New Zealand Data Sheet

NAME OF THE DRUG Bretaris® Genuair® Aclidinium bromide

DESCRIPTION
Chemical name (IUPAC): [(3R)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octan-3-yl] 2-hydroxy-2,2-dithiophen-2-ylacetate;bromide

INN: Aclidinium bromide
ATC Code: R03BB05
CAS number: 320345-99-1
Molecular formula: C26H30NO4S2Br
Molecular weight: 564.56
Stereochemistry: The product has one optically active centre. Aclidinium bromide is a single stereoisomer with the (3R) configuration.

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 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.

PRESENTATION
Each delivered dose of Bretaris Genuair (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.

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 laminate pouch, placed in a cardboard carton.

INDICATIONS
Bretaris Genuair is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
DOSAGE AND ADMINISTRATION

Use in adults
The recommended dose is one inhalation of 322 μg aclidinium twice daily.
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
There is no relevant use of Bretaris Genuair in children and adolescents (under 18 years of age) in the indication of COPD.

Use in the elderly
No dose adjustments are required for elderly patients (see section Pharmacokinetics).

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

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

Method of Administration
For inhalation use.
Patients should be instructed on how to administer the product correctly.

CONTRAINDICATIONS
Hypersensitivity to aclidinium bromide, atropine or its derivatives, including ipratropium, oxitropium or tiotropium, or to the excipients (see section Excipients).

WARNINGS AND 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 this occurs, treatment with Bretaris Genuair should be stopped and other treatments considered.

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, a re-evaluation of the patient
and the patients’ treatment regimen should be conducted.

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).

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

**Effects on Fertility**
Studies in rats have shown slight reductions in fertility only at dose levels much higher than the maximum human exposure to aclidinium bromide (see Preclinical safety data). 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.

Studies in animals have shown fetotoxicity only at dose levels much higher than the maximum human exposure to aclidinium bromide (see Preclinical safety data). Aclidinium bromide should only be used during pregnancy if the expected benefits outweigh the potential risks.

**Use in Lactation**
It is unknown whether aclidinium bromide and/or its metabolites are excreted in human milk. As animal studies have shown excretion of small amounts of aclidinium bromide and/or metabolites into milk, 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.

**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 headache or blurred vision may influence the ability to drive or to use machinery.
ADVERSE EFFECTS

The most frequently reported adverse reactions with Bretaris Genuair were headache (6.6%) and nasopharyngitis (5.5%).

The frequencies assigned to the undesirable effects listed below are based on crude incidence rates of adverse reactions (i.e. events attributed to Bretaris Genuair) observed with Bretaris Genuair 322 μg (636 patients) in the pooled analysis of one 6-month and two 3-month randomised, placebo-controlled clinical trials.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from available data).

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Preferred term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Sinusitis</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis</td>
<td>Common</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Common</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Blurred vision</td>
<td>Uncommon</td>
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<tr>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dysphonia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Urinary retention</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

INTERACTIONS

Interaction with Other Medicinal Products

Co-administration of aclidinium bromide with other anticholinergic-containing medicinal products has not been studied and is not recommended.

Although no formal in vivo drug interaction studies have been performed, inhaled aclidinium bromide has been used concomitantly with other COPD medicinal products including sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids without clinical evidence of drug interactions.

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 (P-gp) substrate drugs or drugs metabolised by cytochrome P450 (CYP450) enzymes and esterases (see section Pharmacokinetics).

OVERDOSAGE

Contact the Poisons Information Centre on 0800 POISON (0800 764 766) 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.

FURTHER INFORMATION ACTIONS
Pharmacotherapeutic group: Anticholinergics
ATC Code: R03BB05.

Mechanism of Action
Aclidinium bromide is a competitive, selective muscarinic receptor antagonist (also known as an anticholinergic), with a longer residence time at the M3 receptors than the M2 receptors. M3 receptors mediate contraction of airway smooth muscle. Inhaled aclidinium bromide acts locally in the lungs to antagonise M3 receptors of airway smooth muscle and induce bronchodilator. Nonclinical in vitro and in vivo studies showed rapid, dose-dependent and long-lasting inhibition by aclidinium of acetylcholine-induced bronchoconstriction. Aclidinium bromide is quickly broken down in plasma, the level of systemic anticholinergic side effects is therefore low.

Pharmacodynamics effects
Clinical efficacy studies showed that Bretaris Genuair provided clinically meaningful improvements in lung function (as measured by the forced expiratory volume in 1 second [FEV1]) 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 FEV1 relative to baseline of 227-268 mL at steady-state.

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 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; 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, 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 at the therapeutic dose or its metabolites do not inhibit or induce any of the cytochrome P450 (CYP450) enzymes and do not inhibit esterases (carboxylesterase, acetylcholinesterase and butyrylcholinesterase). In *vitro* studies have shown that aclidinium bromide or the metabolites of aclidinium bromide are not substrates or inhibitors of P-glycoprotein.

**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**
Because aclidinium bromide acts locally in the lungs and is quickly broken down in
plasma there is no direct relationship between pharmacokinetics and pharmacodynamics.

**Special populations**

**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.

**Hepatically-impaired patients**
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.

**Renally-impaired patients**
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.

**OTHER**

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

**Bronchodilation**
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 FEV1). 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) FEV1 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.

**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. The Table below shows symptom relief obtained after 6 months treatment with Bretaris
Genuair.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Improvement over placebo</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>Bretaris</td>
<td>Genuair</td>
<td>Placebo</td>
</tr>
<tr>
<td>TDI</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Percentage of Patients who achieved MCID(^a)</td>
<td>56.9</td>
<td>45.5</td>
<td>1.68-fold(^c) increase in likelihood</td>
</tr>
<tr>
<td>Mean Change from baseline</td>
<td>1.9</td>
<td>0.9</td>
<td>1.0 unit</td>
</tr>
<tr>
<td>SGRQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of Patients who achieved MCID(^b)</td>
<td>57.3</td>
<td>41.0</td>
<td>1.87-fold(^c) increase in likelihood</td>
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<tr>
<td>Mean Change from baseline</td>
<td>-7.4</td>
<td>-2.8</td>
<td>- 4.6 units</td>
</tr>
</tbody>
</table>

\(^a\) 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.

Pooled efficacy analysis of the 6-month and 3-month placebo controlled studies demonstrated a statistically significant reduction in the rate of moderate to severe exacerbations (requiring treatment with antibiotics or corticosteroids or resulting in hospitalisations) with aclidinium 322 μg twice daily compared to placebo (rate per patient per year: 0.31 vs 0.44 respectively; p=0.0149).

**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).

**Paediatric population**

The European Medicines Agency has waived the obligation to submit the results of studies with Bretaris Genuair in all subsets of the paediatric population in COPD (see Posology and method of administration).

**Preclinical safety data**

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential and toxicity to reproduction and development.

Effects in nonclinical studies with respect to cardiovascular parameters (increased heart rates in dogs), reproductive toxicity (fetotoxic effects), and fertility (slight decreases in
conception rate, number of corpora lutea, and pre- and post-implantation losses) were observed only at exposures considered sufficiently in excess of the maximum human exposure indication to be of little relevance to clinical use. The low toxicity observed in nonclinical toxicity studies is in part due to rapid metabolism of aclidinium bromide in plasma and the lack of significant pharmacological activity of the major metabolites. The safety margins for human systemic exposure with 400 µg twice daily over the no observed adverse effect levels in these studies ranged from 17- to 187-fold.

Chemical Structure

![Chemical Structure Image]

Excipients with known effect
Each metered dose contains 12.6 mg lactose monohydrate.

PHARMACEUTICAL PRECAUTIONS

Shelf life
3 years
To be used within 90 days of opening the pouch.

Special Precautions for Storage
This medicinal product does not require any special storage conditions.
Keep the Genuair inhaler protected inside the sealed pouch until the administration period starts.

PACKAGE QUANTITIES
- 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.

MEDICINE SCHEDULE
Prescription Only Medicine

SPONSOR DETAILS
Te Arai BioFarma Limited
PO Box 46205
The Genuair inhaler: instructions for use

This section contains information on how to use your Genuair inhaler. If you have any questions about how to use your inhaler, please ask your doctor, pharmacist or nurse for assistance.

Before using the Genuair inhaler, please read the full instructions.

Becoming familiar with Bretaris Genuair

Remove the Genuair inhaler from the pouch and become familiar with its components.

How to Use Bretaris Genuair

To use your Genuair inhaler there are 2 steps you need to perform after removing the cap:

Step 1: Press and RELEASE the green button and breathe out completely, away from the inhaler.

Step 2: Place your lips tightly around the mouthpiece of the Genuair inhaler and inhale STRONGLY and DEEPLY through the inhaler.

After inhalation, remember to replace the protective cap.

Getting Started

- Before first use, tear the sealed pouch along the notch and remove the Genuair inhaler.
- When you are about to take your dose of medicinal product, remove the protective cap by lightly squeezing the arrows marked on each side and pulling outwards (see image 1).
• Look to see that nothing is blocking the mouthpiece.

• Hold the Genuair inhaler **horizontally** with the mouthpiece towards you and the green button facing **straight up** (see image 2).

![IMAGE 2]

**STEP 1:** PRESS the green button all the way down and then RELEASE it (see images 3 and 4).

**DO NOT CONTINUE TO HOLD THE GREEN BUTTON DOWN.**

![IMAGE 3](press)  ![IMAGE 4](release)

Stop and Check: Make sure dose is ready for inhalation

• Make sure the coloured control window has changed to **green** (see image 5).

• The green control window confirms that your medicine is ready for inhalation.

![IMAGE 5](green)

**IF THE COLOURED CONTROL WINDOW STAYS RED, PLEASE REPEAT PRESS AND RELEASE ACTIONS (SEE STEP 1).**
Before bringing the inhaler to your mouth, breathe out completely. Do not breathe out into the inhaler.

**STEP 2:** Put your lips tightly around the mouthpiece of the Genuair inhaler and inhale **STRONGLY** and **DEEPLY** through the mouthpiece (see image 6).

This strong, deep breath pulls the medicinal product through the inhaler into your lungs.

- While you breathe in you will hear a "**CLICK**" which signals that you are using the Genuair inhaler correctly.
- Keep breathing in even after you have heard the inhaler “**CLICK**” to be sure you get the full dose.
- Remove the Genuair inhaler from your mouth and hold your breath for as long as is comfortable, then breathe out slowly through your nose.

Note: Some patients may experience a mild sweet or slightly bitter taste, depending on the patient, when inhaling the medicinal product. Do not take an extra dose if you do not taste anything after inhaling.

**Stop and Check:** Make sure you have inhaled correctly

- Make sure the control window has turned to **red** (see image 7). This confirms that you have inhaled your full dose correctly.
IF THE COLOURED CONTROL WINDOW IS STILL GREEN, PLEASE REPEAT INHALING STRONGLY AND DEEPLY THROUGH THE MOUTHPIECE (SEE STEP 2).

- If the window still does not change to red, you may have forgotten to release the green button before inhaling or may not have inhaled correctly. If that happens, try again.

Make sure you have RELEASED the green button and take a STRONG deep breath in through the mouthpiece.

Note: If you are unable to inhale correctly after several attempts, consult your doctor.

- Once the window has turned red, replace the protective cap by pressing it back onto the mouthpiece (see image 8).

When should you get a new Genuair inhaler?

- The Genuair inhaler is equipped with a dose indicator to show you approximately how many doses are left in the inhaler. The dose indicator moves down slowly, displaying intervals of 10 (60, 50, 40, 30, 20, 10, 0) (see image A). Every Genuair inhaler will deliver at least 60 doses.

When a red striped band appears in the dose indicator (see image A), this means you are nearing your last dose and you should obtain a new Genuair inhaler.

Note: If your Genuair inhaler appears to be damaged or if you lose the cap, your inhaler should be replaced. You DO NOT NEED to clean your Genuair inhaler. However, if you wish to clean it you should do so by wiping the outside of the mouthpiece with a dry tissue or paper towel.
NEVER use water to clean the Genuair inhaler, as this may damage your medicine.

**How do you know that your Genuair inhaler is empty?**

- When 0 (zero) appears in the middle of the dose indicator, you should continue using any doses remaining in the Genuair inhaler.

- When the last dose has been prepared for inhalation, the green button will not return to its full upper position, but will be locked in a middle position (see image B). Even though the green button is locked, your last dose may still be inhaled. After that, the Genuair inhaler cannot be used again and you should start using a new Genuair inhaler.

![IMAGE B](image)