AUSTRALIAN PRODUCT INFORMATION – BRETARIS® GENUAIR® (ACLIDINIUM BROMIDE)

1. NAME OF THE MEDICINE

aclidinium bromide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BRETARIS GENUAIR 322 micrograms inhalation powder consists of an adhesive mixture of micronised aclidinium bromide and α-lactose monohydrate, contained in a device-metered, dry powder inhaler.

Each delivered dose (the dose leaving the mouthpiece) contains 375 micrograms aclidinium bromide equivalent to 322 micrograms of aclidinium. This corresponds to a metered dose of 400 micrograms aclidinium bromide equivalent to 343 micrograms aclidinium.

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 delivered from a white inhaler with an integral dose indicator and a green dosage button.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BRETARIS GENUAIR is indicated as a long-term 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 BRETARIS GENUAIR twice daily, once in the morning and once at night.

Method of administration
BRETARIS GENUAIR must be administered only by the oral inhalation route. BRETARIS GENUAIR 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
BRETARIS GENUAIR 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. PHARMACOLOGICAL PROPERTIES).

Use in patients with impaired renal function
No dose adjustments are required for patients with renal impairment (see section 5. PHARMACOLOGICAL PROPERTIES).

Use in patients with impaired hepatic function
No dose adjustments are required for patients with hepatic impairment (see section 5. PHARMACOLOGICAL PROPERTIES).

4.3 CONTRAINDICATIONS

BRETARIS GENUAIR is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, including ipratropium, oxitropium or tiotropium or to any other component of this product (see section 2. QUALITATIVE AND QUANTITATIVE COMPOSITION).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Asthma
BRETARIS GENUAIR should not be used for the treatment of asthma; clinical trials of aclidinium bromide in asthma have not been conducted.

Paradoxical bronchospasm
As with other inhalation therapies, administration of BRETARIS GENUAIR may cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, treatment with BRETARIS GENUAIR should be discontinued immediately and alternative therapy instituted.

Deterioration of disease
Aclidinium bromide is a maintenance bronchodilator and 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 BRETARIS GENUAIR 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 BRETARIS GENUAIR beyond the maximum dose is not appropriate

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

Experience in patients with cardiovascular comorbidities in clinical trials is limited (see section 5.1 PHARMACODYNAMIC PROPERTIES). These conditions may be affected by the anticholinergic mechanism of action.

Anticholinergic activity
Dry mouth, which has been observed with anticholinergic treatment, may in the long term be associated with dental caries.

Consistent with its anticholinergic activity, BRETARIS GENUAIR should be used with caution in patients with symptomatic prostatic hyperplasia or bladder-neck obstruction or with narrow-angle glaucoma (even though direct contact of the product with the eyes is very unlikely).

Excipients
BRETARIS GENUAIR contains lactose. Therefore, patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in the elderly
No dosage adjustment is required for elderly patients.

Paediatric use
BRETARIS GENUAIR should not be used in patients under 18 years of age.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The co-administration of BRETARIS GENUAIR with inhaled anticholinergic (e.g. tiotropium bromide, glycopyrronium, aclidinium) containing medicinal products has not been studied and is therefore, like for other anticholinergics, not recommended.

In vitro studies have shown that aclidinium bromide or the metabolites of aclidinium bromide at the therapeutic dose are not expected to cause interactions with P glycoprotein substrate drugs or drugs metabolised by cytochrome P450 (CYP450) enzymes and esterases (see section 5. PHARMACOLOGICAL PROPERTIES).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Studies in rats have shown slight reductions in male and female fertility only at dose levels much higher than the maximum human exposure to aclidinium bromide. Fertility was unaffected in rats with inhalational administration at doses up to 0.86 mg/kg/day (females) or 1.84 mg/kg/day (males), yielding plasma AUC values for aclidinium bromide > 62 times higher than in patients at the recommended human dose. It is considered unlikely that BRETARIS GENUAIR 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 aclidinium bromide in pregnant women. 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 24 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 11 times the plasma AUC in patients). Aclidinium bromide was not teratogenic in either animal species.

Because there are no adequate and well-controlled studies in pregnant women, BRETARIS GENUAIR 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 bromide and/or its metabolites are excreted in human milk. Excretion of small amounts of aclidinium bromide and/or metabolites into milk has been shown in the rat, with postnatal body weight gain suppressed in the offspring of animals given the drug 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 7 times the clinical plasma AUC). A decision must be made whether to discontinue breast-feeding or to discontinue therapy with BRETARIS GENUAIR taking into account the benefit of breast-feeding for the child and the benefit of long-term BRETARIS GENUAIR therapy to the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Aclidinium bromide may have minor influence on the ability to drive and use machines. The occurrence of blurred vision, dizziness or headache following the administration of aclidinium bromide may influence the ability to drive or to use machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety data below reflect exposure of 636 patients to BRETARIS GENUAIR 322 micrograms twice daily in three placebo-controlled trials. Two of these trials were 12-weeks and one was 24-weeks in duration. In these trials, 367 and 269 COPD patients were exposed to BRETARIS GENUAIR 322 micrograms twice daily for 12 weeks and 24 weeks, respectively. In this population, 5.1% of patients who received placebo and 4.6% of patients who received BRETARIS GENUAIR 322 micrograms discontinued the studies prematurely due to adverse events.

A placebo-controlled trial in 1791 patients with moderate to very severe COPD treated with BRETARIS GENUAIR up to 36 months identified a similar pattern of adverse reactions.

Table 1 summarises the adverse reactions from the three placebo-controlled clinical trials that occurred with a frequency of ≥1% in the BRETARIS GENUAIR groups.

Table 1: Adverse Reactions (% Patients) in Placebo-Controlled Clinical Trials

	Treatment	
System Organ Class Adverse Reactions	**BRETARIS GENUAIR** (N = 636)	**Placebo** (N = 640)
Gastrointestinal disorders		
Diarrhoea	2.7	1.4
Vomiting	1.1	0.5
Toothache	1.1	0.8
Infections and Infestations		
Sinusitis	1.7	0.8
Rhinitis	1.6	1.2
Injury, poisoning and procedural complications		
Fall	1.1	0.5
Nervous System disorders		
Headache	6.6	5.0

	Treatment	
System Organ Class Adverse Reactions	**BRETARIS GENUAIR** (N = 636)	**Placebo** (N = 640)
Respiratory disorders		
Nasopharyngitis	5.5	3.9
Cough	3.0	2.2

Other adverse reactions that occurred in the BRETARIS GENUAIR groups at a frequency of <1% where rates exceeded that in the placebo group include:

Cardiac disorders: cardiac failure
Gastrointestinal disorders: abdominal discomfort, dry mouth
Infections and infestations: candidiasis, tooth abscess
Metabolism and nutrition disorders: diabetes mellitus
Musculoskeletal and connective tissue disorders: osteoarthritis
Respiratory, thoracic and mediastinal disorders: dysphonia
Eye disorder: blurred vision
Renal and urinary disorders: urinary retention

Long-term safety trials

BRETARIS GENUAIR was studied in three long-term safety trials, two double-blind and one open-label, ranging from 40 to 52 weeks in patients with moderate to severe COPD. In these trials, 1005 patients were treated with BRETARIS GENUAIR at the recommended dose of 322 micrograms twice daily. The adverse events reported in the long term safety trials were similar to those occurring in the placebo-controlled trials of 3 to 6 months.

Post-marketing experience

Table 2 includes post-marketing events 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.

Table 2: Adverse Drug Reactions from Post-marketing Experience

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		
Immune system disorders			Hypersensitivity	Angioedema Anaphylactic reaction
Skin and subcutaneous tissue disorders		Rash Pruritus		
Nervous system disorder		Dizziness		

Gastrointestinal disorders	Nausea	Stomatitis		

Reporting of suspected adverse reactions
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 http://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).

High doses of aclidinium bromide may lead to anticholinergic signs and symptoms. However, single inhaled doses up to 6,000 micrograms aclidinium bromide have been administered to healthy subjects without systemic anticholinergic adverse effects. Additionally, no clinically relevant adverse effects were observed following 7-day twice daily dosing of up to 800 micrograms aclidinium bromide in healthy subjects.

Acute intoxication by inadvertent medicinal product ingestion of aclidinium bromide is unlikely due to its low oral bioavailability and the breath-actuated dosing mechanism of the Genuair inhaler.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Aclidinium bromide is a competitive muscarinic receptor antagonist (also known as an anticholinergic), 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. Nonclinical *in vitro* and *in vivo* studies showed rapid, dose-dependent and long-lasting inhibition by aclidinium bromide of acetylcholine-induced bronchoconstriction. Aclidinium bromide is quickly broken down in plasma, the level of systemic anticholinergic side effects is therefore low.

Effects on cardiac electrophysiology
No effects on QT interval (corrected using either the Fridericia or Bazett method or individually-corrected) were observed when aclidinium bromide (200 micrograms or 800 micrograms) was administered once daily for 3 days to healthy subjects in a thorough QT study.

In addition, no clinically significant effects of BRETARIS GENUAIR on cardiac rhythm were observed on 24-hour Holter monitoring after 3 months treatment of 336 patients (of whom 164 received BRETARIS GENUAIR 322 micrograms twice daily).

Clinical Trials
The BRETARIS GENUAIR Phase III clinical development programme included 269 patients treated with BRETARIS GENUAIR 322 micrograms twice daily in one 6-month randomised, placebo-controlled study and 190 patients treated with BRETARIS GENUAIR 322 micrograms twice daily in one 3-month randomised, placebo-controlled study. Efficacy

was assessed by measures of lung function and symptomatic outcomes such as breathlessness, disease-specific health status, use of rescue medication and occurrence of exacerbations.

Lung function
Clinical efficacy studies showed that BRETARIS GENUAIR provided clinically meaningful improvements in lung function (as measured by the forced expiratory volume in 1 second [FEV_1]) over 12 hours following morning and evening administration, which were evident within 30 minutes of the first dose (increases from baseline of 124-133 mL). Maximal bronchodilation was achieved within 1-3 hours after dosing with mean peak improvements in FEV_1 relative to baseline of 227-268 mL at steady-state.

In the 6-month study, patients receiving BRETARIS GENUAIR 322 micrograms twice daily experienced a clinically meaningful improvement in their lung function (as measured by FEV_1). Maximal bronchodilatory effects were evident from day one and were maintained over the 6-month treatment period. After 6 months treatment, the mean improvement in morning pre-dose (trough) FEV_1 compared to placebo was 128 mL (95% CI=85-170; p<0.0001).

Similar observations were made with BRETARIS GENUAIR in the 3 month study.

In the long-term safety studies, BRETARIS GENUAIR was associated with bronchodilatory efficacy when administered over a 1-year treatment period.

Disease-Specific Health Status and Symptomatic Benefits
BRETARIS GENUAIR provided clinically meaningful improvements in breathlessness (assessed using the Transition Dyspnoea Index [TDI]) and disease-specific health status (assessed using the St George's Respiratory Questionnaire [SGRQ]). The Table below shows symptom relief obtained after 6 months treatment with BRETARIS GENUAIR.

Variable	Treatment		Improvement over placebo	p-value
	BRETARIS GENUAIR	Placebo		
TDI				
Percentage of Patients who achieved MCID[a]	56.9	45.5	1.68-fold[c] increase in likelihood	0.004
Mean Change from baseline	1.9	0.9	1.0 unit	<0.001
SGRQ				
Percentage of Patients who achieved MCID[b]	57.3	41.0	1.87-fold[c] increase in likelihood	<0.001
Mean Change from baseline	-7.4	-2.8	-4.6 units	<0.0001

a Minimum clinically important difference (MCID) of at least 1 unit change in TDI.
b MCID of at least -4 units change in SGRQ.
c Odds ratio, increase in the likelihood of achieving the MCID compared to placebo.

Patients treated with BRETARIS GENUAIR required less rescue medication than patients treated with placebo (a reduction of 0.95 puffs per day at 6 months [p=0.005]). BRETARIS GENUAIR also improved daily symptoms of COPD (dyspnoea, cough and sputum production) and night time and early morning symptoms.

Long Term Safety and Efficacy Trial up to 3 Years
The effect of aclidinium bromide on the occurrence of major adverse cardiovascular events (MACE) was assessed in a randomised, double-blind, placebo-controlled, parallel-group study in 3630 adult patients between 40 and 91 years of age with moderate to very severe

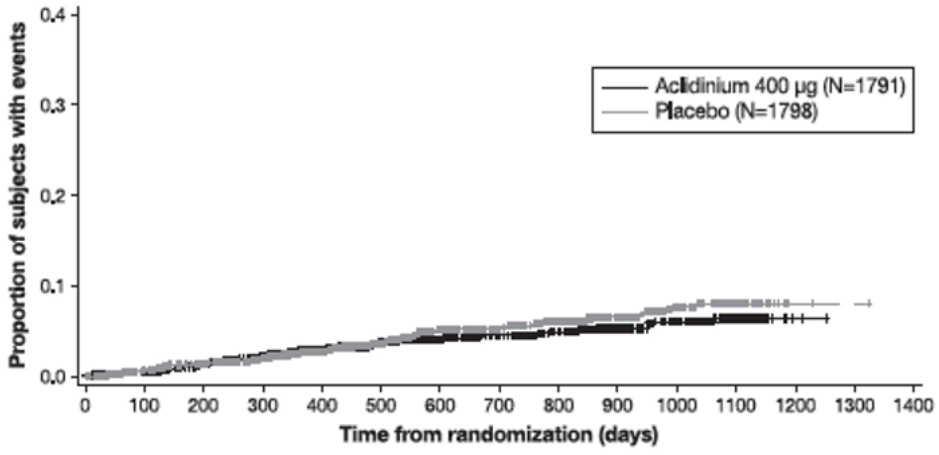
COPD treated for up to 36 months. 58.7 % were male and 90.7% were Caucasian, with a mean post-bronchodilator FEV_1 of 47.9% of predicted value and a mean CAT (COPD Assessment Test) of 20.7. All patients had a history of cardiovascular or cerebrovascular disease and/or significant cardiovascular risk factors. 59.8% of patients had at least one COPD exacerbation within the past 12 months from the screening visit. Approximately 48% of enrolled patients had a prior history of at least 1 documented previous cardiovascular event; cerebrovascular disease (13.1%), coronary artery disease (35.4%), peripheral vascular disease or history of claudication (13.6%).

The study had an event-driven design and was terminated once sufficient MACE events for the primary safety analysis were observed. Patients discontinued treatment if they experienced a MACE event and entered into the post-treatment follow-up period during the study. 70.7% of patients completed the study per investigator assessment. The median time on-treatment in the BRETARIS GENUAIR and placebo groups was 1.1 and 1 year, respectively. The median time on-study in the BRETARIS GENUAIR and placebo groups was approximately 1.4 and 1.3 years, respectively.

The primary safety endpoint was the time to first occurrence of MACE, defined as any of the following adjudicated events: cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal ischemic stroke. The frequency of patients with at least one MACE was 3.85% vs. 4.23% patients in the BRETARIS GENUAIR and placebo groups, respectively. BRETARIS GENUAIR did not increase the MACE risk in patients with COPD compared to placebo when added to current background therapy (hazard ratio (HR) 0.89; 95%CI: 0.64, 1.23). The upper bound of the confidence interval excluded a pre-defined risk margin of 1.8.

The Kaplan-Meier-based cumulative event probability is presented in Figure 1.

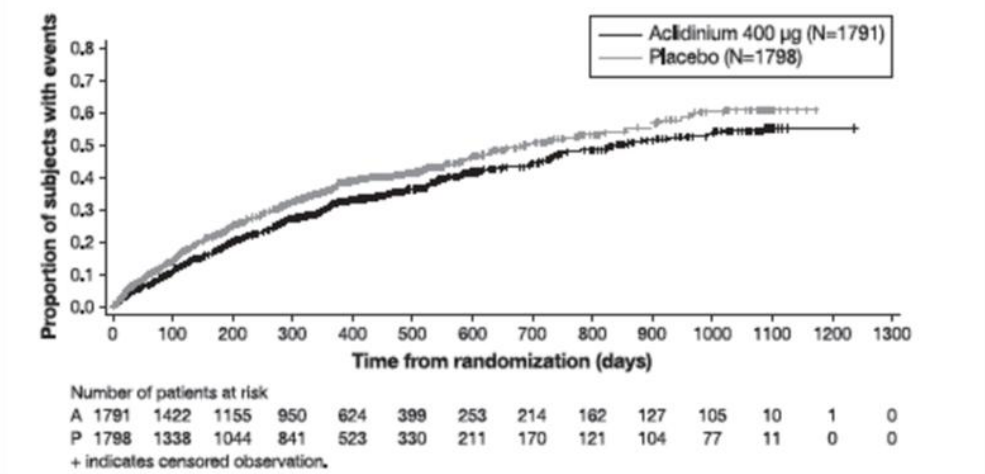
Figure 1: Estimated Cumulative Incidence of First MACE



The rate of moderate or severe COPD exacerbations per patient per year during the first year of treatment was evaluated as the primary efficacy endpoint in the study. Moderate to severe exacerbations were defined as worsening of COPD symptoms (e.g. dyspnoea, cough, sputum) for at least 2 consecutive days that required a treatment with antibiotics and/or systemic corticosteroids or resulted in hospitalisation or led to death. Patients treated with BRETARIS GENUAIR 400 micrograms BID showed a statistically significant reduction of 22% compared to placebo (rate ratio [RR] 0.78; 95% CI 0.68 to 0.89; p<0.001). In addition, BRETARIS GENUAIR showed a statistically significant reduction of 35% in the

rate of hospitalisation due to COPD exacerbations while on-treatment during the first year compared with placebo (RR 0.65; 95% CI 0.48 to 0.89; p=0.006).

Figure 2: Time to first moderate or severe COPD exacerbation (days), on-treatment analysis, Kaplan-Meier plot (Full Analysis Set)



COPD: chronic obstructive pulmonary disease.
p-value for comparing aclidinium 400 micrograms versus placebo is based on the Log-rank test stratified by baseline COPD severity and smoking status <0.001.

The Kaplan-Meier curves indicate that the time to first moderate or severe COPD exacerbation was delayed in the aclidinium 400 micrograms group while on treatment compared to the placebo group (see Figure 2). Patients in the aclidinium bromide 400 micrograms group had a 18% relative reduction of the risk of an exacerbation (HR 0.82; 95% CI [0.73, 0.92], p<0.001).

Exercise tolerance
In a 3-week crossover, randomised, placebo-controlled clinical study BRETARIS GENUAIR was associated with a statistically significant improvement in exercise endurance time in comparison to placebo of 58 seconds (95% CI=9-108; p=0.021; pre-treatment value: 486 seconds). BRETARIS GENUAIR statistically significantly reduced lung hyperinflation at rest (functional residual capacity [FRC]=0.197 L [95% CI=0.321, 0.072; p=0.002]); residual volume [RV]=0.238 L [95% CI=0.396, 0.079; p=0.004] and also improved trough inspiratory capacity (by 0.078 L; 95% CI=0.01, 0.145; p=0.025) and reduced dyspnoea during exercise (Borg scale) (by 0.63 Borg units; 95% CI=1.11, 0.14; p=0.012).

The efficacy and safety of aclidinium bromide (400 micrograms BID) beyond 1 year has not been evaluated.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Aclidinium bromide is rapidly absorbed from the lung, achieving maximum plasma concentrations within 5 minutes of inhalation in healthy subjects, and normally within the first 15 minutes in chronic obstructive pulmonary disease (COPD) patients. The fraction of the inhaled dose that reaches the systemic circulation as unchanged aclidinium is very low at less than 5%.

Steady state peak plasma concentrations achieved after dry powder inhalation by COPD patients of 400 micrograms aclidinium bromide were approximately

224 (± 94) picograms/mL. Steady-state plasma levels were attained within seven days of twice daily dosing.

Distribution

Whole lung deposition of inhaled aclidinium bromide via the Genuair inhaler averaged approximately 30% of the metered dose.

The plasma protein binding of aclidinium bromide determined *in vitro* most likely corresponded to the protein binding of the metabolites due to the rapid hydrolysis of aclidinium bromide 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 bromide is albumin.

Metabolism

Aclidinium bromide is rapidly and extensively hydrolysed to its pharmacologically inactive alcohol- and carboxylic acid-derivatives. 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. 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 low absolute bioavailability of inhaled aclidinium bromide (<5%) is because aclidinium bromide 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 bromide.

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.

Elimination

The effective half-life of aclidinium was approximately 10 hours following inhalation of twice daily 400 microgram doses in COPD patients.

Following intravenous administration of 400 micrograms radiolabelled aclidinium bromide 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 200 micrograms and 400 micrograms of aclidinium bromide by healthy subjects or COPD patients, 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.

Linearity/non-linearity

Aclidinium bromide demonstrated kinetic linearity and a time-independent pharmacokinetic behaviour in the therapeutic range.

Pharmacokinetic/pharmacodynamic relationship
Aclidinium bromide acts locally in the lungs and is quickly broken down in plasma. Consequently, there is no direct relationship between pharmacokinetics and pharmacodynamics.

Pharmacokinetics in special patient groups

Elderly patients
The pharmacokinetic properties of aclidinium bromide in patients with moderate to severe COPD appear to be similar in patients aged 40–59 years and in patients aged ≥70 years. Therefore, no dose adjustment is required for elderly COPD patients.

Patients with renal impairment
No significant pharmacokinetic differences were observed between subjects with normal renal function and subjects with renal impairment. Therefore, no dose adjustment and no additional monitoring are required for renally-impaired COPD patients.

Patients with hepatic impairment
No studies have been performed on hepatically-impaired patients. As aclidinium bromide is metabolised mainly by chemical and enzymatic cleavage in the plasma, hepatic dysfunction is very unlikely to alter its systemic exposure. No dose adjustment is required for hepatically-impaired COPD patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
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.

Carcinogenicity
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 50 and 21 times the plasma AUC in patients at the recommended dose and approximately 120 and 11 times the local dose in the lung.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate

6.2 INCOMPATIBILITIES

Refer to section 4.2 DOSE AND METHOD OF ADMINISTRATION and section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

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
To be used within 90 days of opening the pouch.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.

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

6.5 NATURE OF CONTENTS OF CONTAINER

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

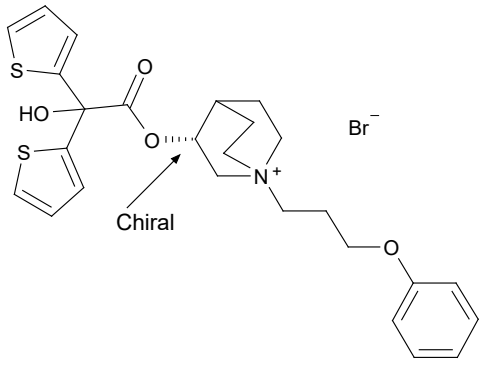
Not all pack sizes may be marketed.

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

Chemical Structure



Stereochemistry: The product has one optically active centre. Aclidinium bromide is a single stereoisomer with the (3*R*) configuration.

Chemical name (IUPAC): (3*R*)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1-(3-phenoxypropyl)-1λ^5-azabicyclo[2.2.2]octan-1-ylium bromide

INN:	aclidinium bromide
CAS number:	320345-99-1
Molecular formula:	$C_{26}H_{30}NO_4S_2Br$
Molecular weight:	564.56
Pharmacotherapeutic group:	Anticholinergics
ATC Code:	R03BB05

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

A. Menarini Australia Pty Ltd
Level 8, 67 Albert Ave
Chatswood NSW 2067
Australia

9. DATE OF FIRST APPROVAL

25 March 2014

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
2, 6.3	Minor editorial changes