in specific patient populations. These are patients with prolonged treatment at the highest recommended dose of VANNAIR and patients administered concomitant CYP3A4-inhibitors (see section 4.5). Monitoring for signs of adrenal dysfunction is advisable in these patient groups. For these patients additional systemic glucocorticosteroid cover should be considered during periods of stress, a severe asthma attack or elective surgery.

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.

Care should be taken when commencing VANNAIR treatment, particularly if there is any reason to suspect that adrenal function is impaired from previous systemic steroid therapy.

Bone density

Whilst corticosteroids may have an effect on bone mass at high doses, studies with budesonide treatment in adults at recommended doses, have not demonstrated any significant effect on bone mineral density. No information regarding the effect of VANNAIR at higher doses is available.

Bone mineral density measurements in children should be interpreted with caution as an increase in bone area in growing children may reflect an increase in bone volume. In three large medium to long term (12 months - 6 years) studies in children (5-16 years), no effects on bone mineral density were observed after treatment with budesonide (189 – 1322 µg/day) compared to nedocromil, placebo or age matched controls. However, in a randomised 18 month study (n=176; 5-10 years), bone mineral density was significantly decreased by 0.11 g/cm^2 (p=0.023) in the group treated with inhaled budesonide via Turbuhaler compared with the group treated with inhaled disodium cromoglycate. The dose of budesonide was 400µg bd for 1 month, 200 µg bd for 5 months and 100 µg bd for 12 months and the dose of disodium cromoglycate 10mg tid. The clinical significance of this result remains uncertain.

Growth

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

It is recommended that the height of children and adolescents receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained, if possible.

Physicians should carefully weigh the benefits of the corticosteroid therapy against the possible risks of growth suppression.

Oropharyngeal Candida Infection

Candida infection in the oropharynx has been reported due to drug deposition in association with inhalation therapy. To minimise the risk of oropharyngeal candida infection, the patient should be instructed to rinse their mouth out with water after inhaling the maintenance dose. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroids.

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, VANNAIR 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.

Patients with other medical conditions

Infections / Tuberculosis

Signs of existing infection may be masked by the use of high doses of glucocorticosteroids and new infections may appear during their use.

As with all inhaled medication containing corticosteroids, VANNAIR should be administered with caution in patients with active or quiescent pulmonary tuberculosis or fungal, bacterial or viral infections of the respiratory system.

Sensitivity to sympathomimetic amines

In patients with increased susceptibility to sympathomimetic amines (e.g. inadequately controlled hyperthyroidism), formoterol should be used with caution.

Thyrotoxicosis

VANNAIR pMDI should be administered with caution in patients with thyrotoxicosis.

Cardiovascular disorders

Beta-2-agonists have an arrhythmogenic potential that must be considered before commencing treatment for bronchospasm. Cardiovascular effects, such as increases in systolic blood pressure and heart rate, may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses.

The effects of formoterol in acute as well as chronic toxicity studies were seen mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These are known pharmacological manifestations seen after administration of high doses of beta-2-adrenoceptor agonists.

Patients with pre-existing cardiovascular conditions may be at greater risk of developing adverse cardiovascular effects following administration of beta-2-adrenoreceptor agonists. Caution is advised when formoterol is administered to patients with severe cardiovascular disorders such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

QTc-interval prolongation

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

Hypokalaemia

VANNAIR should be administered with caution in patients predisposed to low levels of serum potassium.

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. Potentially serious hypokalaemia may result.

Concomitant treatment of beta-2 adrenoceptor agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the beta-2 adrenoceptor agonist.

Particular caution is advised in unstable or acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments (see section 4.5). Patients receiving digoxin are particularly sensitive to hypokalaemia. Serum potassium levels should therefore be monitored in such situations.

Diabetes mellitus

VANNAIR should be administered with caution in patients with diabetes mellitus.

Due to the blood-glucose increasing effects of beta-2- stimulants extra blood glucose controls are initially recommended when diabetic patients are commenced on formoterol.

Pneumonia in COPD patients

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

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

Drug interaction potential

Concomitant treatment with ritonavir, itraconazole, ketoconazole or other potent CYP3A4 inhibitors should be avoided (see section 4.5). If this is not possible, the time interval between administration of the interacting drugs should be as long as possible.

In vivo studies have shown that oral administration of ketoconazole or itraconazole (known inhibitors of CYP3A4 activity in the liver and in the internal mucosa, also see section 4.5) may cause an increase of the systemic exposure to budesonide, and consequently lead to systemic adverse reactions, such as Cushing's Syndrome. This is of limited importance for short-term (1-2 weeks) treatment, but should be taken into consideration during long-term treatment.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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

FORMOTEROL

Beta-receptor blocking agents:

Beta-receptor blocking agents (including eye drops), especially those that are non-selective, may partially or totally inhibit the effect of beta-2-agonists, such as formoterol. These medicines may also increase airway resistance. Therefore the use of these medicines in asthma patients is not recommended.

Other sympathomimetic agents:

Other beta-adrenergic stimulants or sympathomimetic amines such as ephedrine should not be given concomitantly with formoterol, since the effects will be cumulative. Patients who have already received large doses of sympathomimetic amines should not be given formoterol.

Xanthine derivatives, mineralocorticosteroids and diuretics:

Hypokalaemia may result from beta-2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, mineralocorticosteroids, and diuretics such as thiazides and loop diuretics (see section 4.4).

Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines:

The adverse cardiovascular effects of formoterol may be exacerbated by concurrent administration of medicines associated with QT interval prolongation. For this reason caution is advised when formoterol is administered to patients already taking monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines or antihistamines associated with QT interval prolongation (e.g. terfenadine, astemizole) as these can prolong the QTc-interval and increase the risk of cardiovascular effects such as ventricular arrhythmias.

L-Dopa, L-thyroxine, oxytocin and alcohol:

L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta-2-sympathomimetics.

BUDESONIDE

CYP3A4 inhibitors

The metabolism of budesonide is primarily mediated by the enzyme CYP3A4. Potent CYP3A4 inhibitors may therefore increase plasma levels and thus systemic exposure to budesonide (see section 4.4). This is of limited clinical importance for short-term (1-2 weeks) treatment with potent CYP3A4 inhibitors but should be taken into consideration during long-term treatment

If a patient requires long-term concomitant treatment with VANNAIR and a potent CYP3A4 inhibitor, the benefit should be weighed against the increased risk of systemic corticosteroid side effects, patients should be monitored for corticosteroid side effects and/or a reduction of the inhaled corticosteroid dose could be considered.

At recommended doses, cimetidine has a slight but clinically insignificant effect and omeprazole has no effect on the pharmacokinetics of oral budesonide.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

VANNAIR should only be used in pregnancy if the potential benefits outweigh the potential risks to the foetus. Only after special consideration should VANNAIR be used during the first 3 months and shortly before delivery.

VANNAIR should be used during labour only if the potential benefit justifies the potential risk.

For VANNAIR pMDI or the concomitant treatment with budesonide and formoterol 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.

In animal studies formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels (see section 5.3). Data in more than on 17 000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide.

Breast-feeding

Administration of VANNAIR pMDI 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.

Budesonide is excreted in breast milk; however, due to the relatively low doses used via the inhaled route, the amount of drug present in the breast milk, if any, is likely to be low. Consequently, no effects due to budesonide are anticipated in breast-fed children whose mothers are receiving therapeutic doses of VANNAIR.

It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

Since VANNAIR pMDI contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side effects of beta-2 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 and/or formoterol, are given below, listed by system organ class and frequency. Frequencies are defined

as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1000) and very rare (< 1/10 000).

Frequency	SOC	Reaction
Common	*Cardiac disorders:*	Palpitations
	Infections and infestations:	Candida infections in oropharynx
		Pneumonia (in COPD patients)
	Nervous system disorders:	Headache, tremor
	Respiratory, thoracic and mediastinal disorders:	Mild irritation in the throat, coughing, hoarseness
Uncommon	*Cardiac disorders:*	Tachycardia
	Gastrointestinal disorders:	Nausea, diarrhoea
	Metabolism and nutrition disorders	Weight gain
	Musculoskeletal and connective tissue disorders:	Muscle cramps
	Nervous system disorders:	Dizziness, taste disturbances, thirst, tiredness
	Psychiatric disorders:	Agitation, restlessness, nervousness, sleep disturbances
Rare	*Cardiac disorders:*	Cardiac arrhythmias, 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
	Metabolism and nutrition disorders	Hypokalaemia
Very rare	*Cardiac disorders:*	Angina pectoris
		Prolongation of the QTc-interval
	Endocrine disorders:	Signs or symptoms of systemic glucocorticosteroid effects, e.g. Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density
	Eye disorders	Cataract
		Glaucoma
	Metabolism and nutrition disorders:	Hyperglycaemia
	Psychiatric disorders:	Anxiety Depression Behavioural disturbances

Frequency	SOC	Reaction
	Vascular disorders	Variations in blood pressure

Treatment with beta-2 adrenoceptor agonists may also result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Table 2: Adverse events occurring at an incidence of ≥ 3% and more commonly than placebo in the Symbicort group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment[a]	SYMBICORT 200/6 µg N = 771 %	Budesonide 200 µg N = 275 %	Formoterol 6 µg N = 779 %	Placebo N = 781 %
Adverse Event[b]				
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average duration of exposure (days)	255.2	157.1	240.3	223.7

[a] All treatments were administered twice daily
[b] Sorted by decreasing order of frequency across all treatment groups.

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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Formoterol

An overdose of formoterol would likely lead to effects that are typical for beta-2 adrenoceptor agonists: tremor, headache, palpitations. Hypotension, metabolic acidosis, prolonged QTc-interval, arrhythmia, nausea, vomiting, hypokalaemia and hyperglycaemia may also occur.

Supportive and symptomatic treatment may be indicated. Beta-blockers should be used with care because of the possibility of inducing bronchospasm in sensitive individuals.

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

Budesonide

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, such as hypercorticism and adrenal suppression.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACEUTICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

VANNAIR contains budesonide and formoterol, which have different modes of action and show additive effects in terms of reduction of asthma and chronic obstructive pulmonary disease (COPD) exacerbations. The specific properties of budesonide and formoterol allow the combination to be used as maintenance treatment for asthma and for symptomatic treatment of patients with moderate to severe COPD. The respective mechanisms of action of both drugs are discussed below.

Budesonide

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

Formoterol

Formoterol is a selective beta-2-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependent, with an onset of effect within 1-3 minutes after inhalation. The duration of effect is at least 12 hours after a single dose.

CLINICAL EFFICACY AND SAFETY

Asthma

<u>Vannair pMDI</u>

Clinical comparability was demonstrated by a long-term safety study, which showed that the safety profile and tolerability of VANNAIR pMDI were similar to that of Symbicort Turbuhaler.

<u>Symbicort Turbuhaler</u>

Clinical studies have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. The effect on lung function of Symbicort Turbuhaler was equal to that of the free combination of budesonide and formoterol in separate inhalers in adults and exceeded that of budesonide alone in adults and children. The free combination of budesonide and

formoterol does not mask the onset or severity of exacerbations. There was no sign of attenuation of the anti-asthmatic effect over time.

Symbicort Turbuhaler has been proven in clinical trials to improve patient symptoms, reduce the use of short-acting reliever medication and increase asthma control when compared to inhaled corticosteroid treatment alone. Furthermore, formoterol and budesonide in separate inhalers have been shown to reduce nocturnal awakenings, decrease the rate of exacerbations and improve the quality of life.

COPD

In one 12-month study and one 6 month study in patients with COPD, VANNAIR 200/6 was superior to placebo, budesonide and formoterol for post-dose FEV_1 and pre-dose (trough) FEV_1. In the 12-month study, VANNAIR 200/6 was also superior to placebo and to formoterol for both the number of, and the time to first severe COPD exacerbation (a worsening of COPD requiring oral steroid use or hospitalisation). Thus, the contribution of both budesonide and formoterol to the effect of VANNAIR was demonstrated. VANNAIR 200/6 also significantly reduced breathlessness, daily rescue medication use, night-time awakenings and improved health-related quality of life compared with placebo in both studies. Serial FEV_1 measures over 12 hours were obtained in subsets of patients in both studies. The median time to onset of bronchodilation (>15% improvement in FEV_1) was seen within 5 minutes at the end of treatment in patients receiving VANNAIR 200/6. Maximal improvement in FEV_1 occurred at approximately 2 hours post-dose and post-dose bronchodilator effect was generally maintained over 12 hours. The treatment was well tolerated.

5.2 PHARMACOKINETICS

Absorption

Symbicort® Turbuhaler (a dry powder inhaler containing budesonide and formoterol) and the corresponding monoproducts (Pulmicort® Turbuhaler and Oxis® Turbuhaler, respectively) have been shown to be bioequivalent with regard to systemic exposure of budesonide and formoterol, respectively.

In addition, the pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and formoterol as monoproducts or as Symbicort® Turbuhaler. Thus, there was no evidence of pharmacokinetic interactions between budesonide and formoterol when given together.

Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation.

Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation.

Distribution and Biotransformation

Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 L/kg for formoterol and 3 L/kg for budesonide. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites,

6 beta-hydroxy-budesonide and 16α-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 eliminated by metabolism in the liver followed by renal excretion. After inhalation of formoterol via Turbuhaler, 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 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 L/min) and the plasma elimination half-life after i.v. dosing averages 4 hours.

Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 year old asthmatic children. Per kg 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 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

The toxicity observed in animal studies with budesonide and formoterol was similar whether budesonide or formoterol were given in combination or separately. The effects were associated with pharmacological actions and were dose dependent.

In animal reproduction studies, glucocorticosteroids 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 (see section 4.6). 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 to man.

VANNAIR pMDI contains the excipients povidone (polyvinylpyrrolidone) K25, macrogol (polyethylene glycol) 1000 and the pressurised liquid propellant apaflurane (HFA 227). The safe use of apaflurane has been fully evaluated in preclinical studies. Povidones have a history of safe use in man for many years, which supports the view that povidones are essentially biologically inert. Macrogols are recognised as safe excipients in pharmaceuticals, food and cosmetic products. Furthermore, toxicity studies carried out using VANNAIR pMDI have shown no evidence of any local or systemic toxicity or irritation attributable to the excipients.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Apaflurane (HFA 227)
- Povidone K25
- Macrogol (polyethylene glycol) 1000

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF-LIFE

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

6.4 SPECIAL PRECUATIONS FOR STORAGE

Do not store above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

A pressurised container, comprising of an internally coated aluminium can, sealed with a metering valve and fitted into a plastic actuator. Each inhaler delivers 120 actuations of budesonide/formoterol 80/4.5 or 160/4.5 micrograms (delivered dose) after initial priming. Each inhaler is individually wrapped in a foil laminate pouch containing a desiccant.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND HANDLING

Return unused and expired medicines to your local pharmacy for disposal.

Instructions for use

See section 4.2 and the Consumer Medicine Information.

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.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

1 February 2007

10. DATE OF REVISION OF THE TEXT

27 July 2020

CDS 260720

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Pneumonia in COPD patients subsection amended in line with recent data.
4.5	Modified pharmacokinetic interactions text
4.6	Update to figures based on latest data
4.8	New ADR (pneumonia) included in Table 1
8.	PO Box amended
General	Eformoterol amended to formoterol in line with international approved name.