

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Eklira Genuair 322 micrograms inhalation powder

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 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

Eklira Genuair is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) (see section 5.1).

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 acclidinium bromide or to the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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:

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:

Cardiac arrhythmias, including atrial fibrillation and paroxysmal tachycardia were seen after the administration of Eklira Genuair (see section 4.8). Therefore, Eklira Genuair should be used with caution in patients with cardiac arrhythmias, a history of cardiac arrhythmias or with risk factors for cardiac arrhythmias.

Experience in patients with cardiovascular comorbidities in clinical trials is limited (see section 5.1). 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, total 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 foetotoxicity 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/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 Eklira 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 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 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 or on post-marketing study results.

A placebo-controlled trial in 1791 patients with moderate to very severe COPD treated with Eklira Genuair up to 36 months did not identify other adverse reactions.

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	Cardiac arrhythmias, including atrial fibrillation and paroxysmal tachycardia	Uncommon
	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

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 HPRA Pharmacovigilance, Website: www.hpra.ie

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 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 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 [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.

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 and safety

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 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 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; $p=0.0149$).

Long Term Safety and Efficacy Trial up to 3 years

The effect of aclidinium bromide on the occurrence of major adverse cardiovascular events (MACE) was assessed in a randomised, double-blind, placebo-controlled, parallel-group study in 3630 adult patients between 40 and 91 years of age with moderate to very severe COPD, treated for up to 36 months. 58.7% were male and 90.7% were Caucasian, with a mean postbronchodilator FEV1 of 47.9% of predicted value and a mean CAT (COPD Assessment Test) of 20.7. All patients had a history of cardiovascular or cerebrovascular disease and/or significant cardiovascular risk factors. 59.8% of patients had at least one COPD exacerbation within the past 12 months from the screening visit. Approximately 48% of enrolled patients had a prior history of at least 1 documented previous cardiovascular event; cerebrovascular disease (13.1%), coronary artery disease (35.4%), peripheral vascular disease or history of claudication (13.6%).

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

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

The rate of moderate or severe COPD exacerbations per patient per year during the first year of treatment was evaluated as the primary efficacy endpoint in the study. Patients treated with Eklira Genuair showed a statistically significant reduction of 22% compared to placebo (rate ratio [RR] 0.78; 95% CI 0.68 to 0.89; $p<0.001$). In addition, Eklira Genuair showed a statistically significant reduction of 35% in the rate of hospitalisations due to COPD exacerbations while on-treatment during the first year compared with placebo (RR 0.65; 95% CI 0.48 to 0.89; $p=0.006$).

The Eklira Genuair group showed a statistically significant delay in the time to first moderate or severe exacerbation while on-treatment compared to the placebo group. Patients in the aclidinium bromide group had a 18% relative reduction of the risk of an exacerbation (HR 0.82; 95% CI [0.73, 0.92], $p<0.001$).

Exercise tolerance

In a 3-week crossover, randomised, placebo-controlled clinical study 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

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 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, carcinogenic potential, and toxicity to reproduction and development.

Effects in nonclinical studies with respect to cardiovascular parameters (increased heart rates in dogs), reproductive toxicity (foetotoxic 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

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.

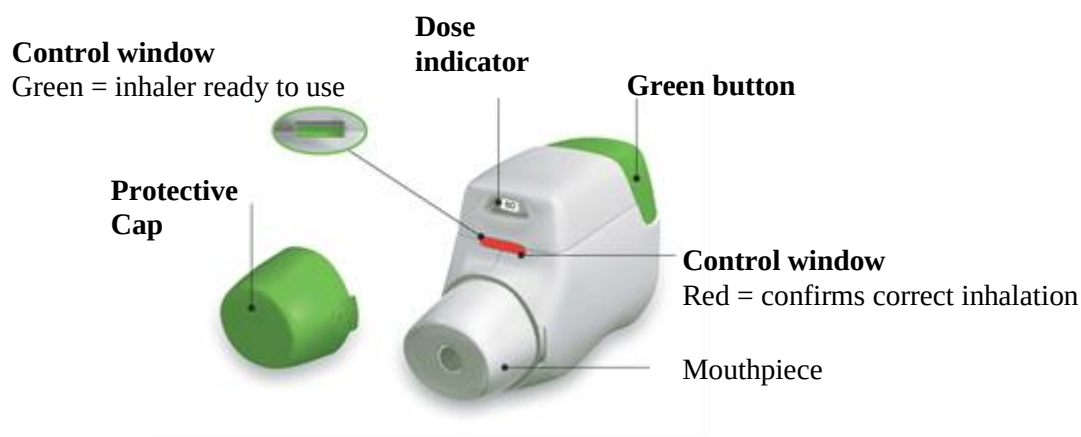


Figure A

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).

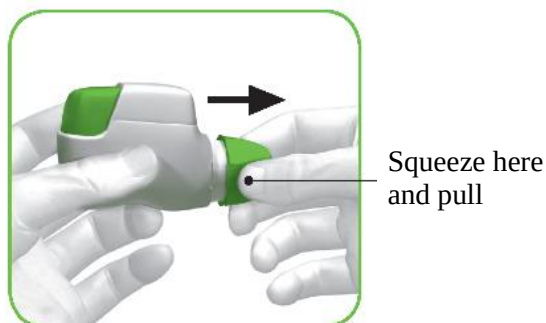


Figure B

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).

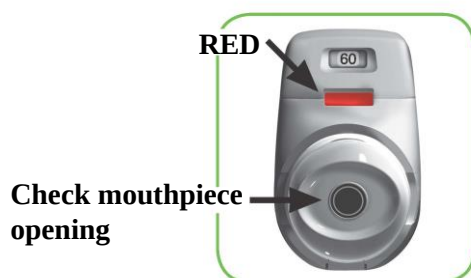


Figure C

- 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).

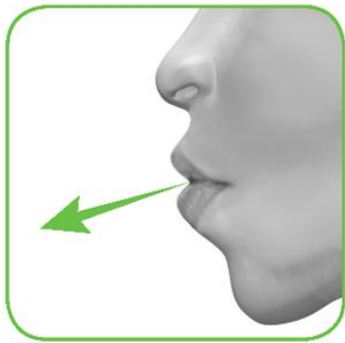


Figure I

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.

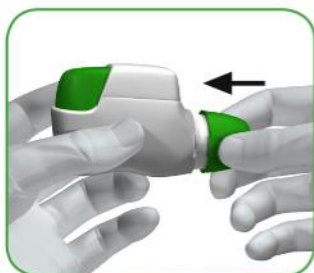


Figure M

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.

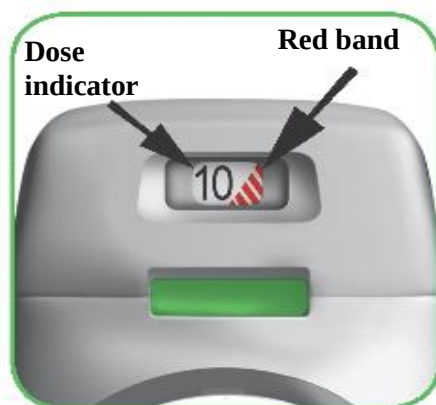


Figure N

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

Covis Pharma Europe B.V.
Gustav Mahlerplein 2
1082MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/778/001
EU/1/12/778/002
EU/1/12/778/003

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

20th February 2025

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