AUSTRALIAN PRODUCT INFORMATION – BRIMICA® GENUAIR® 340/12 (aclidinium bromide and formoterol fumarate dihydrate) Powder for Inhalation

1 NAME OF THE MEDICINE

aclidinium bromide and formoterol fumarate dihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BRIMICA GENUAIR 340/12 contains an adhesive mixture of micronised aclidinium bromide, formoterol fumarate dihydrate (hereafter referred to as formoterol) and α-lactose monohydrate, contained in a metered device, dry powder inhaler.

Each metered dose is equal to 400 micrograms aclidinium bromide (equivalent to 343 micrograms aclidinium) and 12 micrograms formoterol fumarate dihydrate.

Each delivered dose (the dose leaving the mouthpiece) contains 396 micrograms aclidinium bromide (equivalent to 340 micrograms aclidinium) and 11.8 micrograms formoterol fumarate dihydrate.

List of excipients with known effect: Contains lactose.

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

The inhalation powder is white or almost white, and is delivered from a white inhaler with an integral dose indicator and an orange dosage button.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BRIMICA GENUAIR 340/12 is indicated as a long-term twice daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

4.2 DOSE AND METHOD OF ADMINISTRATION

Use in adults

The recommended dose is one inhalation of BRIMICA GENUAIR 340/12 twice daily, once in the morning and once at night.

Method of Administration

BRIMICA GENUAIR 340/12 must be administered only by the oral inhalation route. BRIMICA GENUAIR 340/12 should be administered in the morning and at night and should be taken 12 hours apart. If a dose is missed the next dose should be taken as soon as possible. However, if it is nearly time for the next dose, the missed dose should be skipped.

Use in children

BRIMICA GENUAIR 340/12 should not be used in patients under 18 years of age.

Use in the elderly

No dose adjustments are required for elderly patients (see section 5.2 PHARMACOKINETIC PROPERTIES).

Use in patients with impaired renal function

No dose adjustments are required for patients with renal impairment (see section 5.2 PHARMACOKINETIC PROPERTIES).

Use in patients with impaired hepatic function

No dose adjustments are required for patients with hepatic impairment (see section 5.2 PHARMACOKINETIC PROPERTIES).

4.3 CONTRAINDICATIONS

Patients with hypersensitivity to aclidinium bromide, formoterol fumarate dihydrate or to any other component of BRIMICA GENUAIR 340/12.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Asthma

BRIMICA GENUAIR 340/12 should not be used for the treatment of asthma; clinical studies of BRIMICA GENUAIR 340/12 in the treatment of asthma have not been conducted.

Paradoxical bronchospasm

In clinical studies, paradoxical bronchospasm was not observed in patients using BRIMICA GENUAIR 340/12. However, paradoxical bronchospasm has been observed with other inhalation therapies. If this occurs, medication should be stopped and other treatment considered.

Deterioration of disease

BRIMICA GENUAIR 340/12 is intended for the maintenance treatment of COPD. BRIMICA GENUAIR 340/12 should not be used for the relief of acute episodes of bronchospasm, i.e. as a rescue therapy. In the event of a change in COPD intensity while the patient is being treated with BRIMICA GENUAIR 340/12 so that the patient considers additional rescue medication is required, medical advice and a re-evaluation of the patient and the patient's treatment regimen should be conducted. An increase in the daily dose of BRIMICA GENUAIR 340/12 beyond the maximum dose is not appropriate.

Sympathomimetic amines

In patients with increased susceptibility to sympathomimetic amines (e.g. inadequately controlled hyperthyroidism), BRIMICA GENUAIR 340/12 should be used with caution.

Cardiovascular effects

Patients with a myocardial infarction during the previous 6 months, unstable angina, or hospitalisation within the previous 12 months for heart failure functional classes III and IV as per the “New York Heart Association” were excluded from the clinical studies, therefore BRIMICA GENUAIR 340/12 should be used with caution in these patients groups.

β_2-adrenergic agonists may produce increases in pulse rate and blood pressure, electrocardiogram (ECG) changes such as T-wave flattening, ST segment depression and prolongation of the QTc-interval in some patients. In case such effects occur, treatment may need to be discontinued.

Cardiac arrhythmias, including atrial fibrillation and paroxysmal tachycardia were seen after the administration of BRIMICA GENUAIR 340/12 (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Therefore, BRIMICA GENUAIR 340/12 should be used with caution in patients with cardiac arrhythmias, a history of cardiac arrhythmias or with risk factors for cardiac arrhythmias.

Systemic effects

BRIMICA GENUAIR 340/12 should be used with caution in patients with severe cardiovascular disorders, convulsive disorders, thyrotoxicosis and phaeochromocytoma.

Metabolic effects of hyperglycaemia and hypokalaemia may be observed with high doses of β_2-adrenergic agonists. In Phase III clinical studies, the frequency of notable increases in blood glucose with BRIMICA GENUAIR 340/12 was low (0.1%) and similar to placebo. Hypokalaemia is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment. Hypokalaemia increases susceptibility to cardiac arrhythmias.

Due to its anticholinergic activity, BRIMICA GENUAIR 340/12 should be used with caution in patients with symptomatic prostatic hyperplasia, urinary retention or narrow-angle glaucoma (even though direct contact of the product with the eyes is very unlikely). Dry mouth, which has been observed with anticholinergic treatment, may in the long term be associated with dental caries.

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in the elderly

No pharmacokinetic studies have been performed with aclidinium/formoterol in elderly subjects.

Paediatric use

BRIMICA GENUAIR 340/12 should not be used in patients under 18 years of age.

Effects on laboratory tests

No available data.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

COPD medicinal products

Co-administration of BRIMICA GENUAIR 340/12 with other inhaled anticholinergic (e.g. tiotropium bromide, glycopyrronium, aclidinium) and/or long-acting β_2-adrenergic agonist (e.g. indacaterol, salmeterol, formoterol) containing medicinal products has not been studied, therefore caution should be taken when co-administering BRIMICA GENUAIR 340/12 with these drugs.

Although no formal in vivo drug interaction studies have been performed with BRIMICA GENUAIR 340/12, it has been used concomitantly with other COPD medicinal products including short-acting β_2-adrenergic bronchodilators, methylxanthines, and oral and inhaled steroids without clinical evidence of drug interactions.

Metabolic interactions

In vitro studies have shown that aclidinium or its metabolites at the therapeutic dose are not expected to cause interactions with P-glycoprotein (P-gp) substrate drugs or drugs metabolised by cytochrome P450 (CYP450) enzymes and esterases. Formoterol does not inhibit the CYP450 enzymes at therapeutically relevant concentrations.

Hypokalaemic treatment

Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of β_2-adrenergic agonists, therefore caution is advised in their concomitant use.

β-adrenergic blockers

β-adrenergic blockers may weaken or antagonise the effect of β_2-adrenergic agonists. If β-adrenergic blockers are required (including eye drops), cardioselective β-adrenergic blockers are preferred, although they should be administered with caution.

Other pharmacodynamic interactions

BRIMICA GENUAIR 340/12 should be administered with caution to patients being treated with medicines known to prolong the QTc interval such as monoamine oxidase inhibitors, tricyclic antidepressants, antihistamines or macrolides because the action of formoterol, a component of BRIMICA GENUAIR 340/12, on the cardiovascular system may be potentiated by these medicinal products. Medicinal products that are known to prolong the QTc interval are associated with an increased risk of ventricular arrhythmias.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No animal studies have been conducted with aclidinium and formoterol in combination to evaluate effects on fertility. In studies with the individual active components, fertility was unaffected in rats with inhalational administration of aclidinium bromide at doses up to 0.86mg/kg/day (females) or 1.84 mg/kg/day (males), yielding plasma AUC values for aclidinium bromide >78 times higher than in patients at the recommended human dose. No effect on male or female fertility was observed with formoterol in rats dosed orally at 60 mg/kg/day. It is considered unlikely that BRIMICA GENUAIR 340/12 administered at the recommended dose will affect fertility in humans.

Use in pregnancy – Pregnancy Category B3

There are no data available on the use of BRIMICA GENUAIR 340/12 in pregnant women. No animal embryofetal development studies have been conducted with aclidinium and formoterol in combination.

Aclidinium bromide and/or its metabolites were shown to cross the placenta in rats. Developmental toxicity studies in animals revealed delayed ossification of fetuses in rats treated at ≥ 0.78 mg/kg/day by inhalation (yielding 29 times the plasma AUC for aclidinium bromide in patients at the recommended dose) and decreased fetal weight in rabbits with oral administration at ≥ 300 mg/kg/day; these doses were maternotoxic. Embryofetal development was unaffected in the rabbit at inhalational doses ≤ 3.58 mg/kg/day (yielding 13 times the plasma AUC in patients). Aclidinium bromide was not teratogenic in either animal species.

In studies completed by other companies, no teratogenic effects have been observed in rats receiving formoterol fumarate at doses up to 1.2 mg/kg/day by inhalation or oral doses of up to 60 mg/kg/day or in rabbits given formoterol fumarate at oral doses of up to 500 mg/kg/day over the period of organogenesis. Decreases in birth weight and increases in perinatal mortality have been observed when formoterol fumarate was given to rats at oral doses greater than 0.2 mg/kg/day during late gestation.

β_2-adrenoceptor agonists including formoterol may inhibit labour due to a relaxant effect on uterine smooth muscle.

Because there are no adequate and well-controlled studies in pregnant women, BRIMICA GENUAIR 340/12 should only be used during pregnancy if the expected benefits justify the potential risks to the fetus.

Use in lactation

It is unknown whether aclidinium (and/or its metabolites) are excreted in human milk.

Studies in rats have shown excretion of small amounts of aclidinium (and/or its metabolites) and formoterol into milk. Postnatal body weight gain was suppressed in the offspring of animals given aclidinium bromide during pregnancy and lactation at ≥ 0.20 mg/kg/day by inhalation (there was no effect at 0.018 mg/kg/day, estimated to yield around 8 times the clinical plasma AUC), and increased postnatal mortality was observed with formoterol at maternal oral doses of 0.2 mg/kg/day, with retardation of pup growth at 15 mg/kg/day.

A decision must be made whether to discontinue breast-feeding or to discontinue therapy with BRIMICA GENUAIR 340/12 taking into account the benefit of breast-feeding for the child and the benefit of long-term BRIMICA GENUAIR 340/12 therapy to the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

BRIMICA GENUAIR 340/12 has no or negligible influence on the ability to drive and use machines. The occurrence of blurred vision or dizziness may influence the ability to drive or to use machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety profile of BRIMICA GENUAIR 340/12 is based on the experience with BRIMICA GENUAIR 340/12 and the individual components which comprised exposure in clinical trials at the recommended therapeutic dose for up to 12 months and in post-marketing experience. Adverse events associated with BRIMICA GENUAIR 340/12 were similar to those of the individual components. As BRIMICA GENUAIR 340/12 contains aclidinium bromide and formoterol fumarate dihydrate, the type and severity of adverse events associated with each of the components may be expected with BRIMICA GENUAIR 340/12.

A total of 1222 patients (527 females and 695 males) with moderate to severe COPD were treated with BRIMICA GENUAIR 340/12 at the recommended therapeutic dose. The incidence of adverse events associated with BRIMICA GENUAIR 340/12 is based on a pooled analysis of three placebo-controlled trials in patients with COPD of at least 6 months duration or on experience with individual components. In these trials, 720 COPD patients were treated with BRIMICA GENUAIR 340/12 at the recommended dose of twice daily. Of these, 557 patients were treated with BRIMICA GENUAIR 340/12 for at least 6 months and 127 patients were treated with BRIMICA GENUAIR 340/12 for at least 12 months.

Across these studies, 8.4% of patients who received placebo and 7.2% of patients who received BRIMICA GENUAIR 340/12 twice daily discontinued prematurely due to adverse events. Pooled data from these placebo-controlled clinical trials in COPD patients showed that the most frequently reported adverse reactions with BRIMICA GENUAIR 340/12 were nasopharyngitis (7.9%) and headache (6.8%).

Clinical Trial Adverse Drug Reactions

Table 1 summarises the common adverse reactions that occurred with a frequency of ≥1.0% in the BRIMICA GENUAIR 340/12 group in the three placebo-controlled clinical trials from 6 to 12 months duration, where the rates in the BRIMICA GENUAIR 340/12 group exceeded placebo by 0.5%.

Table 1: Adverse Events with ≥ 1.0% Frequency with BRIMICA GENUAIR 340/12 in Placebo-Controlled Clinical Trials in COPD up to 12 Months Duration

	Treatment			
Adverse Reactions Body System Event	**BRIMICA GENUAIR 340/12**	**Placebo**	**Aclidinium bromide**	**Formoterol fumarate**
	(N =720) n (%)	(N =526) n (%)	(N=722) n (%)	(N=716) n (%)
Respiratory, Thoracic and Mediastinal Disorders				
Nasopharyngitis	57 (7.9)	33 (6.3)	50 (6.9)	58 (8.1)
Oropharyngeal pain	21 (2.9)	12 (2.3)	12 (1.7)	11 (1.5)
Infections and Infestations				
Urinary Tract Infection	30 (4.2)	19 (3.6)	22 (3.0)	21 (2.9)
Influenza	14 (1.9)	6 (1.1)	9 (1.2)	12 (1.7)
Tooth abscess	10 (1.4)	3 (0.6)	5 (0.7)	4 (0.6)
Nervous System				
Headache	49 (6.8)	29 (5.5)	50 (6.9)	56 (7.8)
Dizziness	15 (2.1)	8 (1.5)	7 (1.0)	15 (2.1)
Tremor	8 (1.1)	2 (0.4)	3 (0.4)	8 (1.1)
Musculoskeletal and Connective Tissues				
Muscle spasms	15 (2.1)	6 (1.1)	5 (0.7)	13 (1.8)
Non-cardiac chest pain	9 (1.3)	3 (0.6)	4 (0.6)	3 (0.4)
Gastrointestinal System				
Dry Mouth	13 (1.8)	2 (0.4)	6 (0.8)	6 (0.8)
Investigations				
Blood creatine phosphokinase increased	9 (1.3)	3 (0.6)	3 (0.4)	7 (1.0)
Hematuria	8 (1.1)	3 (0.6)	3 (0.4)	8 (1.1)
Psychiatric Disorders				
Insomnia	11 (1.5)	5 (1.0)	5 (0.7)	16 (2.2)

Other adverse reactions that occurred in the BRIMICA GENUAIR 340/12 group at a frequency of <1.0% and at a higher frequency than placebo include:
Cardiac disorders: tachycardia
Eye disorders: blurred vision
Ear and labyrinth disorders: cerumen impaction
Gastrointestinal Disorders: diverticulum
General disorders and administration site conditions: product taste abnormal
Infections and Infestations: cellulitis, fungal infection
Investigations: gamma-glutamyltransferase increased, prostatic specific antigen increased
Metabolism and Nutrition Disorders: hypercholesterolemia
Psychiatric Disorders: anxiety
Respiratory, Thoracic and Mediastinal Disorders: dysphonia, pulmonary congestion, pulmonary mass

The following adverse reactions, not already listed above, were reported in clinical trials of the individual components of BRIMICA GENUAIR 340/12 and are listed in each component PI:

Formoterol fumarate

System Organ Class	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1,000, <1/100)**	**Rare (≥1/10,000, <1/1000)**	**Very rare <1/10,000**
Cardiac disorders	Palpitations			Oedema peripheral
Central nervous system disorders	Tremor	Fatigue		Dysgeusia

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1000)	Very rare <1/10,000
Gastrointestinal disorders				Nausea
Immune system disorders				Hypersensitivity reactions including hypotension Urticarial, angioneuriotic oedema Oedema including conjunctival pruritus irritation and eyelid oedema Exanthema
Local irritation	Throat Irritation			
Musculoskeletal system		Muscle cramps Myalgia		
Psychiatric disorders		Agitation Nervousness		
Respiratory tract, thoracic and mediastinal disorders	Cough Pharyngitis	Dyspnoea Chest pain Increased sputum Bronchospasm		

Aclidinium bromide

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1000)	Unknown
Cardiac disorders				Cardiac failure
Gastrointestinal disorders	Diarrhoea Vomiting			Abdominal discomfort
Infections and infestations	Sinusitis Rhinitis			Candidiasis
Injury, poisoning and prodedural complications				Fall

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1000)	Unknown
Metabolism and nutrition disorders				Diabetes mellitus
Musculoskeletal system				Osteoarthritis
Respiratory tract, thoracic and mediastinal disorders	Cough			
Renal and urinary disorders		Urinary retention		

The following post-marketing events have been reported in patients treated with Foradile. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Metabolism and nutrition disorders: hypokalaemia, hyperglycaemia
Investigations: electrocardiogram QT prolonged, blood pressure increased (including hypertension)
Skin and subcutaneous tissue disorders: rash
Cardiac disorders: Angina pectoris, cardiac arrhythmias e.g. atrial fibrillation, ventricular extrasystoles, tachyarrhythmia
Respiratory, thoracic and mediastinal disorders: Cough

Aclidinium:

The following post-marketing events have been reported in patients treated with aclidinium bromide. Adverse drug reactions are listed according to system organ classes in MedDRA and the frequency established in the EU SmPC.

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1000)	Unknown
Cardiac disorders		Cardiac arrhythmias, including atrial fibrillation and paroxysmal tachycardia Tachycardia Palpitations		
Skin and subcutaneous tissue disorders		Rash Pruritus		
Immune system disorders			Hypersensitivity	Angioedema Anaphylactic reaction
Gastrointestinal disorders		Stomatitis		

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

There is limited evidence on the management of overdose with BRIMICA GENUAIR 340/12. High doses of BRIMICA GENUAIR 340/12 may lead to signs and symptoms that are typical of anticholinergic (e.g. dry mouth, blurred vision, nausea and tachycardia) and/or β_2-adrenergic agents (e.g. hypertension, tremor, headache, tachycardia, palpitations, dizziness and muscle spasms).

BRIMICA GENUAIR 340/12 should be discontinued in case of overdose. Supportive and symptomatic treatment is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics, ATC code: R03AL05

Mechanism of action

BRIMICA GENUAIR 340/12 contains two bronchodilators: aclidinium is a long-acting muscarinic antagonist (also known as an anticholinergic) and formoterol is a long-acting β_2-adrenergic agonist. The combination of these substances with different mechanisms of action results in additive efficacy compared to that achieved with either component alone. As a consequence of the differential density of muscarinic receptors and β_2-adrenoceptors in the central and peripheral airways of the lung, muscarinic antagonists should be more effective in relaxing central airways and β_2-adrenergic agonists should be more effective in relaxing peripheral airways; relaxation of both central and peripheral airways with combination treatment may contribute to its beneficial effects on lung function. Further information regarding these two substances is provided below.

Aclidinium is a competitive muscarinic receptor antagonist, with subnanomolar affinity for all five human muscarinic receptor subtypes (M_1-M_5) and a longer residence time at the M_3 receptors than the M_2 receptors. M_3 receptors mediate contraction of airway smooth muscle. Inhaled aclidinium bromide acts locally in the lungs to antagonise M_3 receptors of airway smooth muscle and induce bronchodilation. Aclidinium has also been shown to provide benefits to patients with COPD in terms of symptom reduction, improvement in disease-specific health status, reduction in exacerbation rates and improvements in exercise tolerance. Since aclidinium bromide is quickly broken down in plasma, the level of systemic anticholinergic side effects is therefore low.

Formoterol is a potent selective β_2-adrenoceptor agonist. Bronchodilation is induced by causing direct relaxation of airway smooth muscle as a consequence of the increase in cyclic AMP through activation of adenylate cyclase. In addition to improving pulmonary function, formoterol has been shown to improve symptoms and quality of life in patients with COPD.

Pharmacodynamic effects

Clinical efficacy studies showed that BRIMICA GENUAIR 340/12 provides clinically meaningful improvements in lung function (as measured by the forced expiratory volume in 1 second [FEV_1]) over 12 hours following administration.

BRIMICA GENUAIR 340/12 demonstrated a rapid onset of action within 5 minutes of the first inhalation relative to placebo ($p<0.0001$). The onset of action of BRIMICA GENUAIR 340/12 was comparable to the effect of the fast-acting β_2-agonist formoterol 12 micrograms. Maximal bronchodilator effects (peak FEV_1) relative to baseline were evident from day one (304 mL) and were maintained over the 6-month treatment period (326 mL).

Cardiac electrophysiology

No clinically relevant effects of BRIMICA GENUAIR 340/12 on ECG parameters (including QT-interval) compared with aclidinium, formoterol and placebo were seen in Phase III studies of 6 to 12 months duration conducted in approximately 4,000 patients with COPD. No clinically significant effects of BRIMICA GENUAIR 340/12 on cardiac rhythm were observed on 24-hour Holter monitoring in a subset of 551 patients, of whom 114 received BRIMICA GENUAIR 340/12 twice daily.

Duration and Persistence of Effects on Lung Function

A 12-hour serial spirometry substudy, which evaluated the bronchodilation time-profile over 12 hrs post-dose, was performed in both the ACLIFORM-COPD (n=366) and AUGMENT (n=270) clinical studies. Statistically significant and clinically relevant adjusted mean increases from baseline in FEV_1 were observed with BRIMICA GENUAIR 340/12 compared to placebo at all post-dose time points from 5 min post-dose to 12 hrs post-dose on Day 1 and from 0.5 hrs to 12 hrs post-dose at week 24 (see Figure 1 and Figure 2).

Figure 1: LS mean changes from baseline in FEV1 (L) in the 12 hour post-dose on Day 1: ACLIFORM-COPD (Spirometry Substudy Population)

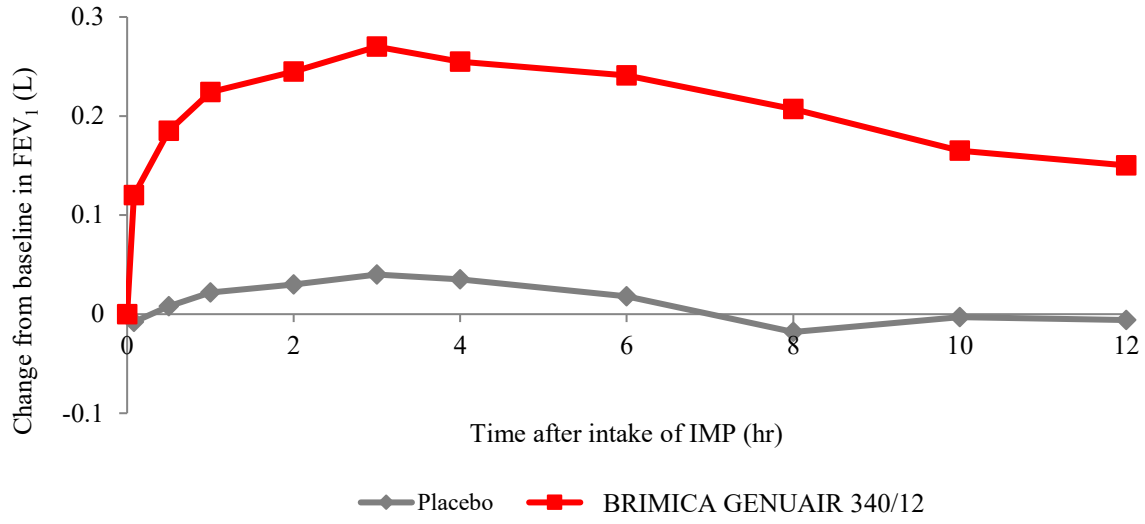
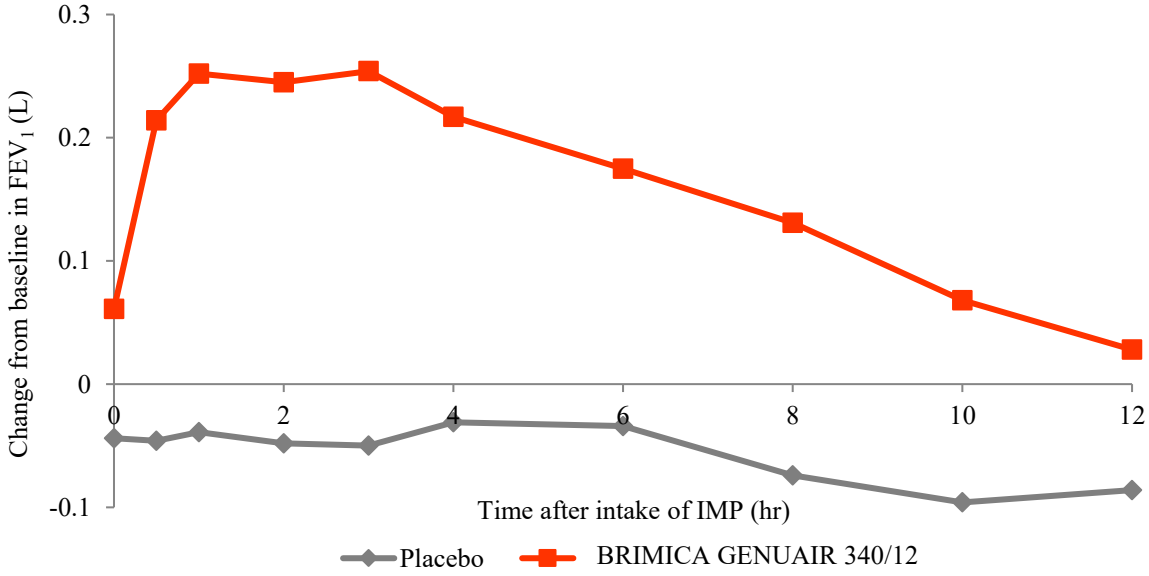


Figure 2: LS mean changes from baseline in FEV1 (L) in the 12 hour post-dose at week 24: ACLIFORM-COPD (Spirometry Substudy Population)



Clinical trials

Study demographics and trial design

The efficacy of BRIMICA GENUAIR 340/12 was established in two 6-month randomised, double-blind, placebo and active-controlled pivotal clinical trials (ACLIFORM-COPD and AUGMENT). The persistence of efficacy was assessed in a 6-month extension of the AUGMENT study and in a further 12-month randomised controlled study, where the long-term safety was also evaluated. These studies enrolled 3986 patients aged ≥ 40 years who had a clinical diagnosis of stable moderate to severe COPD (with post-bronchodilator FEV_1 of ≥ 30% to < 80% of predicted normal value) and a history of smoking of at least 10 pack-years. During these studies, patients were permitted to continue their stable treatment with inhaled corticosteroids, low doses of oral corticosteroids, oxygen therapy (if less than 15 hrs/day) or methylxanthines and to use

salbutamol as rescue medication. The study design and patient demographics for these studies is described in Table 2.

Table 2: Summary of Patient Demographics for Clinical Trials in COPD (ITT Population)

Study #	Trial design	Dosage, route of administration and duration	Study subjects [b] (n=number)	Mean age [b] (Range)	Gender
M/40464/30 (ACLIFORM-COPD)	Multi-centre, placebo and active controlled, randomised, double-blind, parallel group	AB/FF, 400/12 micrograms AB/FF, 400/6 micrograms AB, 400 micrograms FF, 12 micrograms Placebo Twice daily Oral inhalation 24 weeks	AB/FF 400/12 micrograms: n=385 AB/FF 400/6 micrograms: n=381 AB 400 micrograms: n=385 FF 12 micrograms: n=384 Placebo: n=194	63 years (40-85 years)	Male: 67.6% Female: 32.4%
LAC-MD-31 (AUGMENT)	Multi-centre, placebo and active controlled, randomised, double-blind, parallel group	AB/FF, 400/12 micrograms AB/FF, 400/6 micrograms AB, 400 micrograms FF 12 micrograms Placebo Twice daily Oral inhalation 24 weeks	AB/FF 400/12 micrograms: n=335 AB/FF 400/6 micrograms: n=333 AB 400 micrograms: n=337 FF 12 micrograms: n=332 Placebo: n=332	64 years (40-93 years)	Male: 53.1% Female: 46.9%
LAC-MD-36[a] (Long-term extension of AUGMENT)	Multi-centre, placebo and active controlled, randomised, double-blind, parallel group	AB/FF, 400/12 micrograms AB/FF, 400/6 micrograms AB, 400 micrograms FF 12 micrograms Placebo Twice daily Oral inhalation 28 weeks	AB/FF 400/12 micrograms: n=184 AB/FF 400/6 micrograms: n=205 AB 400 micrograms: n=194 FF 12 micrograms: n=192 Placebo: n=146	63 years (40-93 years)	Male: 52.6% Female: 47.4%
LAC-MD-32	Multi-centre, active controlled, randomised, double-blind, parallel group	AB/FF, 400/12 micrograms FF 12 micrograms Twice daily Oral inhalation 52 weeks	AB/FF 400/12 micrograms: n=392 FF 12 micrograms: n=198	64 years (40-89 years)	Male: 55.1% Female: 44.9%

AB=aclidinium bromide; FF=formoterol fumarate dihydrate; ITT=Intent-to-Treat
[a] Note that LAC-MD-36 is a continuation of Study LAC-MD-31; Number of study subjects for LAC-MD-36 enrolled patients
[b] Safety population which includes all patients who took at least one dose of IMP (Investigational Medicinal Product) and counted once

In the pooled pivotal 6-month studies ACLIFORM-COPD and AUGMENT, the mean post-bronchodilator percent predicted FEV_1 at screening was 53.9% (range: 28.0-85.8%).

The co-primary endpoints in both pivotal studies (ACLIFORM-COPD and AUGMENT) where the changes from baseline in FEV_1 at 1 hour post-dose and in trough FEV_1 at week 24 (compared to aclidinium bromide 400 micrograms and formoterol fumarate dihydrate 12 micrograms, respectively) to demonstrate the bronchodilator contributions of aclidinium and formoterol in BRIMICA GENUAIR 340/12, respectively. Secondary endpoints were improvement from baseline to week 24 in the Transition Dyspnoea Index (TDI) focal score and the change from baseline to week 24 in the St. George's Respiratory Questionnaire (SGRQ) total score. Other efficacy variables included: rescue medication usage, COPD exacerbations, COPD symptoms (recorded using an electronic patient diary) and other measures of lung function (FEV_1 at various time points, forced vital capacity and inspiratory capacity).

Effects on lung function

Inhalation of BRIMICA GENUAIR 340/12 twice daily by patients with moderate to severe COPD resulted in statistically and clinically meaningful improvements in lung function (as measured by FEV_1) relative to placebo in both ACLIFORM-COPD and AUGMENT.

In ACLIFORM-COPD, BRIMICA GENUAIR 340/12 showed statistically significant improvements in FEV_1 at 1 hour post-dose relative to placebo and aclidinium bromide of 299 mL and 125 mL, respectively (both $p<0.0001$) and statistically significant improvements in trough FEV_1 relative to placebo and formoterol fumarate of 143 mL and 85 mL, respectively (both $p<0.0001$) at week 24. In AUGMENT, BRIMICA GENUAIR 340/12 showed statistically significant improvements in FEV_1 at 1 hour post-dose relative to placebo and aclidinium bromide of 284 mL and 108 mL (both $p<0.0001$), respectively, and improvements in trough FEV_1 relative to placebo and formoterol fumarate of 130 mL ($p<0.0001$) and 45 mL ($p=0.01$), respectively.

The lung function effects of BRIMICA GENUAIR 340/12 were observed within 5 minutes of the first dose and were maintained over the dosing interval. There was a sustained effect over time in the 6 months (see Figure 3 and Figure 4 for representative data from ACLIFORM-COPD) and one year Phase III studies.

Figure 3: LS mean changes from baseline to time points up to week 24 in FEV1 (L) at 1 hour post-dose: ACLIFORM-COPD

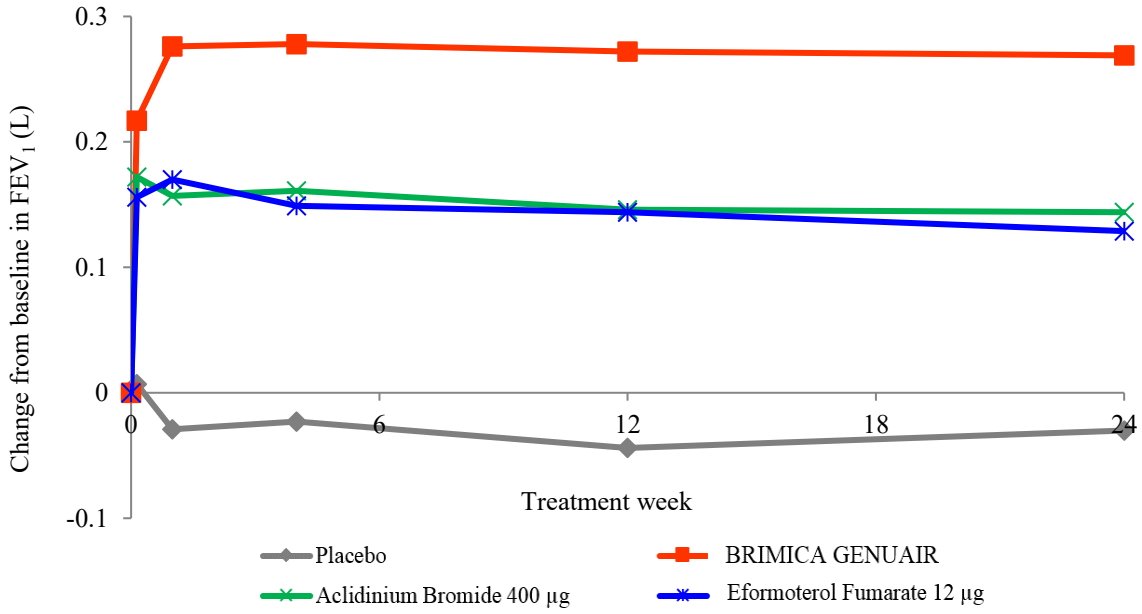
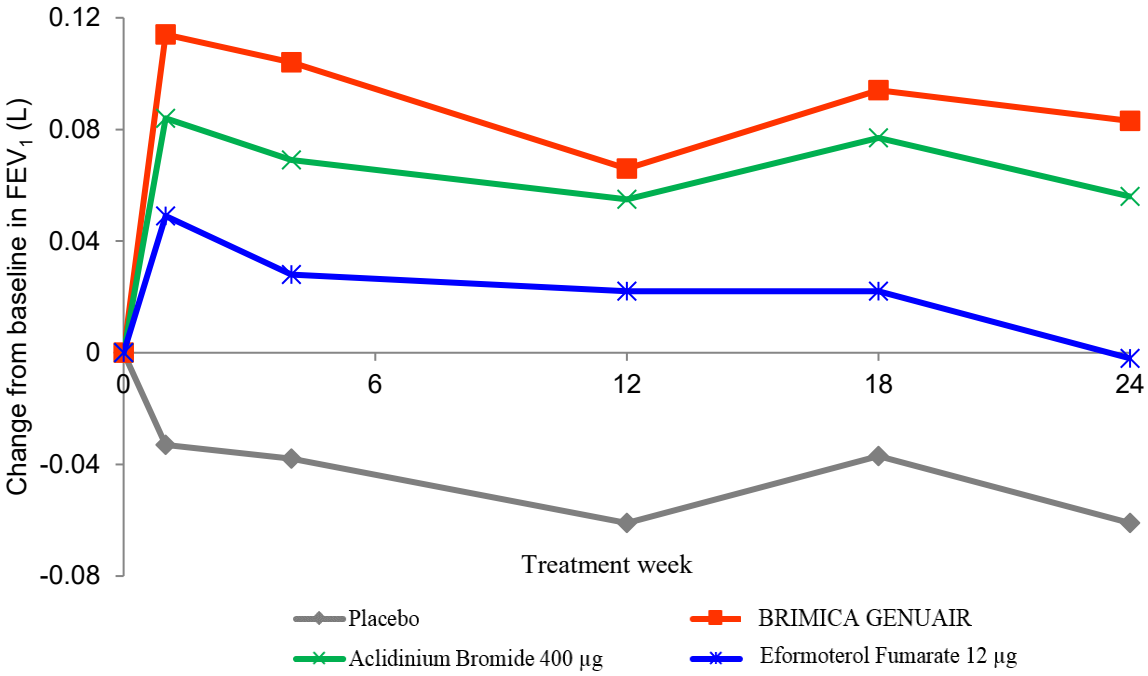


Figure 4: LS mean changes from baseline to time points up to week 24 in trough FEV1 (L): ACLIFORM-COPD



Symptom relief and disease-specific health status

The effects of BRIMICA GENUAIR 340/12 on dyspnoea and disease-specific health status were evaluated using the Transition Dyspnoea Index (TDI), and the St. George's Respiratory Questionnaire (SGRQ), respectively.

Following 24 weeks of treatment, BRIMICA GENUAIR 340/12 provided statistically significant ($p<0.0001$) and clinically meaningful improvements in breathlessness (assessed by the TDI) with a mean difference compared to placebo of 1.29 units and 1.44 units in ACLIFORM-COPD and AUGMENT, respectively. Significantly more patients treated with BRIMICA GENUAIR 340/12 had an increase in TDI focal score greater than the minimal clinically important difference (MCID) of 1 unit compared to placebo in both studies (Table 3). Improvements were observed in each of the individual TDI domains (functional impairment, magnitude of effort and magnitude of task) at all time points in both ACLIFORM-COPD and AUGMENT when compared to placebo ($p<0.05$ for each measure).

Following 24 weeks of treatment, BRIMICA GENUAIR 340/12 provided improvements in disease-specific health status (assessed by the St. George's Respiratory Questionnaire [SGRQ] total score) relative to placebo (-4.35 units, $p<0.0001$) as well as improvements in all 3 SGRQ domains (symptoms, activities and impact; $p<0.02$ for each domain) in AUGMENT, while only a small decrease in SGRQ total score compared to placebo was observed in ACLIFORM-COPD (-0.65 units, $p=0.598$) due to an unexpectedly large placebo response (see Table 3).

Table 3: Change from baseline in Transition Dyspnoea Index (TDI) and St. George's Respiratory Questionnaire (SGRQ) at week 24 (ACLIFORM-COPD and AUGMENT Studies)

	Mean change from baseline				Percentage of patients who achieved MCID[a]			
	BRIMICA GENUAIR 340/12	Placebo	Improvement over placebo	p-value	BRIMICA GENUAIR 340/12	Placebo	Improvement over placebo[b]	p-value
TDI								
ACLIFORM-COPD	2.51	1.22	1.29	<0.0001	64.8	45.5	2.54-fold	0.0001
AUGMENT	2.02	0.58	1.44	<0.0001	58.1	36.6	2.81-fold	<0.0001
SGRQ								
ACLIFORM-COPD	-7.16	-6.51	-0.65	0.598	55.3	53.2	1.12-fold	0.669
AUGMENT	-6.57	-2.21	-4.35	<0.0001	58.2	38.7	2.26-fold	<0.001

[a] Minimum clinically important difference (MCID): an increase in TDI of ≥1 unit or a decrease in SGRQ of ≥4 units.
[b] Odds ratio, increase in the likelihood of achieving the MCID compared to placebo.

In the pooled analysis of the two 6-month Phase III studies (ACLIFORM-COPD and AUGMENT):

BRIMICA GENUAIR 340/12 showed statistically significant greater improvements in TDI focal score compared to aclidinium (0.4 units, p=0.016) or formoterol (0.5 units, p=0.009). In addition, a higher percentage of patients receiving BRIMICA GENUAIR 340/12 responded with a clinically meaningful improvement in TDI focal score (defined as an increase of at least 1 unit) compared to either aclidinium or formoterol (61.9% compared to 55.7% and 57.0%, respectively; p=0.056 and p=0.100, respectively). BRIMICA GENUAIR 340/12 also showed statistically significant improvements in SGRQ when compared to formoterol (-1.7 units; 95% CI: -3.2 to -0.3; p=0.018).

BRIMICA GENUAIR 340/12 improved daily symptoms of COPD (assessed by E-RS total score) as well as overall night-time symptoms, overall early morning symptoms and symptoms limiting early morning activities compared to placebo, aclidinium bromide and formoterol fumarate (all p<0.05).

COPD exacerbations

Pooled efficacy analysis of the two 6-month Phase III studies demonstrated a statistically significant reduction of 29% in the rate of moderate or severe exacerbations (requiring treatment with antibiotics or corticosteroids or resulting in hospitalisations) with BRIMICA GENUAIR 340/12 compared to placebo (rates per patient per year: 0.29 vs. 0.42, respectively; p=0.036).

In addition, BRIMICA GENUAIR 340/12 statistically significantly delayed the time to first moderate or severe exacerbation compared to placebo (hazard ratio=0.70; p=0.027).

Use of rescue medication

BRIMICA GENUAIR 340/12 reduced the use of rescue medication over 6 months compared to placebo (by 0.9 puffs per day [p<0.0001]), aclidinium (by 0.4 puffs/day [p<0.001]) and formoterol (by 0.2 puffs/day [p=0.062]).

5.2 PHARMACOKINETIC PROPERTIES

When aclidinium and formoterol were administered in combination by the inhaled route, the pharmacokinetics of each component showed no relevant differences from those observed when the medicinal products were administered separately.

Absorption

Following inhalation of a single dose of BRIMICA GENUAIR 340/12, aclidinium and formoterol were rapidly absorbed into plasma, reaching peak plasma concentrations within 5 minutes of inhalation in healthy subjects and within 24 minutes of inhalation in patients with COPD. The peak plasma concentrations at steady state of aclidinium and formoterol observed in patients with COPD treated with BRIMICA GENUAIR 340/12 twice daily for 5 days were reached within 5 minutes post-inhalation and were 128 pg/mL and 17 pg/mL, respectively.

Distribution

Whole lung deposition of inhaled aclidinium via Genuair averaged approximately 30% of the metered dose. The plasma protein binding of aclidinium determined in vitro most likely corresponded to the protein binding of the metabolites due to the rapid hydrolysis of aclidinium in plasma; human plasma protein binding was 87% for the carboxylic acid metabolite and 15% for the alcohol metabolite. The main plasma protein that binds aclidinium is albumin.

The plasma protein binding of formoterol is 61% to 64% (34% primarily to albumin). There is no saturation of binding sites in the concentration range reached with therapeutic doses.

Metabolism

Aclidinium is rapidly and extensively hydrolysed to its pharmacologically inactive alcohol- and carboxylic acid-derivatives. Plasma levels of the acid metabolite are approximately 100-fold greater than those of the alcohol metabolite and the unchanged active substance following inhalation. The hydrolysis occurs both chemically (non-enzymatically) and enzymatically by esterases (principally in plasma), with butyrylcholinesterase being the main human esterase involved in the hydrolysis. The low absolute bioavailability of inhaled aclidinium (<5%) is because aclidinium undergoes extensive systemic and pre-systemic hydrolysis whether deposited in the lung or swallowed. Biotransformation via CYP450 enzymes plays a minor role in the total metabolic clearance of aclidinium. In vitro studies have shown that aclidinium bromide and its major metabolites do not inhibit human CYPs 1A2, 2A6, 2B6, 2B8, 2C9, 2C19, 2D6, 2E1, 3A4/5 or 4A9/11, do not induce CYPs 1A2, 2B6, 2C8, 2C9, 2C19 or 3A4/5, and do not inhibit esterases (carboxylesterase, acetylcholinesterase and butyrylcholinesterase) at therapeutic concentrations. In vitro studies have shown that neither aclidinium bromide nor the main metabolites of aclidinium bromide are inhibitors of P-glycoprotein. The same studies have also demonstrated that aclidinium bromide and its acid metabolite are not substrates of P-glycoprotein however its alcohol metabolite is a potentially weak substrate.

Formoterol is eliminated primarily by metabolism. The prominent pathway involves direct glucuronidation, with O-demethylation followed by glucuronide conjugation being a further metabolic pathway. Cytochrome P450 isoenzymes CYP2D6, CYP2C19, CYP2C9 and CYP2A6 are involved in the O-demethylation of formoterol. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

Excretion

Following inhalation of BRIMICA GENUAIR 340/12 micrograms, with plasma sampling up to 24 hours post-dose, the terminal elimination half-life observed for aclidinium bromide ranged from 11-33 hours and for formoterol from 12-18 hours.

Mean effective half-lives* observed for both aclidinium and formoterol (based on the accumulation ratio) are approximately 10 hours.

**Half-life consistent with product accumulation based on a known dose regimen.*

Following intravenous administration of radiolabelled aclidinium 400 micrograms to healthy subjects, approximately 1% of the dose was excreted as unchanged aclidinium bromide in the urine. Up to 65% of the dose was eliminated as metabolites in the urine and up to 33% as metabolites in the faeces. Following inhalation of aclidinium 200 micrograms and 400 micrograms by healthy subjects or patients with COPD, the urinary excretion of unchanged

aclidinium was very low at about 0.1% of the administered dose, indicating that renal clearance plays a minor role in the total aclidinium clearance from plasma.

The major part of a dose of formoterol is transformed by liver metabolism followed by renal elimination. After inhalation, 6% to 9% of the delivered dose of formoterol is excreted in the urine unchanged or as direct conjugates of formoterol.

Special populations

Elderly patients

No pharmacokinetics studies have been performed with aclidinium/formoterol in elderly subjects. Since no dosage adjustments are needed for either aclidinium or formoterol medicinal products in elderly patients, no dosage adjustment is warranted for aclidinium/formoterol in geriatric patients.

Renally and hepatically impaired patients

There are no data regarding the specific use of aclidinium/formoterol in patients with renal or hepatic impairment. Since no dosage adjustments are needed for either aclidinium or formoterol medicinal products in patients with renal or hepatic impairment, no dosage adjustment is warranted for aclidinium/formoterol.

Race

Following repeated inhalations of BRIMICA GENUAIR 340/12, the systemic exposure of aclidinium and formoterol, as measured by AUC, is similar in Japanese and Caucasian patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Aclidinium bromide

Aclidinium bromide returned equivocal results in assays for bacterial mutagenicity and in the mouse lymphoma-TK assay in vitro. Aclidinium bromide, at high levels of systemic exposure, was devoid of genotoxicity in vivo in the mouse bone marrow micronucleus test and in the unscheduled DNA synthesis (UDS) assay in rat liver. Aclidinium bromide is not considered to pose a genotoxic hazard to patients.

Formoterol fumarate

Mutagenicity tests covering a broad range of experimental endpoints have been conducted. No genotoxic effects were found in any of the in vitro or in vivo tests performed.

Carcinogenicity

Aclidinium bromide

No treatment-related neoplastic lesions were noted in the carcinogenicity studies of 2 years duration in mice and rats, involving inhalational administration. The highest dose levels employed in the respective species (2.45 mg/kg/day in mice and 0.20 mg/kg/day in rats) yield approximately 63 and 26 times the plasma AUC in patients at the recommended dose and approximately 120 and 11 times the local dose in the lung.

Formoterol fumarate

In studies performed by other companies over 2 years in rats and mice, formoterol fumarate, given via the diet or drinking water at very high doses, was associated with increases in a variety of tumour types. In rats, treatment was associated with benign granulosa/theca cell tumours in the ovaries (≥ 0.5 mg/kg/day), mesovarian leiomyomas (≥ 18 mg/kg/day), mammary adenocarcinomas (≥ 36 mg/kg/day) and thyroid C-cell neoplasms (46 mg/kg/day). A mesovarian leiomyoma was also seen in a female rat dosed by inhalation at 130 micrograms/kg/day for two

years (approximately 49 times the MRHD (Maximum Recommended Human Dose) in adults and children on a micrograms/m^2 basis). In mice, these included hepatocellular adenoma and carcinomas (≥ 2 mg/kg/day), leiomyomas and leiomyosarcomas in the female reproductive tract (≥ 2 mg/kg/day) and adrenal subcapsular cell tumours (≥ 66 mg/kg/day). Mammary adenocarcinomas, smooth muscle tumours in the female reproductive tract and effects on the ovary have been reported in rats and mice treated with other β_2-adrenoreceptor agonists and are likely to be secondary to prolonged stimulation of β_2-adrenoreceptors in these tissues.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

In-Use Shelf Life

Keep the Genuair inhaler inside the sealed pouch until the administration period starts.

To be used within 60 days of opening the pouch.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

The inhaler device is a multicomponent device. It is white-coloured with an integral dose indicator and a orange dosage button. The mouthpiece is covered with a removable orange protective cap.

The inhaler is supplied in an aluminium laminated pouch, placed in a cardboard carton.

Carton containing 1 inhaler with 30 unit doses.

Carton containing 1 inhaler with 60 unit doses.

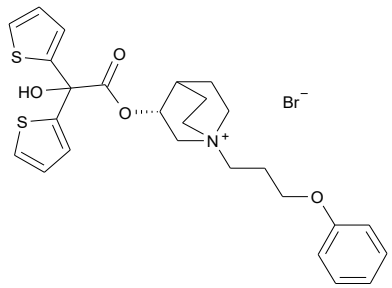
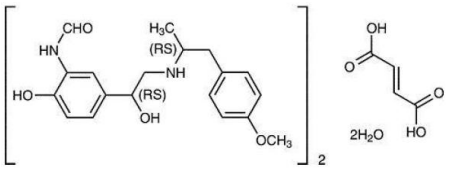
Carton containing 3 inhalers each with 60 unit doses.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

	Aclidinium bromide	Formoterol fumarate dihydrate
Chemical structure:		
Stereochemistry:	The product has one optically active centre. Aclidinium bromide is a single stereoisomer with the (3*R*) configuration.	The product has two optically active centres. Formoterol fumarate dihydrate is a racemate consisting of the (*R*,*R*) and (*S*,*S*) enantiomers.
Chemical name:	(3*R*)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1-(3-phenoxypropyl)-1λ^5-azabicyclo[2.2.2] octan-1-ylium bromide	(±)-N-[2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, E-butenedioate (2:1 salt) dihydrate
Molecular formula:	$C_{26}H_{30}NO_4S_2Br$	$C_{42}H_{52}N_4O_{12}•2H_2O$
Molecular mass:	564.56	840.9
CAS Number:	320345-99-1	183814-30-4
AAN:	aclidinium bromide	formoterol fumarate dihydrate

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only medicine

8 SPONSOR

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Chatswood NSW 2067

Australia

9 DATE OF FIRST APPROVAL

01 May 2015

10 DATE OF REVISION

12 September 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Add precautions for use in patients with cardiac arrhythmias, a history of cardiac arrhythmias or with risk factors for cardiac arrhythmias
4.8	Add cardiac arrhythmias
Heading	Minor editorial changes