The content of this leaflet was approved by the ministry of Health in Feb 2016 and updated according to the guidelines of the Ministry of Health in Dec 2018

1. NAME OF THE MEDICINAL PRODUCT

Eklira Genuair

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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

Eklira 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 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.

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 Eklira 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 aclidinium bromide or to the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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Paradoxical bronchospasm:
administration of Eklira Genuair may cause paradoxical bronchospasm. If this occurs, treatment with Eklira 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.
Eklira 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 and 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, 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:
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 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 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 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 section 5.3). Aclidinium bromide should only be used during pregnancy if the expected benefits outweigh the potential risks.

Breast-feeding
It is unknown whether aclidinium bromide /metabolites are excreted in human milk. animal studies have shown excretion of small amounts of aclidinium bromide and/or metabolites into milk, A risk to newborns/intants cannot be excluded. a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Eklira Genuiar 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 aclidinium bromide (see section 5.3). It is considered unlikely that aclidinium bromide administered at the recommended dose will affect fertility in humans.

4.7 Effects on ability to drive and use machines

Aclidinium bromide may have minor influence on the ability to drive and use machines. The occurrence of headache, dizziness or blurred vision following administration of aclidinium 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 Eklira 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 Eklira Genuair) observed with Eklira 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 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
	Stomatitis	Uncommon
	Dry mouth	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 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

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_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 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 Eklira 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.

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 Eklira Genuair on cardiac rhythm were observed on 24-hour Holter monitoring after 3 months treatment of 336 patients (of whom 164 received Eklira Genuair 322 µg twice daily).

Clinical Efficacy
The Eklira Genuair Phase III clinical development programme included 269 patients treated with Eklira Genuair 322 µg twice daily in one 6-month randomised, placebo-controlled study and 190 patients treated with Eklira 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, Eklira Genuair was associated with bronchodilatory efficacy when administered over a 1-year treatment period.

Bronchodilation
In the 6-month study, patients receiving Eklira 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 Eklira Genuair in the 3 month study.

Disease-Specific Health Status and Symptomatic Benefits
Eklira 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 Eklira Genuair.

Variable	**Treatment**		**Improvement over placebo**	**p-value**
	Eklira 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 Eklira Genuair required less rescue medication than patients treated with placebo (a reduction of 0.95 puffs per day at 6 months [p=0.005]). Eklira 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 Eklira 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). Eklira 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 Eklira Genuair in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Steady state peak plasma concentrations achieved after dry powder inhalation by COPD patients of 400 µg aclidinium bromide were approximately224 pg/mL. Steady-state plasma levels were attained within seven days of twice daily dosing .

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

The plasma protein binding of aclidinium bromide determined *in vitro* most likely corresponded to the protein binding of the metabolites due to the rapid hydrolysis of aclidinium bromide in plasma; 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
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 and effective half-life of aclidinium 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 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.

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.

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

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.

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 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 indicating 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 7- to 73-fold.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

To be used within 90 days of opening the pouch.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
Keep the Genuair 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 unit doses.
Carton containing 1 inhaler with 60 unit doses.
Carton containing 3 inhalers each with 60 unit doses.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal 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 parts of your Genuair inhaler

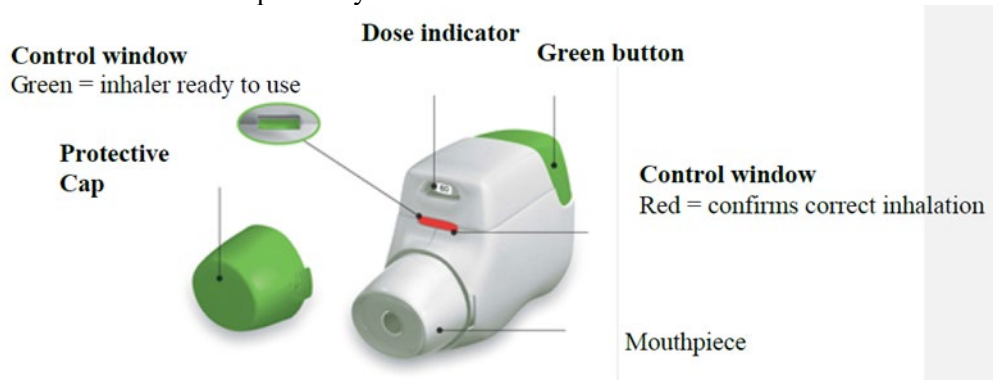


Figure A

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).

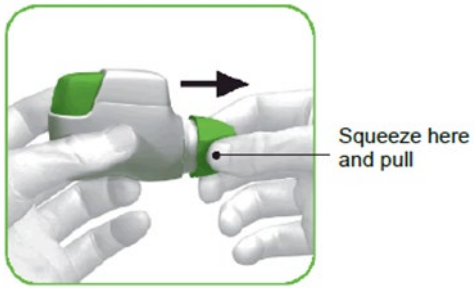


Figure B

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).

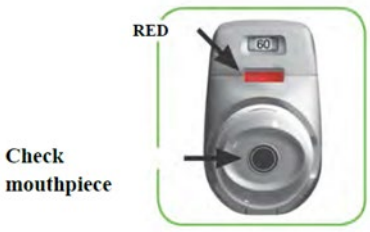


Figure C

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.

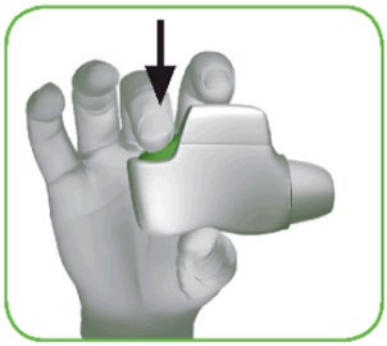
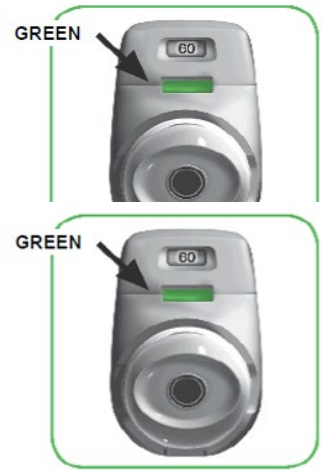


Figure E

Figure F

Stop and Check:



indow is now green (Figure G).

e inhaled.

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

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

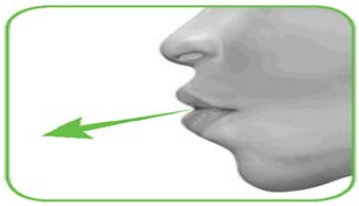


Figure I

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

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 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

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 correctly. If that 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 you have been unable to inhale correctly after repeated attempts.

Push the cap back onto the mouthpiece after each use (Figure M).

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.

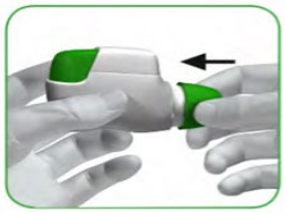


Figure M

Additional information

What should you do if you accidently 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).

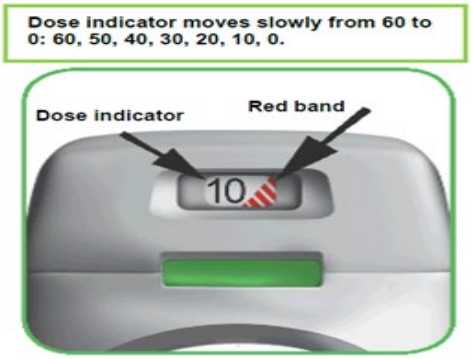


Figure N

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.

MANUFACTURER:
Industrias Farmaceuticas Almirall S.A., Spain

7. REGISTRATION HOLDER:
AstraZeneca (Israel) Ltd.
1 Atirei Yeda St., Kfar Saba 4464301.

Registration number: 151 70 33997