

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Bretaris Genuair 322 micrograms inhalation powder

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

### Excipients with known effect

Each delivered dose contains approximately 12 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Inhalation powder.

White or almost white powder in a white inhaler with an integral dose indicator and a green dosage button.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

#### Posology

The recommended dose is one inhalation of 322 micrograms acclidinium 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.

#### *Elderly*

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

#### *Renal impairment*

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

#### *Hepatic impairment*

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

#### *Paediatric population*

There is no relevant use of Bretaris Genuair in children and adolescents (under 18 years of age) for the indication of COPD.

### Method of administration

For inhalation use.

Patients should be instructed on how to administer the product correctly as the Genuair inhaler may work differently from inhalers the patients may have used previously. It is important to instruct the patients to carefully read the Instructions for Use in the Package Leaflet, which is packed together with each inhaler.

For Instructions for Use, see section 6.6.

### **4.3 Contraindications**

Hypersensitivity to acclidinium bromide or to the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Paradoxical bronchospasm:

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:

Acclidinium 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 acclidinium 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 who had 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 because 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, acclidinium 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:

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Co-administration of acclidinium 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 acclidinium 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 acridinium bromide or the metabolites of acridinium bromide at the therapeutic dose are not expected to cause interactions with active substances that are substrates of P-glycoprotein (P-gp) or active substances metabolised by cytochrome P450 (CYP450) enzymes and esterases (see section 5.2).

#### 4.6 Fertility, pregnancy and lactation

##### Pregnancy

There are no data available on the use of acridinium bromide in pregnant women.

Studies in animals have shown fetotoxicity only at dose levels much higher than the maximum human exposure to acridinium bromide (see section 5.3). Acridinium bromide should only be used during pregnancy if the expected benefits outweigh the potential risks.

##### Breast-feeding

It is unknown whether acridinium bromide / metabolites are excreted in human milk. Animal studies have shown excretion of small amounts of acridinium bromide and/or metabolites into milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Bretaris Genuair therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

##### Fertility

Studies in rats have shown slight reductions in fertility only at dose levels much higher than the maximum human exposure to acridinium bromide (see section 5.3). It is considered unlikely that acridinium bromide administered at the recommended dose will affect fertility in humans.

#### 4.7 Effects on ability to drive and use machines

Acridinium bromide may have a minor influence on the ability to drive and use machines. The occurrence of headache, dizziness or blurred vision following administration of acridinium bromide (see section 4.8) may influence the ability to drive or to use machinery.

#### 4.8 Undesirable effects

##### Summary of the safety profile

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

##### Tabulated summary of adverse reactions

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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

System organ class	Preferred term	Frequency
Infections and infestations	Sinusitis	Common
	Nasopharyngitis	Common
Immune system disorders	Hypersensitivity	Rare
	Angioedema	Not known
	Anaphylactic reaction	Not known
Nervous system disorders	Headache	Common
	Dizziness	Uncommon

Eye disorders	Blurred vision	Uncommon
Cardiac disorders	Tachycardia	Uncommon
	Palpitations	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Dysphonia	Uncommon
Gastrointestinal disorders	Diarrhoea	Common
	Nausea*	Common
	Dry mouth	Uncommon
	Stomatitis	Uncommon
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Pruritus	Uncommon
Renal and urinary disorders	Urinary retention	Uncommon

\* The incidence of nausea in clinical trials was lower for aclidinium bromide than for placebo (43.9 vs 48.3 per 1000 patient-years respectively)

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V.](#)

#### **4.9 Overdose**

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 reactions. Additionally, no clinically relevant adverse reactions 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.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Drugs for obstructive airway diseases, 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 M<sub>3</sub> receptors than the M<sub>2</sub> receptors. M<sub>3</sub> receptors mediate contraction of airway smooth muscle. Inhaled aclidinium bromide acts locally in the lungs to antagonise M<sub>3</sub> 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 of acetylcholine-induced bronchoconstriction. Aclidinium bromide is quickly broken down in plasma, the level of systemic anticholinergic side effects is therefore low.

#### Pharmacodynamic 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 [FEV<sub>1</sub>]) 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<sub>1</sub> relative to baseline of 227-268 mL at steady-state.

### *Cardiac electrophysiology*

No effects on QT interval (corrected using either the Fridericia or Bazett method or individually-corrected) were observed when acclidinium 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).

### Clinical efficacy and safety

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 FEV<sub>1</sub>). 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<sub>1</sub> 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.

Variable	Treatment		Improvement over placebo	p-value
	Bretaris Genuair	Placebo		
<b>TDI</b>				
Percentage of Patients who achieved MCID <sup>a</sup>	56.9	45.5	1.68-fold <sup>c</sup> increase in likelihood	0.004
Mean Change from baseline	1.9	0.9	1.0 unit	<0.001
<b>SGRQ</b>				
Percentage of Patients who achieved MCID <sup>b</sup>	57.3	41.0	1.87-fold <sup>c</sup> 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.

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 acclidinium 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 section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

Acclidinium 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 acclidinium is very low at less than 5%.

Steady state peak plasma concentrations achieved after dry powder inhalation by COPD patients of 400 µg acclidinium bromide were approximately 224 pg/mL. Steady-state plasma levels were attained within seven days of twice daily dosing.

### Distribution

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

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

### Biotransformation

Acclidinium 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 acclidinium bromide (<5%) is because acclidinium 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 acclidinium bromide.

*In vitro* studies have shown that acclidinium 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 acclidinium bromide or the metabolites of acclidinium bromide are not substrates or inhibitors of P-glycoprotein.

### Elimination

The terminal elimination half-life and effective half-life of acclidinium bromide are approximately 14 hours and 10 hours, respectively, following inhalation of twice daily 400 µg doses in COPD patients.

Following intravenous administration of 400 µg radiolabelled acclidinium bromide to healthy subjects, approximately 1% of the dose was excreted as unchanged acclidinium 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 acclidinium bromide by healthy subjects or COPD patients, the urinary excretion of unchanged acclidinium was very low at about 0.1% of the administered dose, indicating that renal clearance plays a minor role in the total acclidinium clearance from plasma.

### Linearity/non-linearity

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

### Special populations

#### *Elderly patients*

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

#### *Hepatically-impaired patients*

No studies have been performed on hepatically-impaired patients. As acclidinium 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.

#### *Race*

Following repeated inhalations, the systemic exposure of acclidinium bromide has been observed to be similar in Japanese and Caucasian patients.

#### Pharmacokinetic/pharmacodynamic relationship

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

### **5.3 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, 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 indicating little relevance to clinical use.

The low toxicity observed in nonclinical toxicity studies is in part due to rapid metabolism of acclidinium 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 7- to 73-fold.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose monohydrate.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

To be used within 90 days of opening the pouch.

### **6.4 Special precautions for storage**

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

### **6.5 Nature and contents of container**

The inhaler device is a multicomponent device made of polycarbonate, acrylonitrile-butadiene-styrene, polyoxymethylene, polyester-butylene-terephthalate, polypropylene, polystyrene and stainless steel. 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 plastic laminate pouch, placed in a cardboard carton.

Carton containing 1 inhaler with 30 doses.

Carton containing 1 inhaler with 60 doses.

Carton containing 3 inhalers each with 60 doses.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **Instructions for Use**

### **Getting Started**

**Read these Instructions for Use before you start using the medicine.**

Become familiar with the parts of your Genuair inhaler.

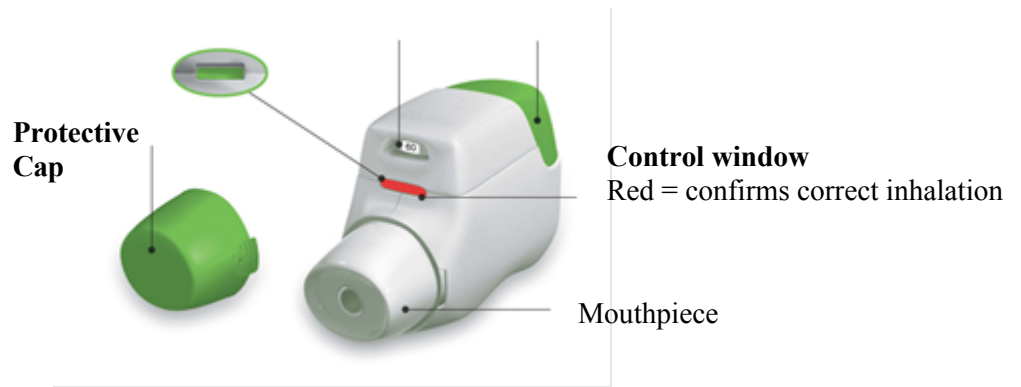
**Control window**

Green = inhaler ready to use

**Dose**

**indicator**

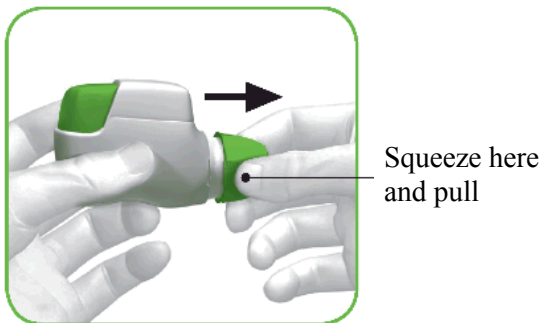
**Green button**



**Figure A**

**Before use:**

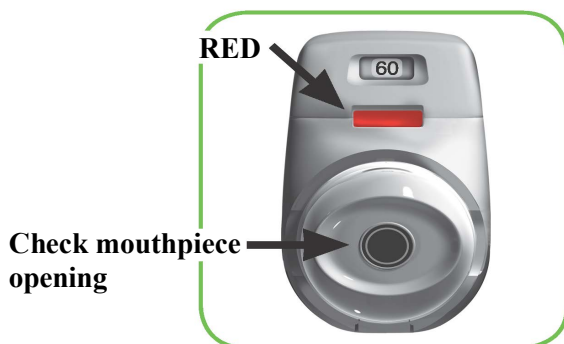
- a) Before first use, tear open the sealed bag and remove the inhaler. Throw away the bag.
- b) Do not press the green button until you are ready to take a dose.
- c) Pull off the cap by lightly squeezing the arrows marked on each side (Figure B).



**Figure B**

**STEP 1: Prepare your dose**

- 1.1 Look in the opening of the mouthpiece and make sure nothing is blocking it (Figure C).
- 1.2 Look at the control window (should be red, Figure C).



**Figure C**

- 1.3 Hold the inhaler horizontally with the mouthpiece facing you and the green button on top (Figure D).



**Figure D**

1.4 Press the green button all the way down to load your dose (Figure E).

When you press the button all the way down, the control window changes from red to green.

Make sure the green button is on top. **Do not tilt.**

1.5 Release the green button (Figure F).

Make sure you release the button so the inhaler can work correctly.



**Figure E**



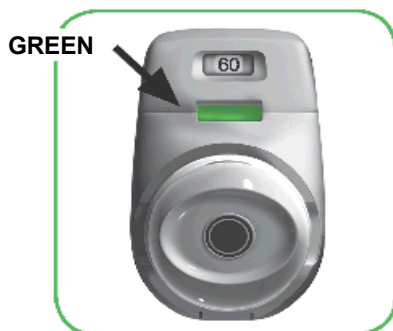
**Figure F**

**Stop and Check:**

1.6 Make sure the control window is now green (Figure G).

Your medicine is ready to be inhaled.

Go to 'STEP 2: Inhale your medicine'.



**Figure G**

**What to do if the control window is still red after pressing the button (Figure H).**



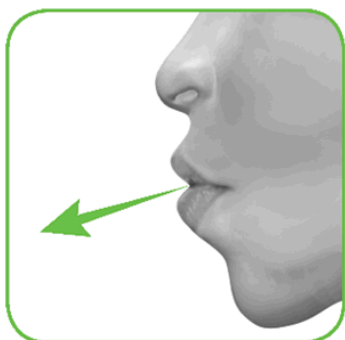
**Figure H**

The dose is not prepared. **Go back to 'STEP 1 Prepare your dose' and repeat steps 1.1 to 1.6.**

## **STEP 2: Inhale your medicine**

Read steps 2.1 to 2.7 fully before use. Do not tilt.

2.1 Hold the inhaler away from your mouth, and **breathe out completely**. Never breathe out into the inhaler (Figure I).



**Figure I**

2.2 Hold your head upright, put the mouthpiece between your lips, and close your lips tightly around it (Figure J).

**Do not hold the green button down while inhaling.**



**Figure J**

2.3 Take a **strong, deep breath** through your mouth. Keep breathing in for as long as possible.

A 'click' will let you know that you are inhaling correctly. Keep breathing in as long as possible after you hear the 'click'. Some patients may not hear the 'click'. Use the control window to ensure you have inhaled correctly.

2.4 Take the inhaler out of your mouth.

2.5 Hold your breath for as long as possible.

2.6 Slowly breathe out away from the inhaler.

Some patients may experience a grainy sensation in their mouth, or a slightly sweet or bitter taste. Do not take an extra dose even if you do not taste or feel anything after inhaling.

### Stop and Check:

2.7 Make sure the control window is now red (Figure K). This means you have inhaled your medicine correctly.



Figure K

### What to do if the control window is still green after inhalation (Figure L).



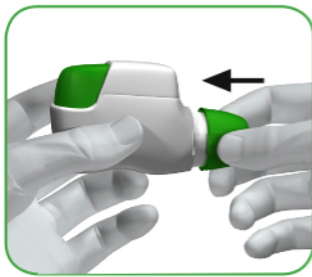
Figure L

This means you have not inhaled your medicine correctly. **Go back to 'STEP 2 Inhale your medicine' and repeat steps 2.1 to 2.7.**

If the control window still does not change to red, you may have forgotten to release the green button before inhaling, or you may not have inhaled strongly enough. If this happens, try again. Make sure you have released the green button, and you have breathed out completely. Then take a strong, deep breath through the mouthpiece.

**Please contact your doctor if the control window is still green after repeated attempts.**

Push the protective cap back onto the mouthpiece after each use (Figure M), to prevent contamination of the inhaler with dust or other materials. You should discard your inhaler if you lose the cap.



**Figure M**

### **Additional information**

#### What should you do if you accidentally prepare a dose?

Store your inhaler with the protective cap in place until it is time to inhale your medicine, then remove the cap and start at Step 1.6.

How does the dose indicator work?

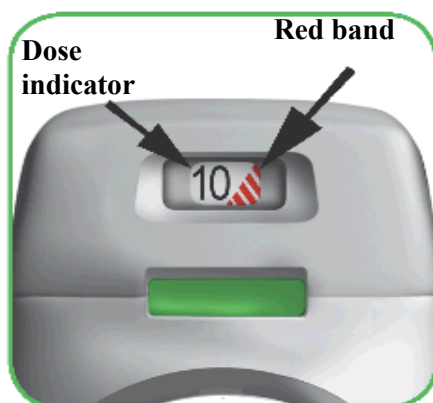
- The dose indicator shows the total number of doses left in the inhaler (Figure N).
- On first use, every inhaler contains at least 60 doses, or at least 30 doses, depending on the pack size.
- Each time you load a dose by pressing the green button, the dose indicator moves by a small amount towards the next number (50, 40, 30, 20, 10, or 0).

#### When should you get a new inhaler?

You should get a new inhaler:

- If your inhaler appears to be damaged or if you lose the cap, or
- When a red band appears in the dose indicator, this means you are nearing your last dose (Figure N), or
- If your inhaler is empty (Figure O).

**Dose indicator moves slowly from 60 to 0: 60, 50, 40, 30, 20, 10, 0.**



**Figure N**

### How do you know that your inhaler is empty?

When the green button will not return to its full upper position and is locked in a middle position, you have reached the last dose (Figure O). Even though the green button is locked, your last dose may still be inhaled. After that, the inhaler cannot be used again and you should start using a new inhaler.



**Figure O**

### How should you clean the inhaler?

NEVER use water to clean the inhaler, as this may damage your medicine.

If you wish to clean your inhaler, just wipe the outside of the mouthpiece with a dry tissue or paper towel.

## **7. MARKETING AUTHORISATION HOLDER**

AstraZeneca AB  
SE-151 85 Södertälje  
Sweden

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/12/781/001  
EU/1/12/781/002  
EU/1/12/781/003

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 20 July 2012  
Date of last renewal: 20 April 2017

## **10. DATE OF REVISION OF THE TEXT**

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

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**



## MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Industrias Farmacéuticas Almirall, S.A.  
Ctra. Nacional II, Km. 593  
08740 Sant Andreu de la Barca  
Barcelona  
Spain

### B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

### C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

#### Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

#### Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

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

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-Authorisation Safety (PAS) Cohort Study of Inhaled Acclidinium Bromide and the Risk of Selected Cardiovascular Endpoints. Full study protocols should be submitted before the study start for CHMP review prior to the product launch.	PASS will start when there are 2000 prescriptions in the defined database.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Bretaris Genuair 322 micrograms inhalation powder  
aclidinium (aclidinium bromide)

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each delivered dose contains 375 micrograms aclidinium bromide equivalent to 322 micrograms of  
aclidinium.

**3. LIST OF EXCIPIENTS**

Also contains: Lactose

**4. PHARMACEUTICAL FORM AND CONTENTS**

1 inhaler containing 30 doses  
1 inhaler containing 60 doses  
3 inhalers each containing 60 doses

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use  
Inhalation use

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

Keep out of the sight and reach of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP  
To be used within 90 days of opening the pouch

**9. SPECIAL STORAGE CONDITIONS**

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

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

AstraZeneca AB  
SE-151 85 Södertälje  
Sweden

AstraZeneca (AstraZeneca logo)

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/12/781/001 30 doses  
EU/1/12/781/002 60 doses  
EU/1/12/781/003 3 inhalers each containing 60 doses

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

bretaris genuair

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Inhaler label**

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

Bretaris Genuair 322 mcg inhalation powder  
aclidinium (aclidinium bromide)  
Inhalation use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP  
To be used within 90 days of opening the pouch.

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

30 doses  
60 doses

**6. OTHER**

AstraZeneca (AstraZeneca logo)

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### **Bretaris Genuair 322 micrograms inhalation powder** Acclidinium (aclidinium bromide)

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

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

#### **What is in this leaflet:**

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

#### **1. What Bretaris Genuair is and what it is used for**

##### **What Bretaris Genuair is**

The active ingredient of Bretaris Genuair is aclidinium bromide, which belongs to a group of medicines called bronchodilators. Bronchodilators relax airways and help keep bronchioles open. Bretaris Genuair is a dry powder inhaler that uses your breath to deliver the medicine directly into your lungs. This makes it easier for chronic obstructive pulmonary disease (COPD) patients to breathe.

##### **What Bretaris Genuair is used for**

Bretaris Genuair is indicated to help open the airways and relieve symptoms of COPD, a serious, long-term lung disease characterised by breathing difficulties. Regular use of Bretaris Genuair can help you when you have ongoing shortness of breath related to your disease and will help you to minimise the effects of the disease on your everyday life.

#### **2. What you need to know before you use Bretaris Genuair**

##### **Do not use Bretaris Genuair**

- if you are allergic to aclidinium bromide or any of the other ingredients of this medicine (listed in section 6).

##### **Warnings and precautions**

Talk to your doctor, pharmacist or nurse before using Bretaris Genuair:

- if you have had heart problems recently.
- if you see halos around lights or coloured images (glaucoma).
- if you have an enlarged prostate, problems passing urine, or a blockage in your bladder.

Bretaris Genuair is indicated for maintenance treatment and should not be used to treat a sudden attack of breathlessness or wheezing. If your COPD symptoms (breathlessness, wheezing, cough) do not improve or get worse you should contact your doctor for advice as soon as possible.



Dry mouth, which has been observed with medicines like Bretaris Genuair, may after using your medicine for a long time, be associated with tooth decay. Therefore, please remember to pay attention to oral hygiene.

Stop taking Bretaris Genuair and seek medical help immediately:

- if you get tightness of the chest, coughing, wheezing or breathlessness immediately after using the medicine. These may be signs of a condition called bronchospasm.

### **Children and adolescents**

Bretaris Genuair is not for use in children or adolescents below 18 years of age.

### **Other medicines and Bretaris Genuair**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Inform your doctor if you have been or are using similar medicines for breathing problems, such as medicines containing tiotropium, ipratropium. Ask your doctor or pharmacist if you are not sure. The use of Bretaris Genuair with these medicines is not recommended.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should not use Bretaris Genuair if you are pregnant or are breast-feeding unless your doctor tells you so.

### **Driving and using machines**

Bretaris Genuair may have minor influence on the ability to drive and use machines. This medicine may cause headache, dizziness or blurred vision. If you are affected by any of these side effects do not drive or use machinery until the headache has cleared, the feeling of dizziness has passed and your vision has returned to normal.

### **Bretaris Genuair contains lactose**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## **3. How to use Bretaris Genuair**

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

The recommended dose is one inhalation twice a day in the morning and evening.

The effects of Bretaris Genuair last for 12 hours; therefore, you should try to use your Bretaris Genuair inhaler at the same time every morning and evening. This ensures that there is always enough medicine in your body to help you breathe more easily throughout the day and night. It will also help you to remember to use it.

The recommended dose can be used for elderly patients and for patients with kidney or liver problems. No dose adjustments are necessary.

COPD is a long-term disease; therefore, it is recommended that Bretaris Genuair is used every day, twice a day and not only when breathing problems or other symptoms of COPD are experienced.

### **Route of administration**

The medicine is for inhalation use.

Refer to the Instructions for Use for instructions on how to use the Genuair inhaler. If you are not sure of how to use Bretaris Genuair, contact your doctor or pharmacist.

You can use Bretaris Genuair any time before or after food or drink.

**If you use more Bretaris Genuair than you should**

If you think you may have used more Bretaris Genuair than you should, contact your doctor or pharmacist.

**If you forget to use Bretaris Genuair**

If you forget a dose of Bretaris Genuair, inhale the dose as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose.

Do not take a double dose to make up for a forgotten dose.

**If you stop using Bretaris Genuair**

This medicine is for long-term use. If you want to stop treatment, first talk to your doctor, as your symptoms may worsen.

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

#### **4. Possible side effects**

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

Allergic reactions may rarely occur (may affect up to 1 in 1,000 people). Stop using the medicine and contact your doctor immediately if you develop swelling of your face, throat, lips or tongue (with or without difficulty breathing or swallowing), dizziness or fainting, faster heart rate or if you get raised severely itchy bumps on your skin (hives) as these may be symptoms of an allergic reaction.

The following side effects may occur whilst using Bretaris Genuair:

**Common:** may affect up to 1 in 10 people

- Headache
- Inflammation of the sinuses (sinusitis)
- Common cold (nasopharyngitis)
- Cough
- Diarrhoea
- Nausea

**Uncommon:** may affect up to 1 in 100 people

- Dizziness
- Dry mouth
- Inflammation of the mouth (stomatitis)
- Hoarseness (dysphonia)
- Faster heart beat (tachycardia)
- Sensation of heart beating (palpitations)
- Difficulty passing urine (urinary retention)
- Blurred vision
- Rash
- Itching of the skin

**Reporting of side effects**

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

## **5. How to store Bretaris Genuair**

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

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

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

To be used within 90 days of opening the pouch.

Do not use the Bretaris Genuair if you notice that the pack is damaged or shows signs of tampering.

After you have taken the last dose, the inhaler has to be disposed of. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Bretaris Genuair contains**

- The active substance is aclidinium bromide. Each delivered dose contains 375 micrograms aclidinium bromide equivalent to 322 micrograms of aclidinium.
- The other ingredient is lactose monohydrate (refer to Section 2 “Bretaris Genuair contains lactose”).

### **What Bretaris Genuair looks like and contents of the pack**

Bretaris Genuair is a white or almost white powder.

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

Pack sizes supplied:

arton containing 1 inhaler with 30 doses.

Carton containing 1 inhaler with 60 doses.

Carton containing 3 inhalers each with 60 doses.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

AstraZeneca AB  
SE-151 85 Södertälje  
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### **Manufacturer**

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**This leaflet was last revised in <{month YYYY}>.**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu/>.

## Instructions for Use

This section contains information on how to use your Genuair inhaler. It is important that you read this information as the Genuair may work differently from inhalers you have used previously. If you have any questions about how to use your inhaler, please ask your doctor, pharmacist or nurse for assistance.

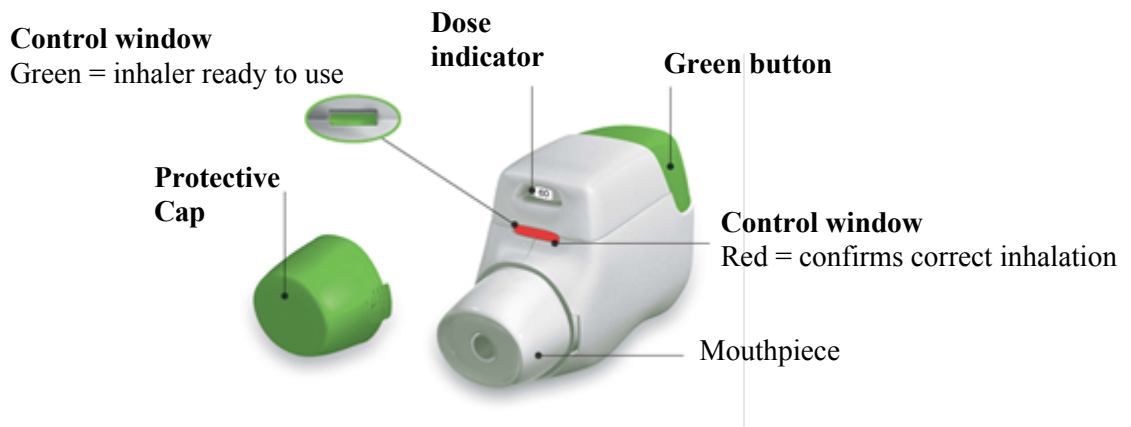
The Instructions for Use is divided into the following sections:

- Getting started
- Step 1: Prepare your dose
- Step 2: Inhale your medicine
- Additional information

## Getting Started

**Read these Instructions for Use before you start using the medicine.**

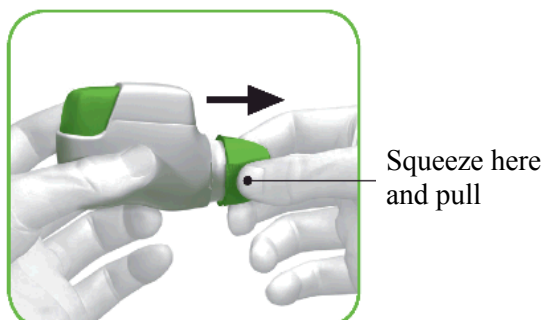
Become familiar with the parts of your Genuair inhaler.



**Figure A**

## Before use:

- Before first use, tear open the sealed bag and remove the inhaler. Throw away the bag.
- Do not press the green button until you are ready to take a dose.
- Pull off the cap by lightly squeezing the arrows marked on each side (Figure B).

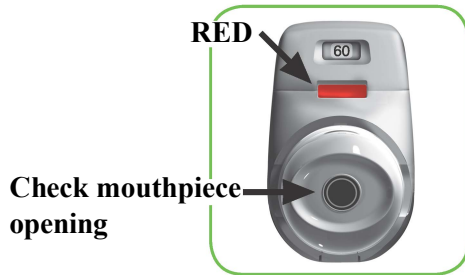


**Figure B**

## STEP 1: Prepare your dose

1.1 Look in the opening of the mouthpiece and make sure nothing is blocking it (Figure C).

1.2 Look at the control window (should be red, Figure C).



**Figure C**

1.3 Hold the inhaler horizontally with the mouthpiece facing you and the green button on top (Figure D).



**Figure D**

1.4 Press the green button all the way down to load your dose (Figure E).

When you press the button all the way down, the control window changes from red to green.

Make sure the green button is on top. **Do not tilt.**

1.5 Release the green button (Figure F).

Make sure you release the button so the inhaler can work correctly.



**Figure E**



**Figure F**

**Stop and Check:**

1.6 Make sure the control window is now green (Figure G).

Your medicine is ready to be inhaled.

Go to ‘STEP 2: Inhale your medicine’.



**Figure G**

**What to do if the control window is still red after pressing the button (Figure H).**



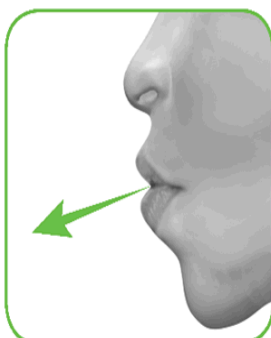
**Figure H**

The dose is not prepared. **Go back to ‘STEP 1 Prepare your dose’ and repeat steps 1.1 to 1.6.**

**STEP 2: Inhale your medicine**

Read steps 2.1 to 2.7 fully before use. Do not tilt.

2.1 Hold the inhaler away from your mouth, and **breathe out completely**. Never breathe out into the inhaler (Figure I).





## Figure I

2.2 Hold your head upright, put the mouthpiece between your lips, and close your lips tightly around it (Figure J).

**Do not hold the green button down while inhaling.**



## Figure J

2.3 Take a **strong, deep breath** through your mouth. Keep breathing in for as long as possible.

A 'click' will let you know that you are inhaling correctly. Keep breathing in as long as possible after you hear the 'click'. Some patients may not hear the 'click'. Use the control window to ensure you have inhaled correctly.

2.4 Take the inhaler out of your mouth.

2.5 Hold your breath for as long as possible.

2.6 Slowly breathe out away from the inhaler.

Some patients may experience a grainy sensation in their mouth, or a slightly sweet or bitter taste. Do not take an extra dose even if you do not taste or feel anything after inhaling.

### Stop and Check:

2.7 Make sure the control window is now red (Figure K). This means you have inhaled your medicine correctly.



**Figure K**

**What to do if the control window is still green after inhalation (Figure L).**



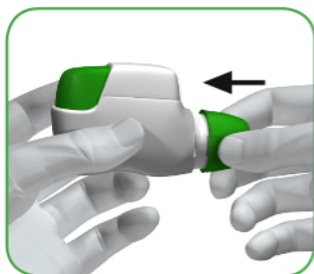
**Figure L**

This means you have not inhaled your medicine correctly. **Go back to ‘STEP 2 Inhale your medicine’ and repeat steps 2.1 to 2.7.**

If the control window still does not change to red, you may have forgotten to release the green button before inhaling, or you may not have inhaled strongly enough. If this happens, try again. Make sure you have released the green button, and you have breathed out completely. Then take a strong, deep breath through the mouthpiece.

**Please contact your doctor if the control window is still green after repeated attempts.**

Push the protective cap back onto the mouthpiece after each use (Figure M), to prevent contamination of the inhaler with dust or other materials. You should discard your inhaler if you lose the cap.



**Figure M**

#### **Additional information**

What should you do if you accidentally prepare a dose?

Store your inhaler with the protective cap in place until it is time to inhale your medicine, then remove the cap and start at Step 1.6.

How does the dose indicator work?

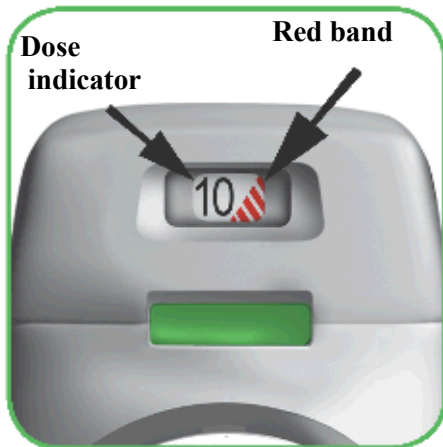
- The dose indicator shows the total number of doses left in the inhaler (Figure N).
- On first use, every inhaler contains at least 60 doses, or at least 30 doses, depending on the pack size.
- Each time you load a dose by pressing the green button, the dose indicator moves by a small amount towards the next number (50, 40, 30, 20, 10, or 0).

When should you get a new inhaler?

You should get a new inhaler:

- If your inhaler appears to be damaged or if you lose the cap, or
- When a red band appears in the dose indicator, this means you are nearing your last dose (Figure N), or
- If your inhaler is empty (Figure O).

**Dose indicator moves slowly from 60 to 0: 60, 50, 40, 30, 20, 10, 0.**



**Figure N**

How do you know that your inhaler is empty?

When the green button will not return to its full upper position and is locked in a middle position, you have reached the last dose (Figure O). Even though the green button is locked, your last dose may still be inhaled. After that, the inhaler cannot be used again and you should start using a new inhaler.



**Figure O**

How should you clean the inhaler?

NEVER use water to clean the inhaler, as this may damage your medicine.

If you wish to clean your inhaler, just wipe the outside of the mouthpiece with a dry tissue or paper towel.