SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trimbow 100/6/12.5

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose leaving the mouthpiece) contains 87.4 micrograms of beclometasone dipropionate, 5.2 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 10.9 micrograms glycopyrronium bromide).

Each metered dose (the dose leaving the valve) contains 100 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate dihydrate and 10 micrograms of glycopyrronium (as 12.5 micrograms glycopyrronium bromide).

Excipient with known effect:

Trimbow 100/6/12.5 contains 8.856 mg ethanol per actuation.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, solution (pressurised inhalation)

Colourless to yellowish liquid solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic Obstructive Pulmonary Disease (COPD)

Trimbow 100/6/12.5 is indicated for maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist (for effects on symptoms control and prevention of exacerbations see section 5.1).

Asthma

Maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and medium dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.

4.2 Posology and method of administration

Posology

The recommended dose is two inhalations twice daily.
The maximum dose is two inhalations twice daily.

Patients should be advised to take Trimbow 100/6/12.5 every day even when asymptomatic.

If symptoms arise in the period between doses, an inhaled, short-acting beta2-agonist should be used for immediate relief.

Asthma
When choosing the starting dose strength of Trimbow (100/6/12.5 micrograms or 200/6/12.5 micrograms), the patients' disease severity, their previous asthma therapy including the inhaled corticosteroid (ICS) dose as well as the patients' current control of asthma symptoms and risk of future exacerbation should be considered.

Stepping-down treatment

Patients should be regularly reassessed by a doctor, so that their doses of beclometasone/formoterol/glycopyrronium remain optimal and are only changed on medical advice. The doses should be titrated to the lowest doses at which effective control of asthma symptoms is maintained.

Special populations

Elderly
No dose adjustment is required in elderly patients (65 years of age and older).

Renal impairment
Trimbow 100/6/12.5 can be used at the recommended dose in patients with renal impairment and a glomerular filtration rate [GFR] of ≥30 to <80 mL/min/1.73 m². Use in patients with severe (GFR <30 mL/min/1.73 m^2) renal impairment or end-stage renal (GFR <15 mL/min/1.73 m^2) disease requiring dialysis, especially if associated with significant body weight reduction, should be considered only if the expected benefit outweighs the potential risk (see sections 4.4 and 5.2).

Hepatic impairment
There are no relevant data on the use of Trimbow 100/6/12.5 in patients with severe hepatic impairment (classified as having Child-Pugh class C) and the medicinal product should be used with caution in these patients (see sections 4.4 and 5.2).

Paediatric population
COPD
There is no relevant use of Trimbow 100/6/12.5 in the paediatric population (under 18 years of age) for the indication of COPD.

Asthma
Trimbow 100/6/12.5 is not indicated for children and adolescents under 18 years of age.

Method of administration

For inhalation use.

To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler correctly by a physician or other healthcare professional, who should also regularly check the adequacy of the patient's inhalation technique (see "*Instructions for use*" below). The patient should be advised to read the Package Leaflet carefully and follow the instructions for use as given in the leaflet.

This medicinal product is provided with a dose counter on the back of the inhaler, which shows how many actuations are left. Each time the patient presses the container a puff of the solution is released and the counter counts down by one.
The patient should be advised not to drop the inhaler as this may cause the counter to count down.

Instructions for use

Priming the inhaler
Before using the inhaler for the first time, the patient should release one actuation into the air in order to ensure that the inhaler is working properly (priming). Before priming the pressurised container, the counter should read 121. After priming, the counter should read 120.

Use of the inhaler
The patient should stand or sit in an upright position when inhaling from the inhaler. The steps below should be followed.
IMPORTANT: steps 2 to 5 should not be performed too quickly:
1. The patient should remove the protective cap from the mouthpiece and check that the mouthpiece is clean and free from dust and dirt or any other foreign objects.
2. The patient should breathe out slowly and as deeply as comfortable, in order to empty the lungs.
3. The patient should hold the inhaler vertically with its body upwards and place the mouthpiece between the teeth without biting. The lips should then be placed around the mouthpiece, with the tongue flat under it.
4. At the same time, the patient should breathe in slowly and deeply through the mouth until the lungs are full of air (this should take approximately 4 – 5 seconds). Immediately after starting to breathe in, the patient should firmly press down on the top of the pressurised container to release one puff.
5. The patient should then hold the breath for as long as comfortably possible, then remove the inhaler from the mouth and breathe out slowly. The patient should not breathe out into the inhaler.
6. The patient should then check the dose counter to ensure it has moved accordingly.

To inhale the second puff, the patient should keep the inhaler in a vertical position for approximately 30 seconds and repeat steps 2 to 6.

If mist appears after the inhalation, either from the inhaler or from the sides of the mouth, the procedure should be repeated from step 2.

After use, the patient should close the inhaler with the protective mouthpiece cap and check the dose counter.

After inhaling, the patient should rinse the mouth or gargle with water without swallowing it or brush the teeth (see also section 4.4).

When to get a new inhaler
The patient should be advised to get a new inhaler when the dose counter shows the number 20. He/she should stop using the inhaler when the counter shows 0 as any puffs left in the device may not be enough to release a full actuation.

Additional instructions for specific groups of patients
For patients with weak hands it may be easier to hold the inhaler with both hands. Therefore, the index fingers should be placed on the top of the pressurised container and both thumbs on the base of the inhaler.

Patients who find it difficult to synchronise aerosol actuation with inspiration of breath may use the AeroChamber Plus spacer device, properly cleaned as described in the relevant leaflet. They should be advised by their doctor or pharmacist about the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled active substance to the lungs. This may be obtained by the patients using the AeroChamber Plus by one continuous slow and deep breath through the spacer, without any delay between actuation and inhalation. Alternatively, patients may simply breathe in

and out (through the mouth) after the actuation, as instructed in the spacer leaflet, to obtain the medicinal product (see sections 4.4 and 5.2).

Cleaning
For the regular cleaning of the inhaler, patients should remove weekly the cap from the mouthpiece and wipe the outside and inside of the mouthpiece with a dry cloth. They should not remove the pressurised container from the actuator and should not use water or other liquids to clean the mouthpiece.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Not for acute use

This medicinal product is not indicated for the treatment of acute episodes of bronchospasm, or to treat an acute disease exacerbation (i.e. as a rescue therapy).

Hypersensitivity

Immediate hypersensitivity reactions have been reported after administration. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of the tongue, lips and face), urticaria or skin rash, treatment should be discontinued immediately, and alternative therapy instituted.

Paradoxical bronchospasm

Paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator (reliever). Treatment should be discontinued immediately, the patient assessed, and alternative therapy instituted if necessary.

Deterioration of disease

It is recommended that treatment should not be stopped abruptly. If patients find the treatment ineffective, they should continue treatment, but medical attention must be sought. Increasing use of reliever bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the therapy. Sudden or progressive deterioration in symptoms is potentially life-threatening and the patient should undergo urgent medical assessment.

Cardiovascular effects

Due to the presence of a long-acting beta2-agonist and a long-acting muscarinic antagonist, Trimbow 100/6/12.5 should be used with caution in patients with cardiac arrhythmias, especially third degree atrioventricular block and tachyarrhythmias (accelerated and/or irregular heartbeat, including atrial fibrillation), idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, severe heart disease (particularly acute myocardial infarction, ischaemic heart disease, congestive heart failure), occlusive vascular diseases (particularly arteriosclerosis), arterial hypertension and aneurysm.
Caution should also be exercised when treating patients with known or suspected prolongation of the QTc interval (QTc > 450 milliseconds for males, or > 470 milliseconds for females), either congenital or induced by medicinal products. Patients diagnosed with the described cardiovascular conditions were excluded from clinical studies with Trimbow. Limited data in asthmatic patients with cardiovascular co-morbidities or risk-factors suggest that these patients are also at higher risk of adverse reactions like local fungal infections or dysphonia (see section 4.8).

If anaesthesia with halogenated anaesthetics is planned, it should be ensured that Trimbow 100/6/12.5 is not administered for at least 12 hours before the start of anaesthesia as there is a risk of cardiac arrhythmias.

Caution is also required when treating patients with thyrotoxicosis, diabetes mellitus, pheochromocytoma and untreated hypokalaemia.

Pneumonia in patients with COPD

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

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

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

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

Systemic corticosteroid effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. The daily dose of Trimbow 100/6/12.5 corresponds to a medium dose of inhaled corticosteroid; furthermore, these effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation, decrease in bone mineral density and, more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Therefore, it is important that the patient is reviewed regularly, and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained (see section 4.2).

Trimbow 100/6/12.5 should be administered with caution in patients with active or quiescent pulmonary tuberculosis and in patients with fungal and viral infections in the airways.

Hypokalaemia

Potentially serious hypokalaemia may result from beta2-agonist therapy. This has the potential to produce adverse cardiovascular effects. Particular caution is advised in patients with severe disease as this effect may be potentiated by hypoxia. Hypokalaemia may also be potentiated by concomitant treatment with other medicinal products which can induce hypokalaemia, such as xanthine derivatives, steroids and diuretics (see section 4.5).
Caution is also recommended when a number of reliever bronchodilators are used. It is recommended that serum potassium levels are monitored in such situations.

Hyperglycaemia

The inhalation of formoterol may cause a rise in blood glucose levels. Therefore, blood glucose should be monitored during treatment following established guidelines in patients with diabetes.

Anticholinergic effect

Glycopyrronium should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or urinary retention. Patients should be informed about the signs and symptoms of acute narrow-angle glaucoma and should be informed to stop treatment and to contact their doctor immediately should any of these signs or symptoms develop.
Additionally, due to the anticholinergic effect of glycopyrronium, the long-term co-administration with other anticholinergic-containing medicinal products is not recommended (see section 4.5).

Patients with severe renal impairment

In patients with severe renal impairment, including those with end-stage renal disease requiring dialysis, especially if associated with a significant body weight reduction, Trimbow 100/6/12.5 should be used only if the expected benefit outweighs the potential risk (see section 5.2). These patients should be monitored for potential adverse reactions.

Patients with severe hepatic impairment

In patients with severe hepatic impairment, Trimbow 100/6/12.5 should be used only if the expected benefit outweighs the potential risk (see section 5.2). These patients should be monitored for potential adverse reactions.

Prevention of oropharyngeal infections

In order to reduce the risk of oropharyngeal candida infection, patients should be advised to rinse their mouth or gargle with water without swallowing it or brush their teeth after inhaling the prescribed dose.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Stepping-down treatment

Patients should be regularly reassessed by a doctor, so that their doses of beclometasone/formoterol/glycopyrronium remain optimal and are only changed on medical advice. The doses should be titrated to the lowest doses at which effective control of asthma symptoms is maintained.

Ethanol contents

This medicinal product contains 8.856 mg of ethanol per actuation, which is equivalent to 17.712 mg per dose of two actuations. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Since glycopyrronium is eliminated mainly by the renal route, interaction could potentially occur with medicinal products affecting renal excretion mechanisms (see section 5.2). The effect of organic cation transport inhibition (using cimetidine as a probe inhibitor of OCT2 and MATE1 transporters) in the kidneys on inhaled glycopyrronium disposition showed a limited increase in its total systemic exposure (AUC_{0-t}) by 16% and a slight decrease in renal clearance by 20% due to co administration of cimetidine.

Beclometasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however, the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such medicinal products.

Pharmacodynamic interactions

Related to formoterol
Non-cardioselective beta-blockers (including eye drops) should be avoided in patients taking inhaled formoterol. If they are administered for compelling reasons, the effect of formoterol will be reduced or abolished.

Concomitant use of other beta-adrenergic medicinal products can have potentially additive effects; therefore, caution is required when other beta-adrenergic medicinal products are prescribed concomitantly with formoterol.

Concomitant treatment with quinidine, disopyramide, procainamide, antihistamines, monoamine oxidase inhibitors, tricyclic antidepressants and phenothiazines can prolong the QT interval and increase the risk of ventricular arrhythmias. In addition, L-dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta2-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors, including medicinal products with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of beta2-agonists (see section 4.4). Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Related to glycopyrronium
The long-term co-administration of Trimbow 100/6/12.5 with other anticholinergic-containing medicinal products has not been studied and is therefore not recommended (see section 4.4).

4.6 Fertility, pregnancy and lactation

There is no experience with or evidence of safety issues on the use of the propellant norflurane (HFA134a) during human pregnancy or lactation. However, studies on the effect of HFA134a on the reproductive function and embryofoetal development in animals revealed no clinically relevant adverse effects.

Pregnancy

There are no or limited amount of data from the use of Trimbow 100/6/12.5 in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). Glucocorticoids are known to cause effects in the early gestation phase, while beta2-sympathomimetics like formoterol have tocolytic effects. Therefore, as a precautionary measure, it is preferable to avoid the use of Trimbow 100/6/12.5 during pregnancy and during labour.

Trimbow 100/6/12.5 should only be used during pregnancy if the expected benefit to the patient outweighs the potential risk to the foetus. Infants and neonates born to mothers receiving substantial doses should be observed for adrenal suppression.

Breast-feeding

There are no relevant clinical data on the use of Trimbow 100/6/12.5 during breast-feeding in humans.

Glucocorticoids are excreted in human milk. It is reasonable to assume that beclometasone dipropionate and its metabolites are also excreted in human milk.
It is unknown whether formoterol or glycopyrronium (including their metabolites) are excreted in human milk but they have been detected in the milk of lactating animals. Anticholinergics like glycopyrronium could suppress lactation.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Trimbow 100/6/12.5 therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No specific studies have been performed with Trimbow 100/6/12.5 with regard to the safety in human fertility. Animal studies have shown impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Trimbow 100/6/12.5 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions in patients with COPD or asthma are respectively: dysphonia (0.3% and 1.5%) and oral candidiasis (0.8% and 0.3%), which are normally associated with inhaled corticosteroids; muscle spasms (0.4% and 0.2%), which can be attributed to the long-acting beta2-agonist component; and dry mouth (0.4% and 0.5%), which is a typical anticholinergic effect.
In asthmatic patients, adverse reactions tend to cluster during the first 3 months following initiation of therapy and become less frequent with longer-term use (after 6 months of treatment).

Tabulated list of adverse reactions

Adverse reactions associated to beclometasone dipropionate/formoterol/glycopyrronium occurred during clinical studies and post-marketing experience as well as adverse reactions listed for the marketed individual components are provided 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 <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from available data).

MedDRA system organ class	Adverse reaction	Frequency
Infections and Infestations	Pneumonia (in COPD patients), pharyngitis, oral candidiasis, urinary tract infection[1], nasopharyngitis[1]	Common
	Influenza[1], oral fungal infection, oropharyngeal candidiasis, oesophageal candidiasis, fungal (oro)pharyngitis, sinusitis[1], rhinitis[1], gastroenteritis[1], vulvovaginal candidiasis[1]	Uncommon
	Lower respiratory tract infection (fungal)	Rare
Blood and lymphatic system disorders	Granulocytopenia[1]	Uncommon
	Thrombocytopenia[1]	Very rare
Immune system disorders	Dermatitis allergic[1]	Uncommon
	Hypersensitivity reactions, including erythema, lips, face, eye and pharyngeal oedema	Rare
Endocrine disorders	Adrenal suppression[1]	Very rare
Metabolism and nutrition disorders	Hypokalaemia, hyperglycaemia	Uncommon
	Decreased appetite	Rare
Psychiatric disorders	Restlessness[1]	Uncommon
	Psychomotor hyperactivity[1], sleep disorders[1], anxiety, depression[1], aggression[1], behavioural changes (predominantly in children) [1]	Frequency not known
	Insomnia	Rare

MedDRA system organ class	Adverse reaction	Frequency
Nervous system disorders	Headache	Common
	Tremor, dizziness, dysgeusia[1], hypoaesthesia[1]	Uncommon
	Hypersomnia	Rare
Eye disorders	Vision, blurred[1] (see also section 4.4)	Frequency not known
	Glaucoma[1], cataract[1]	Very rare
Ear and labyrinth disorders	Otosalpingitis[1]	Uncommon
Cardiac disorders	Atrial fibrillation, electrocardiogram QT prolonged, tachycardia, tachyarrhythmia[1], palpitations	Uncommon
	Angina pectoris (stable[1] and unstable), extrasystoles (ventricular[1] and supraventricular), nodal rhythm, sinus bradycardia	Rare
Vascular disorders	Hyperaemia[1], flushing[1], hypertension	Uncommon
	Extravasation blood	Rare
Respiratory, thoracic and mediastinal disorders	Dysphonia	Common
	Asthmatic crisis[1], cough, productive cough[1], throat irritation, epistaxis[1], pharyngeal erythema	Uncommon
	Bronchospasm paradoxical[1], exacerbation of asthma, oropharyngeal pain, pharyngeal inflammation, dry throat	Rare
	Dyspnoea[1]	Very rare
Gastrointestinal disorders	Diarrhoea[1], dry mouth, dysphagia[1], nausea, dyspepsia[1], burning sensation of the lips[1], dental caries[1], (aphthous) stomatitis	Uncommon
Skin and subcutaneous tissue disorders	Rash[1], urticaria, pruritus, hyperhidrosis[1]	Uncommon
	Angioedema[1]	Rare
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia, pain in extremity[1], musculoskeletal chest pain[1]	Uncommon
	Growth retardation[1]	Very rare
Renal and urinary disorders	Dysuria, urinary retention, nephritis[1]	Rare
General disorders and administration site conditions	Fatigue[1]	Uncommon
	Asthenia	Rare
	Oedema peripheral[1]	Very rare
Investigations	C-reactive protein increased[1], platelet count increased[1], free fatty acids increased[1], blood insulin increased[1], blood ketone body increased[1], cortisol decreased[1]	Uncommon
	Blood pressure increased[1], blood pressure decreased[1]	Rare
	Bone density decreased[1]	Very rare

[1] Adverse reactions reported in the SmPC of at least one of the individual components, but not observed as adverse reactions in the clinical development of Trimbow

Among the observed adverse reactions the following are typically associated with:

Beclometasone dipropionate
Pneumonia, oral fungal infections, lower respiratory tract infection fungal, dysphonia, throat irritation, hyperglycaemia, psychiatric disorders, cortisol decreased, blurred vision.

Formoterol
Hypokalaemia, hyperglycaemia, tremor, palpitations, muscle spasms, electrocardiogram QT prolonged, blood pressure increased, blood pressure decreased, atrial fibrillation, tachycardia, tachyarrhythmia, angina pectoris (stable and unstable), ventricular extrasystoles, nodal rhythm.

Glycopyrronium
Glaucoma, atrial fibrillation, tachycardia, palpitations, dry mouth, dental caries, dysuria, urinary retention, urinary tract infection.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il
Additionally, you should also report to Kamada LTD to email address:
pharmacovigilance@kamada.com

4.9 Overdose

An overdose of Trimbow 100/6/12.5 may produce signs and symptoms due to the individual component's pharmacological actions, including those seen with overdose of other beta2-agonists or anticholinergics and consistent with the known inhaled corticosteroid class effects (see section 4.4). If overdose occurs, the patient's symptoms should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids. ATC code: R03AL09.

Mechanism of action and pharmacodynamic effects

Trimbow contains beclometasone dipropionate, formoterol and glycopyrronium (BDP/FF/G) in a solution formulation resulting in an aerosol with extrafine particles with an average mass median aerodynamic diameter (MMAD) of around 1.1 micrometres and co-deposition of the three components. The aerosol particles of Trimbow are on average much smaller than the particles delivered in non-extrafine formulations. For beclometasone dipropionate, this results in a more potent effect than formulations with a non-extrafine particle size distribution (100 micrograms of beclometasone dipropionate extrafine in Trimbow are equivalent to 250 micrograms of beclometasone dipropionate in a non-extrafine formulation).

Beclometasone dipropionate
Beclometasone dipropionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs. Glucocorticoids are widely used for the suppression of inflammation in chronic inflammatory diseases of the airways. Their action is mediated by the binding to glucocorticoid receptors in the cytoplasm resulting in the increased transcription of genes coding for anti-inflammatory proteins.

Formoterol
Formoterol is a selective beta2-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after a single dose.

Glycopyrronium
Glycopyrronium is a high-affinity, long-acting muscarinic receptor antagonist (anticholinergic) used for inhalation as bronchodilator treatment. Glycopyrronium works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways. Glycopyrronium bromide is a high affinity muscarinic receptor antagonist with a greater than 4-fold selectivity for the human M3 receptors over the human M2 receptor as it has been demonstrated.

Clinical efficacy and safety

COPD

The Phase III clinical development programme in COPD was conducted with BDP/FF/G 100/6/12.5 and included two 52-week active-controlled studies. The TRILOGY study compared BDP/FF/G with a fixed combination of beclometasone dipropionate and formoterol 100/6 micrograms two inhalations twice daily (1,368 randomised patients). The TRINITY study compared BDP/FF/G with tiotropium 18 micrograms inhalation powder, hard capsule, one inhalation once daily; in addition, effects were compared with an extemporary triple combination made of a fixed combination of beclometasone dipropionate and formoterol 100/6 micrograms (corresponding to a delivered dose of 84.6/5.0 micrograms) two inhalations twice daily plus tiotropium 18 micrograms inhalation powder, hard capsule, one inhalation once daily (2,691 randomised patients). Both studies were conducted in patients with a clinical diagnosis of COPD with severe to very severe airflow limitation (FEV_1 less than 50% predicted), with symptoms assessed as a COPD Assessment Test (CAT) score of 10 or above, and with at least one COPD exacerbation in the previous year. The two studies included approximately 20% of patients who used the AeroChamber Plus spacer.

In addition, two Phase IIIb studies were conducted to support the clinical efficacy and safety of BDP/FF/G. TRISTAR was a 26-week active-controlled open label study comparing BDP/FF/G with an extemporary combination made of a fixed combination of fluticasone/vilanterol 92/22 micrograms inhalation powder, one inhalation once daily plus tiotropium 18 micrograms inhalation powder, hard capsule, one inhalation once daily (1,157 randomised patients). TRIBUTE was a 52-week active-controlled study comparing BDP/FF/G with a fixed combination of indacaterol/glycopyrronium 85/43 micrograms inhalation powder, hard capsule, one inhalation once daily (1,532 randomised patients). Both studies were conducted in a similar population of COPD patients as studies TRILOGY and TRINITY.

Reduction of COPD exacerbations

Compared with a fixed combination of beclometasone dipropionate and formoterol, BDP/FF/G reduced the rate of moderate/severe exacerbations over 52 weeks by 23% (rate: 0.41 versus 0.53 events per patient/year; $p = 0.005$). Compared with tiotropium, BDP/FF/G reduced the rate of moderate/severe exacerbations over 52 weeks by 20% (rate: 0.46 versus 0.57 events per patient/year; $p = 0.003$). Compared with a fixed combination of indacaterol and glycopyrronium, BDP/FF/G reduced the rate of moderate/severe exacerbations over 52 weeks by 15% (rate: 0.50 versus 0.59 events per patient/year; $p = 0.043$). Compared with tiotropium, BDP/FF/G also reduced the rate of severe exacerbations (i.e. excluding moderate exacerbations) by 32% (rate: 0.067 versus 0.098 events per patient/year; $p = 0.017$). No differences were observed when comparing BDP/FF/G with the extemporary triple combination made of beclometasone dipropionate and formoterol fixed combination plus tiotropium (moderate/severe exacerbation rate: 0.46 versus 0.45 events per patient/year).

In addition, compared with both a fixed combination of beclometasone dipropionate and formoterol and with tiotropium, BDP/FF/G significantly prolonged the time to first exacerbation (hazard ratio 0.80 and 0.84 respectively; $p = 0.020$ and 0.015 respectively), with no differences between BDP/FF/G and the extemporary triple combination made of beclometasone dipropionate and formoterol fixed combination plus tiotropium (hazard ratio 1.06).

Effects on lung function

Pre-dose FEV_1

Compared with a fixed combination of beclometasone dipropionate and formoterol, BDP/FF/G improved pre-dose FEV_1 by 81 mL after 26 weeks of treatment and by 63 mL after 52 weeks of treatment. Compared with tiotropium, BDP/FF/G improved pre-dose FEV_1 by 51 mL after 26 weeks of treatment and by 61 mL after 52 weeks of treatment. These improvements were statistically significant ($p < 0.001$). Compared with a fixed combination of indacaterol and glycopyrronium, BDP/FF/G improved average pre-dose FEV_1 over the 52-week treatment period by 22 mL ($p=0.018$). Similar improvements, although not statistically significant, were observed at weeks 26 and 52.

No differences were observed when comparing BDP/FF/G and the extemporary triple combination made of a fixed combination of beclometasone dipropionate and formoterol plus tiotropium (difference of 3 mL in pre-dose FEV_1 after 52 weeks of treatment).

2-hour post-dose FEV_1
Compared with a fixed combination of beclometasone dipropionate and formoterol, BDP/FF/G significantly improved 2-hour post dose FEV_1 by 117 mL after 26 weeks of treatment and by 103 mL after 52 weeks of treatment ($p < 0.001$). This endpoint was only measured in the TRILOGY study.

Inspiratory Capacity (IC)
Compared with tiotropium, BDP/FF/G significantly improved IC by 39 mL ($p = 0.025$) and 60 mL ($p = 0.001$) after 26 and 52 weeks of treatment respectively. Similar effects were seen when comparing BDP/FF/G with the extemporary triple combination. This endpoint was only measured in the TRINITY study.

Symptomatic outcomes
BDP/FF/G significantly improved dyspnoea (measured as the Transition Dyspnoea Index – TDI - focal score) after 26 weeks of treatment compared with baseline (by 1.71 units; $p < 0.001$), but the adjusted mean difference versus a fixed combination of beclometasone dipropionate and formoterol was not statistically significant (0.21 units; $p = 0.160$). A responder analysis showed that a significantly greater percentage of patients had a clinically significant improvement (focal score greater than or equal to 1) after 26 weeks with BDP/FF/G than with a fixed combination of beclometasone dipropionate and formoterol (57.4% versus 51.8%; $p = 0.027$). TDI was only measured in the TRILOGY study.
BDP/FF/G was also statistically significantly superior to a fixed combination of beclometasone dipropionate and formoterol, to tiotropium and to a fixed combination of indacaterol and glycopyrronium in terms of improvement in quality of life (measured by the Saint George Respiratory Questionnaire – SGRQ - total score). No differences were observed when comparing BDP/FF/G and the extemporary triple combination made of fluticasone and vilanterol fixed combination plus tiotropium.
A responder analysis showed that a significantly greater percentage of patients had a clinically significant improvement (reduction versus baseline of greater than or equal to 4) after 26 and 52 weeks with BDP/FF/G than with a fixed combination of beclometasone dipropionate and formoterol and with tiotropium.

Asthma
The Phase III clinical development programme in asthma included two randomized, double-blind, active-controlled studies of 52 weeks duration, one performed with the medium ICS dose strength (BDP/FF/G 100/6/12.5; TRIMARAN) and another one with the high ICS dose strength (BDP/FF/G 200/6/12.5; TRIGGER).

Both studies were conducted in adult patients with a clinical diagnosis of asthma who were uncontrolled on dual maintenance treatment using a medium dose (TRIMARAN) or high dose (TRIGGER) ICS/LABA combination (ACQ-7 score ≥1.5). In order to be eligible, patients had to have experienced at least one asthma exacerbation requiring treatment with systemic corticosteroids or emergency department visit or in-patient hospitalisation in the previous year.

The TRIMARAN study compared two twice-daily doses of BDP/FF/G 100/6/12.5 (N=579) with two twice-daily doses of a fixed combination of beclometasone dipropionate (BDP) and formoterol (FF) 100/6 micrograms (delivered dose of 84.6/5.0) (N=576). The TRIGGER study compared two twice-daily doses of BDP/FF/G 200/6/12.5 (N=573) with two twice-daily doses of a fixed combination of BDP and FF 200/6 micrograms alone (delivered dose 177.7/5.1) (N=576) or on top of two once-daily doses of tiotropium 2.5 micrograms (N=288) as an open-label extemporary triple combination arm.

The primary objective of the studies was to demonstrate superiority of either BDP/FF/G 100/6/12.5 or BDP/FF/G 200/6/12.5 (two inhalations twice daily) over the respective fixed dual combination product (medium or high dose ICS/LABA) in terms of the co-primary endpoints (change from baseline in pre-dose FEV_1 at Week 26 and the rate of moderate and severe exacerbation rate over 52 weeks).

The TRIGGER study was not powered to evaluate the comparative efficacy of BDP/FF/G 200/6/12.5 vs. BDP/FF + tiotropium 2.5 micrograms. Descriptive results are included in Table 1.

Median age of patients enrolled in the two pivotal studies was 54 years. Less than 20% of patients were aged 65 years or more and approximately 60% of patients were female. During the study, about 16% (TRIMARAN) and 23% (TRIGGER) of patients used the AeroChamber Plus spacer.

Reduction of asthma exacerbations
In the TRIMARAN study, BDP/FF/G 100/6/12.5 significantly reduced the rate of moderate/severe exacerbations compared with the fixed combination of BDP/FF 100/6 micrograms (adjusted rate ratio 0.846, 95%CI [0.725; 0.987]).

In the TRIGGER study, BDP/FF/G 200/6/12.5 also reduced the rate of moderate/severe exacerbations more than the fixed combination of BDP/FF 200/6 micrograms but this effect did not achieve statistical significance (adjusted rate ratio 0.880, 95%CI [0.751;1.030], p=0.11). Due to the hierarchical testing, all TRIGGER efficacy endpoints and the pre-specified analysis of severe exacerbations (data pooled across TRIMARAN and TRIGGER studies) resulted in nominal p-values only (Table 1).

Data of TRIMARAN and TRIGGER studies suggest that the time to first moderate/severe exacerbation (secondary endpoint) was prolonged in the triple combination arm when compared with the respective dual combination arm.

Effects on lung function
In both studies, BDP/FF/G 100/6/12.5 and BDP/FF/G 200/6/12.5 improved the lung function parameters of pre-dose FEV_1 (co-primary endpoint), $peak_{0\text{-}3h}$ FEV_1, and morning peak expiratory flow (key secondary endpoints), compared with a fixed combination of beclometasone dipropionate and formoterol 100/6 micrograms and 200/6 micrograms, respectively, after 26 weeks of treatment. All improvements were statistically significant (see Table 1).

Table 1 - Results of primary and secondary endpoints

Study	**TRIMARAN**	**TRIGGER**	
Comparison of interest **N = randomised patients per treatment arm**	**BDP/FF/G 100/6/12.5 (N=579) vs BDP/FF[1] 100/6 N=576)**	**BDP/FF/G 200/6/12.5 (N=573) vs BDP/FF[1] 200/6 (N=576)**	**BDP/FF/G 200/6/12.5 (N=573) vs BDP/FF[1] 200/6 + tiotropium 2.5[2] (N=288)**
Primary endpoints			
Pre-dose FEV_1 after 26 weeks (co-primary endpoint)			
Treatment difference	+57 mL	+73 mL	-45 mL
p-value	p = 0.008	p = 0.003*	p = 0.125*
Moderate/severe exacerbations over 52 weeks (co-primary endpoint)			
Adjusted rate per patient/year	1.83 *vs* 2.16	1.73 *vs* 1.96	1.73 vs 1.63
Rate change	-15.4%	-12.0%	+7.0%
p-value	p = 0.033	**p = 0.110 (n.s.)**	p = 0.502*
Key secondary and secondary endpoints			
$Peak_{0\text{-}3h}$ FEV_1 after 26 weeks (key secondary endpoint)			
Treatment difference	+84 mL	+105 mL	-33 mL
p-value	p < 0.001	p < 0.001*	p = 0.271*
Morning peak expiratory flow (PEF) over 26 weeks (key secondary endpoint)			
Treatment difference	+8 L/min	+8 L/min	-0.2 L/min
p-value	p < 0.001	p = 0.001*	p = 0.951*
Rate of severe exacerbations over 52 weeks, pooled analysis (key secondary endpoint)			
Adjusted rate per patient/year	0.24 *vs* 0.31		n. a.
Rate change	-23.0%		
p-value	p = 0.008*		

Time to the first moderate/severe exacerbation over 52 weeks (secondary endpoint)			
Hazard ratio	0.84	0.80	1.03
p-value	p = 0.022*	p = 0.003*	p = 0.777*
Time to the first severe exacerbation over 52 weeks, pooled analysis (secondary endpoint)			
Hazard ratio	0.79		n.a.
p-value	p = 0.011*		

Co-primary endpoints (pre-dose FEV_1 at Week 26 and the rate of moderate and severe exacerbation rate over 52 weeks) and the key secondary endpoints ($peak_{0-3h}$ FEV_1 at Week 26, morning PEF over 26 weeks and the rate of severe exacerbations [pooled analysis of TRIMARAN and TRIGGER] over 52 weeks) were part of the step-down, closed confirmatory testing strategy and thus controlled for multiplicity.

Since the superiority test of one of the co-primary endpoints in the TRIGGER study did not achieve statistical significance, results for TRIGGER efficacy endpoints and the rate of severe exacerbations (pooled analysis) are nominal p-values and presented for descriptive purposes.

Since the TRIGGER study was not powered to evaluate the comparative efficacy of BDP/FF/G 200/6/12.5 vs. BDP/FF 200/6 plus tiotropium 2.5, it is not clear whether the observed differences are real or a random result.

n.a. =not applicable
n.s. = not statistically significant
[1] = fixed combination of beclometasone dipropionate (BDP) plus formoterol fumarate (FF)
[2] = open-label extemporaneous group
* = nominal p-values

Paediatric population

Trimbow is not indicated for children and adolescents under 18 years of age.

5.2 Pharmacokinetic properties

Trimbow – fixed combination
The systemic exposure to beclometasone dipropionate, formoterol and glycopyrronium has been investigated in a pharmacokinetic study conducted in healthy subjects. The study compared data obtained after treatment with a single dose of Trimbow (4 inhalations of 100/6/25 micrograms, a non-marketed formulation containing twice the approved strength of glycopyrronium) or a single dose of the extemporary combination of beclometasone dipropionate/formoterol (4 inhalations of 100/6 micrograms) plus glycopyrronium (4 inhalations of 25 micrograms). The maximum plasma concentration and systemic exposure of beclometasone dipropionate main active metabolite (beclometasone 17-monopropionate) and formoterol were similar after administration of the fixed or extemporary combination. For glycopyrronium, the maximum plasma concentration was similar after administration of the fixed or extemporary combination, while the systemic exposure was slightly higher after administration of Trimbow than with the extemporary combination. This study also investigated the potential pharmacokinetic interaction between the active components of Trimbow by comparing the pharmacokinetic data obtained after a single dose of the extemporary combination or after a single dose of the single components beclometasone dipropionate/formoterol or glycopyrronium. There was no clear evidence of pharmacokinetic interaction, however the extemporary combination showed formoterol and glycopyrronium levels transiently slightly higher immediately after dosing compared with the single components. It is noted that single component glycopyrronium, formulated as pressurised metered dose inhaler, which was used in the PK studies, is not available on the market.
The dose proportionality of systemic and lung exposure to beclometasone dipropionate has been investigated in a pharmacokinetic study conducted in healthy subjects with non-marketed Trimbow formulations, containing twice the approved strength of glycopyrronium (given as metered dose). The study compared data obtained after treatment with a single dose (4 inhalations) of Trimbow 200/6/25 micrograms or a single dose

(4 inhalations) of Trimbow 100/6/25 micrograms (both are non-marketed formulations containing twice the approved strength of glycopyrronium). Trimbow 200/6/25 micrograms treatment resulted in a two times higher systemic and lung exposure to beclometasone dipropionate and to its main active metabolite (beclometasone 17-monopropionate) in comparison to Trimbow 100/6/25 micrograms, which is consistent with the different strengths of the two formulations. The systemic and lung exposure to glycopyrronium and formoterol was similar after the two treatments, although a high variability was observed for glycopyrronium bromide C_{max}.

A comparison across studies showed that the pharmacokinetics of beclometasone 17-monopropionate, formoterol and glycopyrronium is similar in COPD patients, in patients with asthma and in healthy subjects.

Effect of a spacer
In patients with COPD, the use of Trimbow with the AeroChamber Plus spacer increased the lung delivery of beclometasone 17-monopropionate, formoterol and glycopyrronium (maximum plasma concentration increased by 15%, 58% and 60% respectively). The total systemic exposure (as measured by AUC_{0-t}) was slightly reduced for beclometasone 17-monopropionate (by 37%) and formoterol (by 24%), while it was increased for glycopyrronium (by 45%).

Effect of renal impairment
Systemic exposure (AUC_{0-t}) to beclometasone dipropionate, to its metabolite beclometasone 17-monopropionate and to formoterol was not affected by glomerular filtration rate [GFR] of ≥30 to <80 mL/min/1.73 m². For glycopyrronium, there was no impact in subjects with glomerular filtration rate [GFR] of ≥30 to <80 mL/min/1.73 m². However, an increase in total systemic exposure of up to 2.5-fold was observed in subjects with severe renal impairment (glomerular filtration rate below 30 mL/min/1.73 m^2), as a consequence of a significant reduction of the amount excreted in urine (approximately 90% reduction of glycopyrronium renal clearance). Simulations performed with a pharmacokinetic model showed that even when covariates had extreme values (body weight less than 40 kg and concomitant glomerular filtration rate below 27 mL/min/1.73 m²), exposure to Trimbow active substances remains in approximately a 2.5-fold range compared to the exposure in a typical patient with median covariate values.

Beclometasone dipropionate

Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity that is hydrolysed via esterase enzymes to an active metabolite beclometasone 17-monopropionate which has a more potent topical anti-inflammatory activity compared with the pro-drug beclometasone dipropionate.

Absorption, distribution and biotransformation
Inhaled beclometasone dipropionate is rapidly absorbed through the lungs; prior to absorption there is extensive conversion to beclometasone 17-monopropionate via esterase enzymes that are found in most tissues. The systemic availability of the active metabolite arises from lung (36%) and from gastrointestinal absorption of the swallowed dose. The bioavailability of swallowed beclometasone dipropionate is negligible; however, pre-systemic conversion to beclometasone 17-monopropionate results in 41% of the dose being absorbed as the active metabolite. There is an approximately linear increase in systemic exposure with increasing inhaled dose. The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for unchanged beclometasone dipropionate and beclometasone 17-monopropionate respectively. Following intravenous dosing, the disposition of beclometasone dipropionate and its active metabolite is characterised by high plasma clearance (150 and 120 L/h respectively), with a small volume of distribution at steady state for beclometasone dipropionate (20 L) and larger tissue distribution for its active metabolite (424 L). Plasma protein binding is moderately high.

Elimination
Faecal excretion is the major route of beclometasone dipropionate elimination mainly as polar metabolites. The renal excretion of beclometasone dipropionate and its metabolites is negligible. The terminal elimination half-lives are 0.5 hours and 2.7 hours for beclometasone dipropionate and beclometasone 17-monopropionate respectively.

Patients with hepatic impairment
The pharmacokinetics of beclometasone dipropionate in patients with hepatic impairment has not been studied, however, as beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes present in intestinal fluid, serum, lungs and liver to form the more polar products beclometasone 21-monopropionate, beclometasone 17-monopropionate and beclometasone, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of beclometasone dipropionate.

Formoterol

Absorption and distribution
Following inhalation, formoterol is absorbed from both the lung and the gastrointestinal tract. The fraction of an inhaled dose that is swallowed after administration with a metered dose inhaler may range between 60% and 90%. At least 65% of the fraction that is swallowed is absorbed from the gastrointestinal tract. Peak plasma concentrations of the unchanged active substance occur within 0.5 to 1 hours after oral administration. Plasma protein binding of formoterol is 61-64% with 34% bound to albumin. There was no saturation of binding in the concentration range attained with therapeutic doses. The elimination half-life determined after oral administration is 2-3 hours. Absorption of formoterol is linear following inhalation of 12 to 96 micrograms of formoterol.

Biotransformation
Formoterol is widely metabolised and the prominent pathway involves direct conjugation at the phenolic hydroxyl group. Glucuronide acid conjugate is inactive. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Cytochrome P450 isoenzymes CYP2D6, CYP2C19 and CYP2C9 are involved in the O-demethylation of formoterol. Liver appears to be the primary site of metabolism. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

Elimination
The cumulative urinary excretion of formoterol after single inhalation from a dry powder inhaler increased linearly in the 12-96 micrograms dose range. On average, 8% and 25% of the dose was excreted as unchanged and total formoterol, respectively. Based on plasma concentrations measured following inhalation of a single 120 micrograms dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged active substance excreted in the urine, respectively. The relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing. After oral administration (40 to 80 micrograms), 6% to 10% of the dose was recovered in urine as unchanged active substance in healthy subjects; up to 8% of the dose was recovered as the glucuronide. A total 67% of an oral dose of formoterol is excreted in urine (mainly as metabolites) and the remainder in the faeces. The renal clearance of formoterol is 150 mL/min.

Patients with hepatic impairment
The pharmacokinetics of formoterol has not been studied in patients with hepatic impairment; however, as formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment.

Glycopyrronium

Absorption and distribution
Glycopyrronium has a quaternary ammonium structure which limits its passage across biological membranes and produces slow, variable and incomplete gastrointestinal absorption. Following glycopyrronium inhalation, the lung bioavailability was 10.5% (with activated charcoal ingestion) while the absolute bioavailability was 12.8% (without activated charcoal ingestion) confirming the limited gastrointestinal absorption and indicating that more than 80% of glycopyrronium systemic exposure was from lung absorption. After repeated inhalation of twice daily doses ranging from 12.5 to 50 micrograms via pressurised metered dose inhaler in COPD patients, glycopyrronium showed linear pharmacokinetics with little systemic accumulation at steady state (median accumulation ratio 2.2-2.5).
The apparent volume of distribution (V_z) of inhaled glycopyrronium was increased compared to intravenous infusion (6,420 L versus 323 L), reflecting the slower elimination after inhalation.

Biotransformation
The metabolic pattern of glycopyrronium *in vitro* (humans, dogs, rats, mice and rabbits liver microsomes and hepatocytes) was similar among species and the main metabolic reaction was the hydroxylation on the phenyl or ciclopentyl rings. CYP2D6 was found to be the only enzyme responsible for glycopyrronium metabolism.

Elimination
The mean elimination half-life of glycopyrronium in healthy volunteers was approximately 6 hours after intravenous injection while after inhalation in COPD patients it ranged from 5 to 12 hours at steady state. After a glycopyrronium single intravenous injection, 40% of the dose was excreted in the urine within 24 hours. In COPD patients receiving repeated twice daily administration of inhaled glycopyrronium, the fraction of the dose excreted in urine ranged from 13.0% to 14.5% at steady state. Mean renal clearance was similar across the range of doses tested and after single and repeated inhalation (range 281-396 mL/min).

5.3 Preclinical safety data

Safety pharmacology
In an inhalation study in telemetered dogs, the cardiovascular system was a major target system for acute effects of Trimbow (increase in heart rate, decrease in blood pressure, ECG changes at higher doses), effects probably mainly related to the beta2-adrenergic activity of formoterol and the anti-muscarinic activity of glycopyrronium. There was no evidence for over-additive effects of the triple combination when compared with the single components.

Repeated dose toxicity
In repeated dose inhalation studies with Trimbow in rats and dogs of up to 13 weeks duration, the main observed alterations were related to effects on the immune system (probably due to systemic corticosteroid effects of beclometasone dipropionate and its active metabolite beclometasone-17-monopropionate) and on the cardiovascular system (probably related to the beta2-adrenergic activity of formoterol and the anti-muscarinic activity of glycopyrronium). The toxicological profile of the triple combination reflected that of the single active components without a relevant increase in toxicity and without unexpected findings.

Toxicity to reproduction and development
Beclometasone dipropionate/beclometasone-17-monopropionate was considered responsible for reproductive toxicity effects in rats such as reduction of the conception rate, fertility index, early embryonic development parameters (implantation loss), delay in ossification and increased incidence of visceral variations; while tocolytic and anti-muscarinic effects, attributed to the beta2-adrenergic activity of formoterol and the anti-muscarinic activity of glycopyrronium, affected pregnant rats in the late phase of gestation and/or early phase of lactation, leading to loss of pups.

Genotoxicity
Genotoxicity of Trimbow has not been evaluated, however, the single active components were devoid of genotoxic activity in the conventional test systems.

Carcinogenicity
Carcinogenicity studies have not been performed with Trimbow. However, in a 104-week rat inhalation carcinogenicity study and an oral 26-week carcinogenicity study in transgenic Tg-rasH2 mice, glycopyrronium bromide showed no carcinogenic potential and published data concerning long-term studies conducted with beclometasone dipropionate and formoterol fumarate in rats do not indicate a clinically relevant carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA 134a)

Ethanol anhydrous
Hydrochloric acid 1M

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Chemical and physical in-use stability has been demonstrated for 4 months at 25°C.
After dispensing, the medicinal product may be stored for a maximum of 4 months at a temperature up to 25°C.

6.4 Special precautions for storage

Do not freeze.
Do not expose to temperatures higher than 50°C.
Do not pierce the pressurised container.

Prior to dispensing:
Store in a refrigerator (2 -8°C).

After the dispensing:
Store at a temperature of up to 25°C for a maximum of 4 months.

For in-use storage conditions, see section 6.3.

6.5 Nature and contents of container

Pressurised container (coated aluminium), with a metering valve. The pressurised container is inserted in a polypropylene inhaler which incorporates a mouthpiece and a dose counter and is provided with a polypropylene mouthpiece cap.

Pack sizes of 1 container of 120 actuations

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For pharmacists:

Enter the date of dispensing to the patient on the pack.

7. Manufacturer:

Chiesi Farmaceutici S.p.A.,
Parma, Italy

8. Registration Holder:
Kamada Ltd, Beit Kama

Revised in January 2026