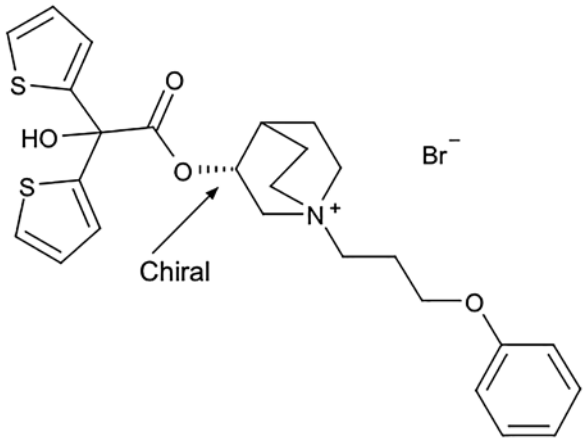
PRODUCT INFORMATION
BRETARIS® GENUAIR®

NAME OF THE MEDICINE
aclidinium bromide

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: 562.56

DESCRIPTION
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.

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

Each delivered dose (the dose leaving the mouthpiece) contains 375 µg aclidinium bromide equivalent to 322 µg of aclidinium. This corresponds to a metered dose of 400 µg aclidinium bromide equivalent to 343 µg aclidinium.
Excipients with known effect: Each metered dose contains 12.6 mg lactose monohydrate.

PHARMACOLOGY
Pharmacodynamics
Pharmacotherapeutic group: Anticholinergics; ATC Code: R03BB05.

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 µg or 800 µg) 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 µg twice daily).

Pharmacokinetics

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%.

Peak plasma concentrations achieved after dry powder inhalation by COPD patients of single doses of 400 µg aclidinium bromide were approximately 80 pg/mL. Steady-state plasma levels were attained within seven days of twice daily dosing, and considering the short half-life steady-state may be reached soon after the first dose. No accumulation on repeat dosing was observed at steady-state.

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.

Biotransformation/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 terminal elimination half-life of aclidinium bromide is approximately 2 to 3 hours.

Following intravenous administration of 400 µg 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 µg and 400 µg 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.

CLINICAL TRIALS

The Bretaris Genuair Phase III clinical development programme included 269 patients treated with Bretaris Genuair 322 µg twice daily in one 6-month randomised, placebo-controlled study and 190 patients treated with Bretaris Genuair 322 µg 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 µg 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.

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 µg BID) beyond 1 year has not been evaluated.

INDICATIONS

Bretaris Genuair is indicated as a long-term maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

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 Description).
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.

PRECAUTIONS

Asthma

Bretaris Genuair should not be used in 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 aclidinium bromide 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 aclidinium bromide beyond the maximum dose is not appropriate

Cardiovascular effects

Cardiovascular safety profile is characterized by the anticholinergic effects.

Bretaris Genuair should be used with caution in patients with a myocardial infarction during the previous 6 months, unstable angina, newly diagnosed arrhythmia within the previous 3 months, or hospitalisation within the previous 12 months for heart failure functional classes III and IV as per the "New York Heart Association". Such patients were excluded from the clinical trials and 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, aclidinium bromide 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).

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 >160 times higher than in patients at the recommended human dose. It is considered unlikely that

aclidinium bromide administered at the recommended dose will affect fertility in humans.

Use in 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 foetuses in rats treated at ≥ 0.78 mg/kg/day by inhalation (yielding 61 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 28 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, aclidinium bromide 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 17 times the clinical plasma AUC). A decision must be made whether to discontinue breast-feeding or to discontinue therapy with aclidinium bromide taking into account the benefit of breast-feeding for the child and the benefit of long-term aclidinium bromide therapy to the woman.

Paediatric use

Bretaris Genuair should not be used in patients under 18 years of age.

Use in the elderly

No dosage adjustment is required for elderly patients.

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 130 and 55 times the plasma AUC in patients at the recommended dose and approximately 120 and 11 times the local dose in the lung.

Effects on ability to drive or use machines

Aclidinium bromide has no or negligible influence on the ability to drive and use machines. The occurrence of blurred vision or headache may influence the ability to drive or to use machinery.

INTERACTIONS WITH OTHER MEDICINES

The co-administration of aclidinium bromide with inhaled anticholinergic-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 Pharmacology).

ADVERSE EFFECTS

The safety data below reflect exposure of 636 patients to Bretaris Genuair 322 µg 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 µg 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 µg discontinued the studies prematurely due to adverse events.

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	**Bretaris Genuair**	**Placebo**
Adverse Reactions	(N = 636)	(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
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 µg 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.

DOSAGE AND ADMINISTRATION

Use in adults

The recommended dose of Bretaris Genuair is one inhalation of 322 µg aclidinium twice daily.

Method of Administration

Bretaris Genuair must be administered only by the oral inhalation route. Bretaris Genuair should be administered at the same times of the day each day. 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 Pharmacology).

Use in patients with impaired renal function

No dose adjustments are required for patients with renal impairment (see section Pharmacology).

Use in patients with impaired hepatic function

No dose adjustments are required for patients with hepatic impairment (see section Pharmacology).

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on the management and treatment of overdose.

High doses of aclidinium bromide may lead to anticholinergic signs and symptoms.

However, single inhaled doses up to 6,000 µg 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 µg 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.

PRESENTATION AND STORAGE CONDITIONS

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 sealed in a protective aluminium laminate 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.

In-use shelf-life

To be used within 90 days of opening the pouch.

Store below 30ºC.

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

NAME AND ADDRESS OF THE SPONSOR

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

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription only medicine

DATE OF FIRST INCLUSION IN THE ARTG

25 March 2014