ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trydonis 87 micrograms/5 micrograms/9 micrograms pressurised inhalation, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose leaving the mouthpiece) contains 87 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 11 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

Trydonis 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

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).

4.2 Posology and method of administration

Posology

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

Special populations

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

Renal impairment
Trydonis can be used at the recommended dose in patients with mild (glomerular filtration rate [GFR] ≥50 to <80 mL/min/1.73 m^2) to moderate (GFR ≥30 to <50 mL/min/1.73 m^2) renal impairment. 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 section 4.4 and section 5.2).

Hepatic impairment
There are no relevant data on the use of Trydonis 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 section 4.4 and section 5.2).

Paediatric population
There is no relevant use of Trydonis in the paediatric population (under 18 years of age) for the indication of COPD.

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 or dose indicator on the back of the inhaler, which shows how many actuations are left. For the 120 actuation pressurised container, each time the patient presses the container a puff of the solution is released and the counter counts down by one. For the 180 actuation pressurised container, each time the patient presses the pressurised container a puff of the solution is released and the indicator rotates by a small amount; the number of puffs remaining is displayed in intervals of 20.
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 120 or 180 actuation pressurised containers, the counter/indicator should read 121 or 180, respectively. After priming, the counter/indicator should read 120 or 180.

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 or dose indicator 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 or dose indicator.

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 or indicator shows the number 20. He/she should stop using the inhaler when the counter or indicator 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, Trydonis 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 Trydonis.

If anaesthesia with halogenated anaesthetics is planned, it should be ensured that Trydonis 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 Trydonis 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.

Trydonis 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 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 using Trydonis 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, Trydonis 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, Trydonis 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.

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 Trydonis 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 Trydonis 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 Trydonis during pregnancy and during labour.

Trydonis 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 Trydonis 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 Trydonis 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 Trydonis 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

Trydonis 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 is normally associated with inhaled corticosteroids; muscle spasms (0.4% and 0.2%), which can be attributed to the long-acting beta2-agonist component; 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 summary 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[1], 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
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

MedDRA system organ class	Adverse reaction	Frequency
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 Trydonis

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

An overdose of Trydonis 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

Trydonis 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 Trydonis 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 Trydonis 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

The Phase III clinical development programme in COPD was conducted with BDP/FF/G 87/5/9 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 Trydonis with the extemporary triple combination. This endpoint was only measured in study TRINITY.

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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Trydonis in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Trydonis – 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 Trydonis (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 Trydonis than with the extemporary combination. This study also investigated the potential pharmacokinetic interaction between the active components of Trydonis 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 BDP/FF/G 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 BDP/FF/G 200/6/25 micrograms or a single dose (4 inhalations) of BDP/FF/G 100/6/25 micrograms (both are non-marketed formulations containing twice the approved strength of glycopyrronium). BDP/FF/G 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 BDP/FF/G 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 and in healthy subjects.

Effect of a spacer
In patients with COPD, the use of Trydonis 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%). See also section 4.2.

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 mild to severe renal impairment. For glycopyrronium, there was no impact in subjects with mild and moderate renal impairment. 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 m^2), exposure to Trydonis 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 (6420 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 Trydonis (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 Trydonis 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 Trydonis 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 Trydonis. 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

Ethanol anhydrous
Hydrochloric acid
Norflurane (propellant)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

120 (from a single or multipack) and 180 actuation pressurised container

22 months.

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°C-8°C).

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 (120 actuations per pressurised container) or dose indicator (180 actuations per pressurised container) and is provided with a polypropylene mouthpiece cap.

Pack sizes:
Pack of 1 container with either 120 or 180 actuations.
Multipack containing 240 actuations (2 containers of 120 actuations each).
Multipack containing 360 actuations (3 containers of 120 actuations each).

Not all pack sizes may be marketed.

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. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1274/002
EU/1/18/1274/003
EU/1/18/1274/004
EU/1/18/1274/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 April 2018
Date of latest renewal: 2nd December 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Trydonis 88 micrograms/5 micrograms/9 micrograms inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose leaving the mouthpiece) contains 88 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 11 micrograms glycopyrronium bromide).

Each metered dose 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

Each inhalation contains 9.9 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder

White or almost white powder in a white inhaler (NEXThaler).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

Posology

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

Special populations

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

Renal impairment
Trydonis can be used at the recommended dose in patients with mild (glomerular filtration rate [GFR] ≥50 to <80 mL/min/1.73 m^2) to moderate (GFR ≥30 to <50 mL/min/1.73 m^2) renal impairment. 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 section 4.4 and section 5.2).

Hepatic impairment
There are no relevant data on the use of Trydonis 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 section 4.4 and section 5.2).

Paediatric population
There is no relevant use of Trydonis in the paediatric population (under 18 years of age) for the indication of COPD.

Method of administration

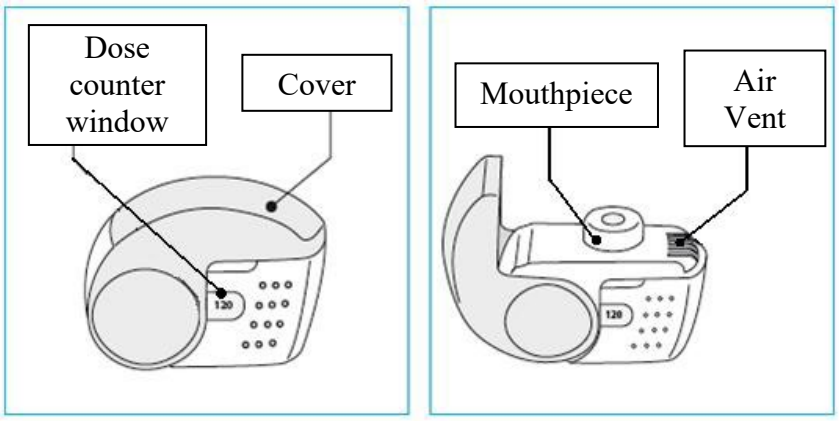
For inhalation use.

The inhaler is a breath-operated inhaler. 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.

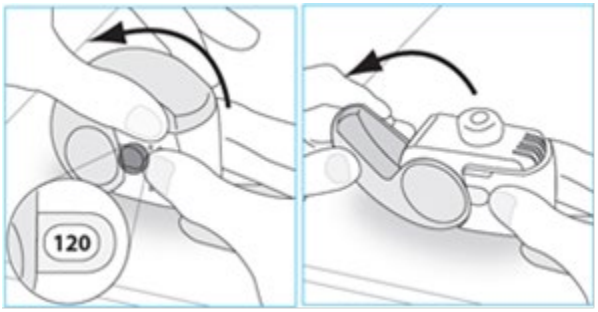
After each inhalation, the patient should rinse the mouth or gargle with water without swallowing it or brush the teeth (see section 4.4).

Instructions for use

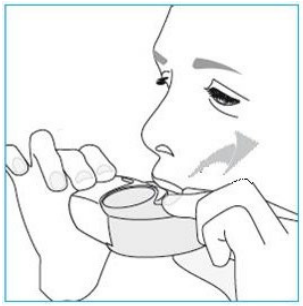


Inform the patient when using a new inhaler
- If the pouch is not sealed or is damaged or if the inhaler looks broken or damaged, the patient should return it to the pharmacist who supplied it and get a new one.
- The patient should write down the date the pouch is opened to the label on the box.
- The dose counter window has to show "120". If the number shown is less than "120", the patient should return the inhaler to the pharmacist who supplied it and get a new one.

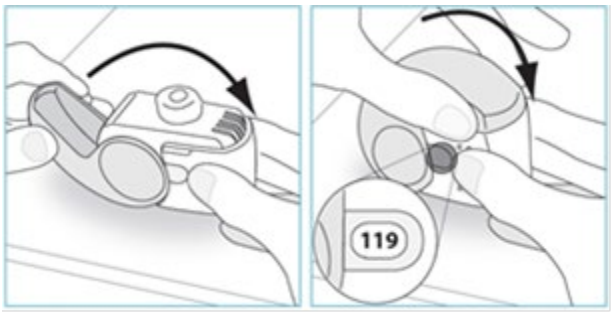
Use of the inhaler
The patient should stand or sit in an upright position when inhaling from the inhaler. The steps below should be followed.
1. The patient should hold the inhaler in the upright position, check the number of doses (any number between "1" and "120" shows that there are doses left) and open the cover fully.



2. The patient should breathe out slowly and as deeply as comfortable, in order to empty the lungs.
3. The patient should place their lips around the mouthpiece, without covering the air vent or inhaling into the air vent.
4. The patient should breathe in forcefully and deeply through the mouth. He/she may notice a taste or hear or feel a click when taking the dose.



5. The patient should then remove the inhaler from the mouth, hold the breath as long as comfortably (5-10 seconds) and then breathe out slowly. The patient should not breathe out into the inhaler.
6. After use, the patient should move the inhaler back to the upright position, close the cover fully and check the dose counter to ensure it has gone down by one.



7. If another dose has to be taken, the patient should repeat steps 1-6.

NOTE: The number of inhalations shown in the window on the shell does not decrease on closing the cover if the patient has not inhaled through the inhaler. The patient should be instructed to only open the inhaler's cover when needed. In the event that the patient has opened the inhaler but not inhaled, and the cover is closed, the dose is moved back to the powder reservoir within the inhaler; the following dose can be safely inhaled.

Cleaning
Regular cleaning of the inhaler is normally not necessary. The patient may clean the inhaler after use with a dry cloth or tissue, but not with water or other liquids.

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, Trydonis 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 Trydonis.

If anaesthesia with halogenated anaesthetics is planned, it should be ensured that Trydonis 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 Trydonis 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.

Trydonis 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, Trydonis 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, Trydonis 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.

Lactose contents

This medicinal product contains lactose.
Lactose contains small amounts of milk proteins, which may cause allergic reactions.

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 Trydonis 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

Pregnancy

There are no or limited amount of data from the use of Trydonis 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 Trydonis during pregnancy and during labour.

Trydonis 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 Trydonis 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 Trydonis 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 Trydonis 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

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

4.8 Undesirable effects

Summary of the safety profile

In a 4-week study, the safety profile of Trydonis inhalation powder was similar to the one observed for Trydonis pressurised solution.

The most frequently reported adverse reactions in patients with COPD or asthma with Trydonis pressurised solution 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. Similarly, dry mouth was reported in 2 patients (0.6%) with Trydonis inhalation powder. 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
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

MedDRA system organ class	Adverse reaction	Frequency
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 Trydonis

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

4.9 Overdose

An overdose of Trydonis 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

Trydonis contains beclometasone dipropionate, formoterol and glycopyrronium (BDP/FF/G) in a dry powder formulation resulting in an extrafine aerosol with extrafine particles and co-deposition of the three components. The aerosol particles of Trydonis 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 Trydonis 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

Trydonis inhalation powder
The development programme of Trydonis inhalation powder was conducted with BDP/FF/G 88/5/9 and included one 4-week non-inferiority study. Study TRI-D was a multicentre, randomized, double-blind, double-dummy, active controlled, 3-way cross-over study that compared 3 treatment periods of 4 weeks each with BDP/FF/G inhalation powder, BDP/FF/G pressurised inhalation, solution or a fixed-dose combination of beclometasone dipropionate and formoterol 100/6 micrograms pressurised inhalation solution, each delivered as 2 inhalations twice daily, separated by 2-week wash-outs in patients with stable, moderate-to-severe COPD. The co-primary efficacy endpoints were the change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalised by time and in trough FEV_1 at 24 hours on Day 28.

Effects on lung function
366 patients were randomized. Non-inferiority of BDP/FF/G inhalation powder *versus* BDP/FF/G pressurised inhalation solution was demonstrated for both co-primary endpoints, with the lower limits of confidence interval of the adjusted mean differences falling above the non-inferiority threshold of -50 mL: the adjusted mean differences (95% CI) were -20 mL (-35; -6) for FEV_1 $AUC_{0\text{-}12h}$, and 3 mL (-15; 20) for trough FEV_1 at 24 hours on Day 28.

Both BDP/FF/G powder inhalation and pressurised inhalation solution significantly improved FEV_1 $AUC_{0\text{-}12h}$ *versus* the fixed-dose combination of beclometasone dipropionate and formoterol pressurised inhalation solution by 85 mL (95% CI: 70; 99) and 105 mL (95% CI: 90; 120), respectively ($p < 0.001$ for both).

Inspiratory flow
An open-label placebo study was conducted to verify that the inspiratory flow which could be generated through the inhaler is not influenced by patient's age, disease and disease severity, and therefore the activation and delivery of active substances from the device could be achieved in all patients. The primary endpoint was the percentage of patients in each age and disease group able to activate the inhaler. Eighty-nine patients, in the age range 5-84 years, including patients with moderate and severe asthma ($FEV_1 > 60\%$ and $\leq 60\%$ predicted, respectively), and patients with moderate and severe COPD ($FEV_1 \geq 50\%$ and $< 50\%$ predicted, respectively) participated in the study. All patients, irrespective of age, disease and disease severity, were able to generate sufficient inspiratory flow to activate the inhaler. In an additional open label placebo study, patients with mild to severe COPD, regardless of their functional limitation, were able to effectively activate and use the inhaler.

<u>*Trydonis pressurised solution*</u>
The development programme of Trydonis pressurised solution in COPD was conducted with BDP/FF/G 87/5/9 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). The TRIBUTE study compared 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).

Reduction of COPD exacerbations
BDP/FF/G reduced the rate of moderate/severe exacerbations over 52 weeks by 23% compared with a fixed combination of beclometasone dipropionate and formoterol (rate: 0.41 *versus* 0.53 events per patient/year; $p = 0.005$), by 20% compared with tiotropium (rate: 0.46 *versus* 0.57 events per patient/year; $p = 0.003$) and by 15% compared with a fixed combination of indacaterol and glycopyrronium (rate: 0.50 *versus* 0.59 events per patient/year; $p = 0.043$). 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).

Effects on lung function
Compared with a fixed combination of beclometasone dipropionate and formoterol, BDP/FF/G improved pre-dose FEV_1 by 71 mL after 28 days, 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).

Symptomatic outcomes
BDP/FF/G was 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).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Trydonis in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Trydonis - fixed combination

The pharmacokinetic of beclometasone dipropionate (and its active metabolite beclometasone 17-monopropionate), formoterol and glycopyrronium bromide has been investigated in a pharmacokinetic study conducted in healthy subjects comparing Trydonis inhalation powder with the pressurised solution formulation, both delivering beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide at a strength of 100/6/12.5 µg/inhalation, (8 inhalations corresponding to a total dose of 800/48/100 µg). The relative total systemic exposure was assessed without the use of activated charcoal ingestion to account for both the active substance absorbed from the lung and from the gastrointestinal tract, while the relative lung bioavailability was investigated by using an activated charcoal ingestion to exclude active substance absorption from the gastrointestinal tract.
Beclometasone dipropionate was rapidly absorbed showing a peak in plasma concentration at 10 min post-dose for both Trydonis inhalation powder and the pressurised inhalation solution. Administration of the inhalation powder resulted in an increased total systemic exposure (1.2-fold for C_{max} and 2.4-fold for AUC_{0-t}) and lung bioavailability (1.3-fold for C_{max} and 2.5-fold for AUC_{0-t}) when compared to the pressurised solution. Beclometasone 17-monopropionate was rapidly formed showing a peak in plasma concentration at about 15-30 min after administration of the medicinal product. Administration of the inhalation powder resulted in a slightly lower total systemic exposure compared to the pressurised solution (-17% for C_{max} and -16% for AUC_{0-t}) while the lung bioavailability was equivalent for AUC_{0-t} but slightly lower for C_{max} (-13%).
Formoterol was rapidly absorbed showing a peak in plasma concentration at 10 min post-dose for both the inhalation powder and the pressurised inhalation solution. Administration of the inhalation powder resulted in an increased total systemic exposure (1.6-fold for C_{max} and 1.2-fold for AUC_{0-t}) and lung bioavailability (1.8-fold for C_{max} and 1.9-fold for AUC_{0-t}) when compared to the pressurised solution.
The pharmacokinetic profile of glycopyrronium bromide was characterised by a rapid absorption with plasma peak concentration at 10 min post-dose for both the inhalation powder and the pressurised inhalation solution. The total systemic exposure resulted equivalent for the inhalation powder in comparison to the pressurised solution but was 2.2-fold higher when assessed as maximum concentration. The lung bioavailability was higher for the inhalation powder, with a 2.9-fold increase in C_{max} and a 1.2-fold increase in AUC_{0-t}.

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 mild to severe renal impairment. For glycopyrronium, there was no impact in subjects with mild and moderate renal impairment. 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 Trydonis 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 Trydonis (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 Trydonis 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 Trydonis 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 Trydonis. 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

Lactose monohydrate (may contain milk proteins)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

21 months.

After first opening the pouch, the medicinal product should be used within 6 weeks and stored in a dry place.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the inhaler in the original package in order to protect from moisture and only remove from the pouch immediately before first use.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The inhaler is a white inhaler with a grey mouthpiece cover and a counter for the inhalations. It consists of a casework comprising of a lower shell with window to display number of inhalations left and an integral cover. When opened, the cover, which also drives the dose counter mechanism, reveals a mouthpiece through which the medicinal product is inhaled.
The lower shell and mouthpiece are made from acrylonitrile butadiene styrene and the cover is made from polypropylene.
The inhaler is packed into a thermo welded Polyamide/Aluminium/Polyethylene (PA/Al/PE) or Polyethylene-Terephthalate/Aluminium/ Polyethylene (PET/Al/PE) pouch.

Pack sizes:
Pack of 1 inhaler containing 120 inhalations
Multipack containing 240 inhalations (2 inhalers of 120 inhalations each).
Multipack containing 360 inhalations (3 inhalers of 120 inhalations each).

Not all pack sizes may be marketed.

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.

7. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1274/006
EU/1/18/1274/007
EU/1/18/1274/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th April 2018
Date of latest renewal: 2nd December 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Chiesi Farmaceutici S.p.A.
Via San Leonardo 96
43122 Parma
Italy

Chiesi SAS
2 rue des Docteurs Alberto et Paolo Chiesi
41260 La Chaussée Saint Victor
France

Chiesi Pharmaceuticals GmbH
Gonzagagasse 16/16
1010 Wien
Austria

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SINGLE PACK

1. NAME OF THE MEDICINAL PRODUCT

Trydonis 87/5/9 micrograms pressurised inhalation, solution
beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 87 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium.

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.

3. LIST OF EXCIPIENTS

Excipients: anhydrous ethanol, hydrochloric acid, propellant: norflurane.
Contains fluorinated greenhouse gases.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation, solution.

1 pressurised container of **120 actuations**.
1 pressurised container of **180 actuations**.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

120 and 180 actuation pressurised container:
After dispensing:
Store below 25°C for a maximum of 4 months.

Dispensing date

9. SPECIAL STORAGE CONDITIONS

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.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1274/002
EU/1/18/1274/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Trydonis 87/5/9 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (including Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Trydonis 87/5/9 micrograms pressurised inhalation, solution
beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 87 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium.

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.

3. LIST OF EXCIPIENTS

Excipients: anhydrous ethanol, hydrochloric acid, propellant: norflurane.
Contains fluorinated greenhouse gases.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation, solution.

Multipack: **240 actuations** (2 pressurised containers of 120 actuations each).
Multipack: **360 actuations** (3 pressurised containers of 120 actuations each).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After dispensing:
Store below 25°C for a maximum of 4 months.

Dispensing date

Also enter the date of dispensing on each individual pack.

9. SPECIAL STORAGE CONDITIONS

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.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1274/004
EU/1/18/1274/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Trydonis 87/5/9 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Trydonis 87/5/9 micrograms pressurised inhalation, solution
beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 87 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium.

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.

3. LIST OF EXCIPIENTS

Excipients: anhydrous ethanol, hydrochloric acid, propellant: norflurane.
Contains fluorinated greenhouse gases.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation, solution.

1 pressurised container of **120 actuations**.

Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After dispensing:
Store below 25°C for a maximum of 4 months.

Dispensing date

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1274/004
EU/1/18/1274/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Trydonis 87/5/9 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ALUMINIUM CONTAINER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trydonis 87/5/9 micrograms pressurised inhalation
beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium

Inhalation use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 actuations
180 actuations

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PLASTIC ACTUATOR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trydonis 87/5/9 mcg

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SINGLE PACK

1. NAME OF THE MEDICINAL PRODUCT

Trydonis 88/5/9 micrograms inhalation powder
beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 88 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium.

Each metered dose contains 100 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate dihydrate and 10 micrograms of glycopyrronium.

3. LIST OF EXCIPIENTS

Excipients: lactose monohydrate and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder

1 NEXThaler inhaler containing **120 inhalations**.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening the pouch, the medicine should be used within 6 weeks and stored in a dry place.

For the patient: enter the date you first open the pouch and stick this label to the bottom of the inhaler.

[Space for the adhesive label, showing the following text:]
Trydonis 88/5/9 Pouch opening date: ../../..

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

Keep the inhaler in the original package in order to protect from moisture and only remove from the pouch immediately before first use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1274/006 (1 inhaler of 120 inhalations)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Trydonis 88/5/9 mcg inhalation powder

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (including Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Trydonis 88/5/9 micrograms inhalation powder
beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 88 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium.

Each metered dose contains 100 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate dihydrate and 10 micrograms of glycopyrronium.

3. LIST OF EXCIPIENTS

Excipients: lactose monohydrate and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder

Multipack: **240 inhalations** (2 NEXThaler inhalers of 120 inhalations each).
Multipack: **360 inhalations** (3 NEXThaler inhalers of 120 inhalations each).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening the pouch, the medicine should be used within 6 weeks and stored in a dry place.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

Keep the inhaler in the original package in order to protect from moisture and only remove from the pouch immediately before first use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1274/007 (2 inhalers of 120 inhalations each)
EU/1/18/1274/008 (3 inhalers of 120 inhalations each)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Trydonis 88/5/9 mcg inhalation powder

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Trydonis 88/5/9 micrograms inhalation powder
beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 88 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium.

Each metered dose contains 100 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate dihydrate and 10 micrograms of glycopyrronium.

3. LIST OF EXCIPIENTS

Excipients: lactose monohydrate and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder.

1 NEXThaler inhaler containing **120 inhalations.**

Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening the pouch, the medicine should be used within 6 weeks and stored in a dry place.

For the patient: enter the date you first open the pouch and stick this label to the bottom of the inhaler.

[Space for the adhesive label, showing the following text:]
Trydonis 88/5/9 Pouch opening date: ../../..

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

Keep the inhaler in the original package in order to protect from moisture and only remove from the pouch immediately before first use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1274/007 (2 inhalers of 120 inhalations each)
EU/1/18/1274/008 (3 inhalers of 120 inhalations each)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Trydonis 88/5/9 mcg inhalation powder

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

POUCH

1. NAME OF THE MEDICINAL PRODUCT

Trydonis 88/5/9 micrograms inhalation powder
beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

Excipients: lactose monohydrate and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder

1 NEXThaler inhaler containing **120 inhalations**.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening the pouch, the medicine should be used within 6 weeks and stored in a dry place.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

Keep the inhaler in the original package in order to protect from moisture and only remove from the pouch immediately before first use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INHALER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trydonis 88/5/9 mcg inhalation powder
beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium

Inhalation use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 inhalations

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Trydonis 87 micrograms/5 micrograms/9 micrograms pressurised inhalation, solution
beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Trydonis is and what it is used for
2. What you need to know before you use Trydonis
3. How to use Trydonis
4. Possible side effects
5. How to store Trydonis
6. Contents of the pack and other information

1. What Trydonis is and what it is used for

Trydonis is a medicine to help breathing that contains the three active substances:
- beclometasone dipropionate,
- formoterol fumarate dihydrate and
- glycopyrronium.

Beclometasone dipropionate belongs to a group of medicines called corticosteroids which act to reduce the swelling and irritation in your lungs.

Formoterol and glycopyrronium are medicines called long-acting bronchodilators. They act in different ways to relax the muscles in your airways, helping to open the airways wider and allowing you to breathe more easily.

Regular treatment with these three active substances helps to relieve and prevent symptoms such as shortness of breath, wheezing and cough in adult patients with chronic obstructive pulmonary disease (COPD). Trydonis can reduce exacerbations (flare-ups) of COPD symptoms**.** COPD is a serious long-term disease in which the airways become blocked and air sacs inside the lungs become damaged, leading to difficulty breathing.

2. What you need to know before you use Trydonis

Do not use Trydonis

If you are allergic to beclometasone dipropionate, formoterol fumarate dihydrate and/or glycopyrronium or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Trydonis is used as a maintenance treatment for your obstructive lung disease. Do not use this medicine to treat a sudden attack of breathlessness or wheezing.

If your breathing gets worse

If you develop worsening shortness of breath or wheezing (breathing with a whistling sound), straight after inhaling your medicine, stop using Trydonis inhaler and use your quick-acting "reliever" inhaler straightaway. You should contact your doctor straightaway. Your doctor will assess your symptoms and if necessary may start you on a different treatment.
See also section 4, "Possible side effects".

If your lung disease gets worse

If your symptoms get worse or are difficult to control (e.g. if you are using a separate "reliever" inhaler more frequently) or if your "reliever" inhaler does not improve your symptoms, see your doctor immediately. Your lung disease may be getting worse and your doctor may need to prescribe different treatment.

Talk to your doctor or pharmacist before using Trydonis:

- if you have any heart problems, such as angina (heart pain, pain in the chest), a recent heart attack (myocardial infarction), heart failure, narrowing of the arteries around your heart (coronary heart disease), disease of your heart valves or any other abnormalities of your heart or if you have a condition known as hypertrophic obstructive cardiomyopathy (also known as HOCM, a condition where the heart muscle is abnormal).

- if you have disorders of your heart rhythm such as irregular heart rate, a fast pulse rate or palpitations or if you have been told that your heart trace (ECG) is abnormal.

- if you have narrowing of the arteries (also known as arteriosclerosis), if you have high blood pressure or if you have an aneurysm (abnormal bulging of the blood vessel wall).

- if you have an overactive thyroid gland.

- if you have low blood levels of potassium (hypokalaemia). The combination of Trydonis with some other COPD medicines or medicines such as diuretics (medicines that make the body lose water, to treat heart disease or high blood pressure), can cause a sharp fall in your blood level of potassium. Therefore, your doctor may wish to measure the potassium levels in your blood from time to time.

- if you have any disease of your liver or kidneys.

- if you have diabetes. High doses of formoterol may increase your blood glucose and therefore you may need to have extra blood tests to check your blood sugar when you start using this medicine, and from time to time during treatment.

- if you have a tumour of the adrenal gland (known as a phaeochromocytoma).

- if you are due to have an anaesthetic. Depending on the type of anaesthetic, it may be necessary to stop using Trydonis at least 12 hours before the anaesthesia.

- if you are being, or have ever been, treated for tuberculosis (TB) or if you have a chest infection.

- if you have an eye problem called narrow-angle glaucoma.

- if you have difficulty passing urine.

- if you have an infection of the mouth or throat.

If any of the above applies to you, tell your doctor before you use Trydonis.
If you have or have had any medical problems or any allergies or if you are not sure if you can use Trydonis, talk to your doctor or pharmacist before using the inhaler.

If you are already using Trydonis

If you are using Trydonis or high doses of other inhaled corticosteroids over long periods and you come into a situation of stress (e.g. being taken to hospital after an accident, having a serious injury or before an operation) you may need more of this medicine. In such a situation, your doctor may need to increase your dose of corticosteroids to cope with the stress and may prescribe them as tablets or injections.
Contact your doctor if you experience blurred vision or other visual disturbances.

Children and adolescents
Do not give this medicine to children and adolescents below the age of 18 years.

Other medicines and Trydonis
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines similar to Trydonis used for your lung disease.

Some medicines may increase the effects of Trydonis and your doctor may wish to monitor you carefully if you are taking these medicines (including some medicines for HIV: ritonavir, cobicistat).

Do not use this medicine with a beta-blocker medicine (used for treating certain heart problems such as angina or for reducing blood pressure) unless your doctor has chosen a beta-blocker that does not affect your breathing. Beta-blockers (including beta-blocker eye-drops) may reduce the effects of formoterol or make it not work at all. On the other hand, using other beta2-agonist medicines (which work in the same way as formoterol) may increase the effects of formoterol.

Using Trydonis together with:

- medicines for treating
  - abnormal heart rhythms (quinidine, disopyramide, procainamide),
  - allergic reactions (antihistamines),
  - symptoms of depression or mental disorders such as monoamine oxidase inhibitors (for example phenelzine and isocarboxazid), tricyclic antidepressants (for example amitriptyline and imipramine), phenothiazines

  can cause some changes in the electrocardiogram (ECG, heart trace). They may also increase the risk of disturbances of heart rhythm (ventricular arrhythmias).

- medicines for treating Parkinson's disease (levodopa), to treat an underactive thyroid gland (levothyroxine), medicines containing oxytocin (which causes uterine contraction) and alcohol can increase the chances of formoterol side effects on the heart.

- monoamine oxidase inhibitors (MAOIs), including medicines with similar properties like furazolidone and procarbazine, used to treat mental disorders, can cause a rise in blood pressure.

- medicines for treating heart disease (digoxin) can cause a fall in your blood potassium level. This may increase the likelihood of abnormal heart rhythms.

- other medicines used to treat COPD (theophylline, aminophylline or corticosteroids) and diuretics may also cause a fall in your potassium level.

- some anaesthetics can increase the risk of abnormal heart rhythms.

- Disulfiram, a medicine used in the treatment of people with alcoholism (drinking problems) or metronidazole, an antibiotic to treat infection in your body can cause side effects (e.g. feeling sick, being sick, stomach pain) due to the small amount of alcohol in Trydonis.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

You should only use Trydonis during pregnancy if you are advised to do so by your doctor. It is preferable to avoid the use of Trydonis during labour due to the inhibitory effects of formoterol on uterine contractions.
You should not use Trydonis during breast-feeding. You and your doctor must make a decision whether to discontinue breast-feeding or to discontinue/abstain from Trydonis therapy taking into account the benefit of breast-feeding for your child and the benefit of therapy for you.

Driving and using machines
Trydonis is unlikely to affect your ability to drive and use machines.

Trydonis contains ethanol
Trydonis contains 8.856 mg of alcohol (ethanol) in each actuation, which is equivalent to 17.712 mg per dose of two actuations. The amount in two actuations of this medicine is equivalent to less than 1 ml of wine or beer. The small amount of alcohol in this medicine will not have any noticeable effects.

3. How to use Trydonis

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is two puffs in the morning and two puffs in the evening.

If you feel that the medicine is not very effective, talk to your doctor.
If you have been using a different inhaler containing beclometasone dipropionate previously, ask your doctor for advice, as the effective dose of beclometasone dipropionate in Trydonis for the treatment of COPD may be lower than that of some other inhalers.

Route of administration
Trydonis is for inhalation use.
You should inhale the medicine through your mouth and this takes the medicine directly into your lungs.

This medicine is contained in a pressurised container in a plastic inhaler with a mouthpiece.

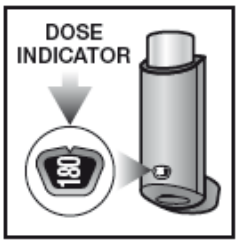
Trydonis is available in two container sizes:
- a container providing 120 puffs
- a container providing 180 puffs.

If you have been prescribed a container providing 120 puffs
There is a counter on the back of the inhaler, which tells you how many doses are left. Each time you press the pressurised container, a puff of medicine is released and the counter will count down by one. Take care not to drop the inhaler as this may cause the counter to count down.

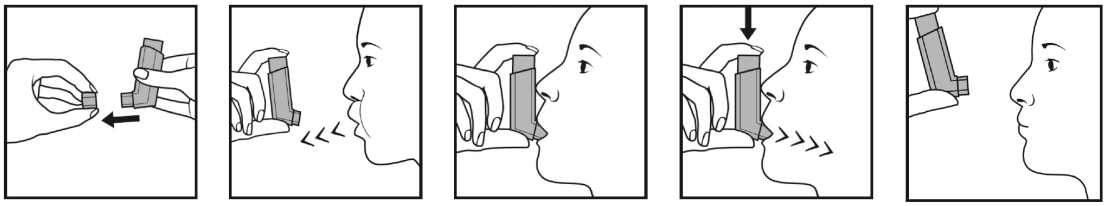
If you have been prescribed a container providing 180 puffs
There is an indicator on the back of the inhaler, which tells you how many doses are left. Each time you press the pressurised container, a puff of medicine is released and the dose indicator rotates by a small amount. The number of puffs remaining is displayed in intervals of 20. Take care not to drop the inhaler as this may cause the dose indicator to count down.

Testing your inhaler
Before using the inhaler for the first time, you should test your inhaler to make sure that it is working properly, as follows.

1. Depending on the container size prescribed to you, check that the dose counter reads 121 and that the dose indicator reads 180
2. Remove the protective cap from the mouthpiece
3. Hold your inhaler upright with the mouthpiece at the bottom
4. Direct the mouthpiece away from yourself and firmly press the pressurised container to release one puff
5. Check the dose counter or dose indicator. If you are testing your inhaler for the first time, the counter should read:

120 - when using the container providing 120 puffs	**180** - when using the container providing 180 puffs
	

How to use your inhaler
Stand or sit up when inhaling.
IMPORTANT: Do not perform steps 2 to 5 too quickly.



1 2 3 4 5

1. Remove the protective cap from the mouthpiece and check that the mouthpiece is clean and free from dust and dirt.
2. Breathe out as slowly and deeply as possible, in order to empty your lungs.
3. Hold the inhaler upright with the mouthpiece at the bottom and place the mouthpiece between your teeth without biting it. Then place your lips around the mouthpiece, with the tongue flat under it.
4. Breathe in slowly and deeply through your mouth to fill your lungs with air (this should take about 4–5 seconds). Just after starting to breathe in, press down firmly on the top of the pressurised container to release one puff.
5. Hold your breath for as long as possible and, finally, remove the inhaler from your mouth and breathe out slowly. Do not breathe out into the inhaler.
6. Check that the dose counter (120 puffs) has moved down by one or that the dose indicator (180 puffs) has rotated by a small amount.

For the second puff, keep the inhaler in the upright position for about half a minute, then repeat steps 2 to 5.

If you see 'mist' coming from the top of the inhaler or the sides of your mouth, this means that Trydonis will not be getting into your lungs as it should. Take another puff, following the instructions starting again from step 2.

After use, replace the protective cap.

To prevent a fungal infection in the mouth and throat, rinse your mouth or gargle with water without swallowing it or brush your teeth after each use of your inhaler.

When to get a new inhaler
You should get a replacement when the counter or indicator shows the number 20. Stop using the inhaler when the counter or indicator shows 0, as any medicine left in the inhaler may not be enough to give you a full puff.

If you have a weak grip, it may be easier to hold the inhaler with both hands: hold the upper part of the inhaler with both index fingers and its lower part with both thumbs.

If you find it difficult to use the inhaler while starting to breathe in, you may use the AeroChamber Plus spacer device. Ask your doctor or pharmacist about this device.
It is important that you read the package leaflet which is supplied with your AeroChamber Plus spacer device and that you carefully follow the instructions on how to use the AeroChamber Plus spacer device and how to clean it.

Cleaning of the Trydonis inhaler
You should clean your inhaler once a week.
1. Do not remove the pressurised container from the inhaler and do not use water or other liquids to clean your inhaler.
2. Remove the protective cap from the mouthpiece by pulling it away from your inhaler.
3. Wipe inside and outside of the mouthpiece and the inhaler with a clean, dry cloth or tissue.
4. Replace the mouthpiece cap.

If you use more Trydonis than you should
It is important that you take your dose as advised by your doctor. Do not exceed your prescribed dose without talking to your doctor.
If you use more Trydonis than you should, side effects, as described in section 4, may occur.
Tell your doctor if you have used more Trydonis than you should and if you experience any of these symptoms. Your doctor may wish to carry out some blood tests.

If you forget to use Trydonis
Use it as soon as you remember. If it is almost time for your next dose, do not take the dose you have missed, but just take the next dose at the correct time. Do not double the dose.

If you stop using Trydonis
It is important to use Trydonis every day. Do not stop using Trydonis or lower the dose, even if you are feeling better or you have no symptoms. If you want to do this, talk to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

There is a risk of worsening shortness of breath and wheezing immediately after using Trydonis and this is known as paradoxical bronchospasm (may affect up to 1 in 1,000 people). If this occurs you should stop using Trydonis and use your quick-acting "reliever" inhaler straightaway to treat the shortness of breath and wheezing. You should contact your doctor straightaway.

Tell your doctor immediately
- if you experience any allergic reactions like skin allergies, hives, skin itching, skin rash (may affect up to 1 in 100 people), reddening of the skin, swelling of the skin or mucous membranes especially of the eyes, face, lips and throat (may affect up to 1 in 1,000 people).
- if you experience eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes. These may be signs of an acute attack of narrow-angle glaucoma (may affect up to 1 in 10,000 people).

Tell your doctor if you have any of the following while using Trydonis as they could be symptoms of a lung infection (may affect up to 1 in 10 people):
- fever or chills
- increased mucus production, change in mucus colour
- increased cough or increased breathing difficulties.

Possible side effects are listed below according to their frequency.

Common (may affect up to 1 in 10 people)
- sore throat
- runny or stuffy nose and sneezing
- fungal infections of the mouth. Rinsing your mouth or gargling with water and brushing your teeth immediately after inhalation may help to prevent these side effects
- hoarseness
- headache
- urinary tract infection.

Uncommon (may affect up to 1 in 100 people)
- flu
- inflammation of the sinuses
- itchy, runny or blocked nose
- fungal infections of the throat or of the food pipe (oesophagus)
- fungal infections of the vagina
- restlessness
- trembling
- dizziness
- abnormal or reduced sense of taste
- numbness
- inflammation of the ear
- irregular heart beat
- changes in the electrocardiogram (heart trace)
- unusually fast heart beat and disorders of the heart rhythm
- palpitations (feeling of abnormal beating of the heart)
- reddening of the face
- increased blood flow to some tissues in the body
- asthma attack
- cough and productive cough
- nose bleeds
- redness of the pharynx
- dry mouth
- diarrhoea
- swallowing difficulties
- feeling sick
- upset stomach
- stomach discomfort after meals
- burning sensation of the lips
- tooth decay
- skin rash, hives, skin itching
- inflammation of the mucous membrane of the mouth with or without ulcers
- increased sweating
- muscle cramps and pain in muscles
- pain in arms or legs
- pain in muscles, bones or joints of the chest
- tiredness
- increase of blood pressure
- fall in the level of some constituents of your blood: of certain white blood cells called granulocytes, of potassium or of cortisol

- irritation of the throat
- increase in the level of some constituents of your blood: glucose, C-reactive protein, number of platelets, insulin, free fatty acid or ketones.

Rare (may affect up to 1 in 1,000 people)
- fungal infections of the chest
- decreased appetite
- sleep disorders (sleeping too little or too long)
- crushing chest pain
- sensation of a missed heart beat or of extra heart beats, unusually slow heart beat
- worsening of asthma
- leakage of blood from a vessel into the tissues surrounding it
- decrease of blood pressure
- weakness
- pain in the back of the mouth and throat
- inflammation of the pharynx
- dry throat
- painful and frequent urination
- difficulty and pain when passing urine
- inflammation of the kidneys.

Very rare (may affect up to 1 in 10,000 people)
- low level in the number of certain blood cells called platelets
- feeling breathless or short of breath
- swelling of the hands and feet
- growth retardation in children and adolescents.

Not known (frequency cannot be estimated from the available data)
- blurred vision.

Using high-dose inhaled corticosteroids over a long time can cause in very rare cases effects on the body:
- problems with how your adrenal glands work (adrenal suppression)
- decrease in bone mineral density (thinning of the bones)
- clouding of the lens of your eyes (cataract).

Trydonis does not contain a high-dose inhaled corticosteroid, but your doctor may wish to measure the cortisol levels in your blood from time to time.

The following side effects can also occur with high-dose inhaled corticosteroids used over a long time, but the frequency is not known (frequency cannot be estimated from the available data) at present:
- depression
- feeling worried, nervous, over-excited or irritable.

These events are more likely to occur in children.

Reporting of side effects
If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Trydonis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

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°C-8°C).

After dispensing (receiving this medicine from your pharmacist):

120 (from a single or multipack) and 180 actuation pressurised container:	Store the inhaler below 25°C for a maximum of 4 months.

Do not throw away any medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other information

What Trydonis contains
The active substances are: beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium.

Each delivered dose (the dose leaving the mouthpiece) contains 87 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 11 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 of glycopyrronium bromide).

The other ingredients are: ethanol anhydrous (see section 2), hydrochloric acid, propellant: norflurane.

This medicine contains fluorinated greenhouse gases.
Each inhaler of 120 actuations contains 10.37 g of norflurane (HFC-134a) corresponding to 0.015 tonne CO_2 equivalent (global warming potential GWP = 1430).
Each inhaler of 180 actuations contains 14.259 g of norflurane (HFC-134a) corresponding to 0.02 tonne CO_2 equivalent (global warming potential GWP = 1430).

What Trydonis looks like and contents of the pack
Trydonis is a pressurised inhalation, solution.

Trydonis comes in a pressurised container (coated aluminium), with a metering valve. The pressurised container is inserted in a plastic inhaler. This incorporates a mouthpiece provided with a plastic protective cap, and either a dose counter (containers with 120 puffs) or a dose indicator (containers with 180 puffs).

Each pack contains one pressurised container either providing 120 puffs or 180 puffs. Additional there are multipacks containing either 240 puffs (2 pressurised containers with 120 puffs, each) or 360 puffs (3 pressurised containers with 120 puffs, each).

Not all pack sizes may be marketed.

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Manufacturer
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This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.

Package leaflet: Information for the user

Trydonis 88 micrograms/5 micrograms/9 micrograms inhalation powder
beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Trydonis is and what it is used for
2. What you need to know before you use Trydonis
3. How to use Trydonis
4. Possible side effects
5. How to store Trydonis
6. Contents of the pack and other information

1. What Trydonis is and what it is used for

Trydonis is a medicine to help breathing that contains the three active substances:
- beclometasone dipropionate,
- formoterol fumarate dihydrate and
- glycopyrronium.

Beclometasone dipropionate belongs to a group of medicines called corticosteroids which act to reduce the swelling and irritation in your lungs.

Formoterol and glycopyrronium are medicines called long-acting bronchodilators. They act in different ways to relax the muscles in your airways, helping to open the airways wider and allowing you to breathe more easily.

Regular treatment with these three active substances helps to relieve and prevent symptoms such as shortness of breath, wheezing and cough in adult patients with chronic obstructive pulmonary disease (COPD). Trydonis can reduce exacerbations (flare-ups) of COPD symptoms. COPD is a serious long-term disease in which the airways become blocked and air sacs inside the lungs become damaged, leading to difficulty breathing.

2. What you need to know before you use Trydonis

Do not use Trydonis

If you are allergic to beclometasone dipropionate, formoterol fumarate dihydrate and/or glycopyrronium or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Trydonis is used as a maintenance treatment for your obstructive lung disease. Do not use this medicine to treat a sudden attack of breathlessness or wheezing.

If your breathing gets worse

If you develop worsening shortness of breath or wheezing (breathing with a whistling sound), straight after inhaling your medicine, stop using Trydonis inhaler and use your quick-acting "reliever" inhaler straightaway. You should contact your doctor straightaway. Your doctor will assess your symptoms and if necessary may start you on a different treatment.
See also section 4, "Possible side effects".

If your lung disease gets worse

If your symptoms get worse or are difficult to control (e.g. if you are using a separate "reliever" inhaler more frequently) or if your "reliever" inhaler does not improve your symptoms, see your doctor immediately. Your lung disease may be getting worse and your doctor may need to prescribe different treatment.

Talk to your doctor or pharmacist before using Trydonis:

- if you have any heart problems, such as angina (heart pain, pain in the chest), a recent heart attack (myocardial infarction), heart failure, narrowing of the arteries around your heart (coronary heart disease), disease of your heart valves or any other abnormalities of your heart or if you have a condition known as hypertrophic obstructive cardiomyopathy (also known as HOCM, a condition where the heart muscle is abnormal).

- if you have disorders of your heart rhythm such as irregular heart rate, a fast pulse rate or palpitations or if you have been told that your heart trace (ECG) is abnormal.

- if you have narrowing of the arteries (also known as arteriosclerosis), if you have high blood pressure or if you have an aneurysm (abnormal bulging of the blood vessel wall).

- if you have an overactive thyroid gland.

- if you have low blood levels of potassium (hypokalaemia). The combination of Trydonis with some other lung medicines or medicines such as diuretics (medicines that make the body lose water, to treat heart disease or high blood pressure), can cause a sharp fall in your blood level of potassium. Therefore, your doctor may wish to measure the potassium levels in your blood from time to time.

- if you have any disease of your liver or kidneys.

- if you have diabetes. High doses of formoterol may increase your blood glucose and therefore you may need to have extra blood tests to check your blood sugar when you start using this medicine, and from time to time during treatment.

- if you have a tumour of the adrenal gland (known as a phaeochromocytoma).

- if you are due to have an anaesthetic. Depending on the type of anaesthetic, it may be necessary to stop using Trydonis at least 12 hours before the anaesthesia.

- if you are being, or have ever been, treated for tuberculosis (TB) or if you have a chest infection.

- if you have an eye problem called narrow-angle glaucoma.

- if you have difficulty passing urine.

- if you have an infection of the mouth or throat.

If any of the above applies to you, tell your doctor before you use Trydonis.
If you have or have had any medical problems or any allergies or if you are not sure if you can use Trydonis, talk to your doctor or pharmacist before using the inhaler.

If you are already using Trydonis

If you are using Trydonis or high doses of other inhaled corticosteroids over long periods and you come into a situation of stress (e.g. being taken to hospital after an accident, having a serious injury or before an operation) you may need more of this medicine. In such a situation, your doctor may need to increase your dose of corticosteroids to cope with the stress and may prescribe them as tablets or injections.
Contact your doctor if you experience blurred vision or other visual disturbances.

Children and adolescents
Do not give this medicine to children and adolescents below the age of 18 years.

Other medicines and Trydonis
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines similar to Trydonis used for your lung disease.

Some medicines may increase the effects of Trydonis and your doctor may wish to monitor you carefully if you are taking these medicines (including some medicines for HIV: ritonavir, cobicistat).

Do not use this medicine with a beta-blocker medicine (used for treating certain heart problems such as angina or for reducing blood pressure) unless your doctor has chosen a beta-blocker that does not affect your breathing. Beta-blockers (including beta-blocker eye-drops) may reduce the effects of formoterol or make it not work at all. On the other hand, using other beta2-agonist medicines (which work in the same way as formoterol) may increase the effects of formoterol.

Using Trydonis together with:

- medicines for treating
  - abnormal heart rhythms (quinidine, disopyramide, procainamide),
  - allergic reactions (antihistamines),
  - symptoms of depression or mental disorders such as monoamine oxidase inhibitors (for example phenelzine and isocarboxazid), tricyclic antidepressants (for example amitriptyline and imipramine), phenothiazines

  can cause some changes in the electrocardiogram (ECG, heart trace). They may also increase the risk of disturbances of heart rhythm (ventricular arrhythmias).

- medicines for treating Parkinson's disease (levodopa), to treat an underactive thyroid gland (levothyroxine), medicines containing oxytocin (which causes uterine contraction) and alcohol can increase the chances of formoterol side effects on the heart.

- monoamine oxidase inhibitors (MAOIs), including medicines with similar properties like furazolidone and procarbazine, used to treat mental disorders, can cause a rise in blood pressure.

- medicines for treating heart disease (digoxin) can cause a fall in your blood potassium level. This may increase the likelihood of abnormal heart rhythms.

- other medicines used to treat obstructive lung disease (theophylline, aminophylline or corticosteroids) and diuretics may also cause a fall in your potassium level.

- some anaesthetics can increase the risk of abnormal heart rhythms.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

You should only use Trydonis during pregnancy if you are advised to do so by your doctor. It is preferable to avoid the use of Trydonis during labour due to the inhibitory effects of formoterol on uterine contractions.
You should not use Trydonis during breast-feeding. You and your doctor must make a decision whether to discontinue breast-feeding or to discontinue/abstain from Trydonis therapy taking into account the benefit of breast-feeding for your child and the benefit of therapy for you.

Driving and using machines
Trydonis is unlikely to affect your ability to drive and use machines.

Trydonis contains lactose
Lactose contains small amounts of milk proteins, which may cause allergic reactions.

3. How to use Trydonis

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is two inhalations in the morning and two inhalations in the evening.

If you feel that the medicine is not very effective, talk to your doctor.
If you have been using a different inhaler containing beclometasone dipropionate previously, ask your doctor for advice, as the effective dose of beclometasone dipropionate in Trydonis for the treatment of your obstructive lung disease may be lower than that of some other inhalers.

Route of administration
Trydonis is for inhalation use.
You should inhale the medicine through your mouth and this takes the medicine directly into your lungs.

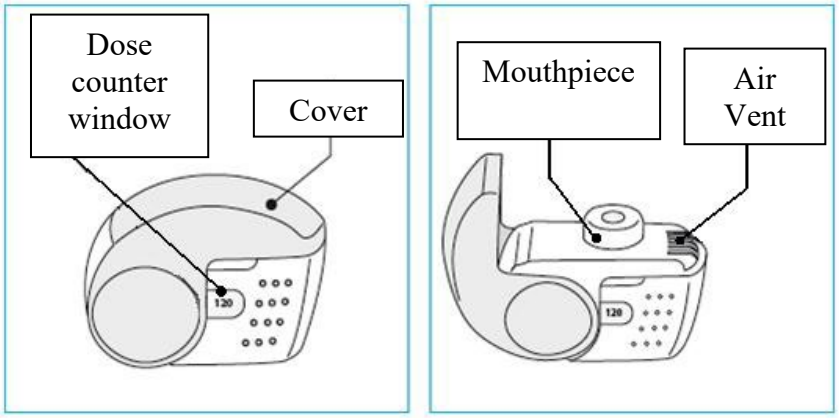
Instructions for use

For information on the contents of the pack, see section 6.

If the pack contents are not the same as described in section 6, return your inhaler to the person who supplied it and get a new one.

- **Do not** remove the inhaler from the pouch if you do not intend to use it immediately.
- Only use your inhaler as indicated.
- Keep the cover closed until you need to take a dose from your inhaler.
- When you are not using your inhaler keep it in a clean and dry place.
- **Do not** attempt to take your inhaler apart for any reason.

A. Key features of your inhaler



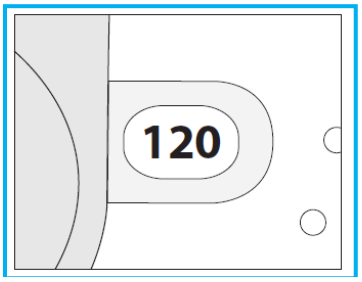
Taking a dose from your inhaler requires three steps: Open, Inhale, Close

B. Before using a new inhaler

1. **Open the pouch and take out your inhaler.**
   - **Do not** use your inhaler if the pouch is not sealed or it is damaged – return it to the pharmacist who supplied it and get a new one.
   - Use the label on the box to write down the date you open the pouch.

2. **Inspect your inhaler.**
   - If your inhaler looks broken or damaged, return it to the pharmacist who supplied it and get a new one.

3. **Check the Dose Counter Window. If your inhaler is new you will see "120" in the Dose Counter Window.**
   - **Do not** use a new inhaler if the number shown is less than "120" – return it to the pharmacist who supplied it and get a new one.



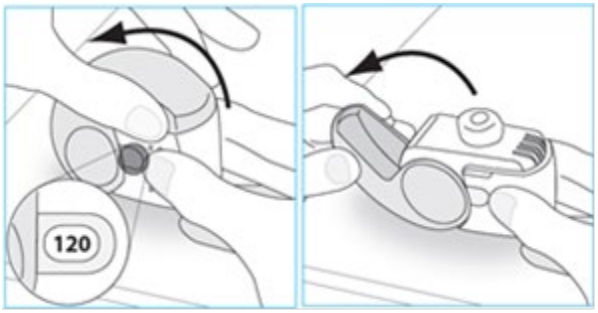
C. How to use your inhaler

C.1. Open

1. **Hold your inhaler firmly in the upright position.**

2. **Check the number of doses left: any number between "1" and "120" shows that there are doses left.**
   - If the Dose Counter Window shows "0" there are no doses left – dispose of your inhaler and get a new one.

3. **Open the cover fully.**



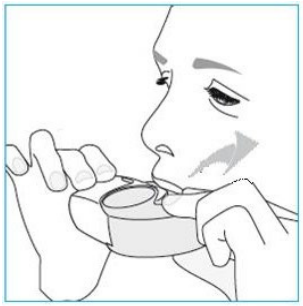
4. **Before inhaling breathe out as far as is comfortable.**
   - **Do not** breathe out through your inhaler.

C.2. Inhale

Whenever possible, stand or sit in an upright position when inhaling.

1. **Lift your inhaler up, bring it to your mouth and place your lips around the mouthpiece.**
   - **Do not** cover the air vent when holding your inhaler.
   - **Do not** inhale through the air vent.

2. **Take a forceful and deep breath through your mouth.**
   - You may notice a taste when you take your dose.
   - You may hear or feel a click when you take your dose.
   - **Do not** inhale through your nose.
   - **Do not** remove your inhaler from your lips during the inhalation.



3. **Remove your inhaler from your mouth.**

4. **Hold your breath for 5 to 10 seconds or as long as is comfortable.**

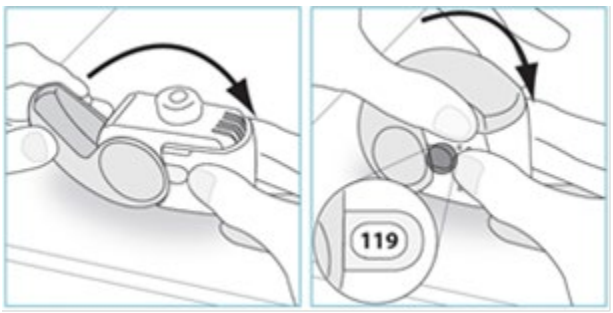
5. **Breathe out slowly.**
   - **Do not** breathe out through your inhaler.

- If you are not sure you are receiving your dose correctly contact your pharmacist or doctor.

C.3. Close

1. **Move your inhaler back to the upright position and close the cover fully.**

2. **Check that the dose counter has gone down by one.**



- If you are not sure the dose counter has gone down by one after inhalation, wait until your next scheduled dose and take this as normal. Do not take an extra dose.

3. If you need to take another dose, repeat steps C.1 to C.3.

D. Cleaning

- Normally, it is not necessary to clean your inhaler.
- If necessary, you may clean your inhaler after use with a dry cloth or tissue.
  - **Do not** clean your inhaler with water or other liquids. Keep it dry.

If you use more Trydonis than you should
It is important that you take your dose as advised by your doctor. Do not exceed your prescribed dose without talking to your doctor.
If you use more Trydonis than you should, side effects, as described in section 4, may occur.
Tell your doctor if you have used more Trydonis than you should and if you experience any of these symptoms. Your doctor may wish to carry out some blood tests.

If you forget to use Trydonis
Use it as soon as you remember. If it is almost time for your next dose, do not take the dose you have missed, but just take the next dose at the correct time. Do not double the dose.

If you stop using Trydonis
It is important to use Trydonis every day. Do not stop using Trydonis or lower the dose, even if you are feeling better or you have no symptoms. If you want to do this, talk to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

There is a risk of worsening shortness of breath and wheezing immediately after using Trydonis and this is known as paradoxical bronchospasm (may affect up to 1 in 1,000 people). If this occurs you should stop using Trydonis and use your quick-acting “reliever” inhaler straightaway to treat the shortness of breath and wheezing. You should contact your doctor straightaway.

Tell your doctor immediately
- if you experience any allergic reactions like skin allergies, hives, skin itching, skin rash (may affect up to 1 in 100 people), reddening of the skin, swelling of the skin or mucous membranes especially of the eyes, face, lips and throat (may affect up to 1 in 1,000 people).
- if you experience eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes. These may be signs of an acute attack of narrow-angle glaucoma (may affect up to 1 in 10,000 people).

Tell your doctor if you have any of the following while using Trydonis as they could be symptoms of a lung infection (may affect up to 1 in 10 people):

- fever or chills
- increased mucus production, change in mucus colour
- increased cough or increased breathing difficulties.

Possible side effects are listed below according to their frequency.

Common (may affect up to 1 in 10 people)

- sore throat
- runny or stuffy nose and sneezing
- fungal infections of the mouth. Rinsing your mouth or gargling with water and brushing your teeth immediately after inhalation may help to prevent these side effects
- hoarseness
- headache
- urinary tract infection.

Uncommon (may affect up to 1 in 100 people)

- flu
- inflammation of the sinuses
- itchy, runny or blocked nose
- fungal infections of the throat or of the food pipe (oesophagus)
- fungal infections of the vagina
- restlessness
- trembling
- dizziness
- abnormal or reduced sense of taste
- numbness
- inflammation of the ear
- irregular heart beat
- changes in the electrocardiogram (heart trace)
- unusually fast heart beat and disorders of the heart rhythm
- palpitations (feeling of abnormal beating of the heart)
- reddening of the face
- increased blood flow to some tissues in the body
- asthma attack
- cough and productive cough
- irritation of the throat
- nose bleeds
- redness of the pharynx
- dry mouth
- diarrhoea
- swallowing difficulties
- feeling sick
- upset stomach
- stomach discomfort after meals
- burning sensation of the lips
- tooth decay
- skin rash, hives, skin itching
- inflammation of the mucous membrane of the mouth with or without ulcers
- increased sweating
- muscle cramps and pain in muscles
- pain in arms or legs
- pain in muscles, bones or joints of the chest
- tiredness
- increase of blood pressure
- fall in the level of some constituents of your blood: of certain white blood cells called granulocytes, of potassium or of cortisol
- increase in the level of some constituents of your blood: glucose, C-reactive protein, number of platelets, insulin, free fatty acid or ketones.

Rare (may affect up to 1 in 1,000 people)

- fungal infections of the chest
- decreased appetite
- sleep disorders (sleeping too little or too long)
- crushing chest pain
- sensation of a missed heart beat or of extra heart beats, unusually slow heart beat
- worsening of asthma
- leakage of blood from a vessel into the tissues surrounding it
- decrease of blood pressure
- weakness
- pain in the back of the mouth and throat
- inflammation of the pharynx
- dry throat
- painful and frequent urination
- difficulty and pain when passing urine
- inflammation of the kidneys.

Very rare (may affect up to 1 in 10,000 people)

- low level in the number of certain blood cells called platelets
- feeling breathless or short of breath
- swelling of the hands and feet
- growth retardation in children and adolescents.

Not known (frequency cannot be estimated from the available data)

- blurred vision.

Using high-dose inhaled corticosteroids over a long time can cause in very rare cases effects on the body:

- problems with how your adrenal glands work (adrenal suppression)
- decrease in bone mineral density (thinning of the bones)
- clouding of the lens of your eyes (cataract).

Trydonis does not contain a high-dose inhaled corticosteroid, but your doctor may wish to measure the cortisol levels in your blood from time to time.

The following side effects can also occur with high-dose inhaled corticosteroids used over a long time, but the frequency is not known (frequency cannot be estimated from the available data) at present:

- depression
- feeling worried, nervous, over-excited or irritable.

These events are more likely to occur in children.

Reporting of side effects

If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Trydonis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Keep the inhaler in the original package in order to protect from moisture and only remove from the pouch immediately before first use.

After first opening the pouch the medicine should be used within 6 weeks and stored in a dry place. Use the adhesive label on the outer carton to write down the date you open the pouch and stick this label to the bottom of the inhaler.

Do not throw away any medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other information

What Trydonis contains
The active substances are: beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium.

Each delivered dose (the dose leaving the mouthpiece) contains 88 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 11 micrograms glycopyrronium bromide).

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

The other ingredients are: lactose monohydrate (see section 2) and magnesium stearate.

What Trydonis looks like and contents of the pack
Trydonis is a white to almost white inhalation powder.

It is provided in a white plastic inhaler called NEXThaler with a grey mouthpiece cover and a counter for the inhalations.
Each inhaler is packed in a sealed protective pouch.

Trydonis is available in packs containing one inhaler, and in multipacks comprising two or three inhalers, providing 120 inhalations each (120, 240 or 360 inhalations).
Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.