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

Duaklir Genuair 340 micrograms /12 micrograms inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose leaving the mouthpiece) contains 396 micrograms of aclidinium bromide (equivalent to 340 micrograms of aclidinium) and 11.8 micrograms of formoterol fumarate dihydrate. This corresponds to a metered dose of 400 micrograms of aclidinium bromide (equivalent to 343 micrograms of aclidinium) and a metered dose of 12 micrograms of formoterol fumarate dihydrate.

Excipients with known effect:
Each delivered dose contains approximately 11 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 turquoise dosage button.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Duaklir 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 Duaklir Genuair 340 micrograms /12 micrograms twice daily.

If a dose is missed, it should be taken as soon as possible and the next dose should be taken at the usual time. A double dose should not be taken to make up for a forgotten dose.

Elderly population
No dose adjustments are required in elderly patients (see section 5.2).

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

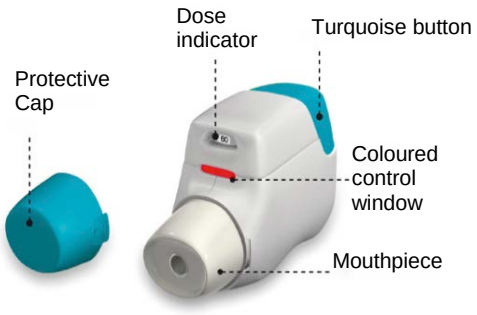
Hepatic impairment
No dose adjustments are required in patients with hepatic impairment (see section 5.2).

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

Method of administration
For inhalation use.

Patients should be instructed on how to administer the product correctly. For detailed instructions, please refer to the patient leaflet. Patients should be advised to carefully read them.

Overview of the instructions for use of Duaklir Genuair



To use the Genuair inhaler there are 2 steps patients need to perform after removing the cap. Patients should hold the Genuair inhaler horizontally with the mouthpiece towards them and the turquoise button facing straight up.

STEP 1: Patients should **PRESS** the turquoise button all the way down (image 1) and then **RELEASE** it (image 2).

Remind patients NOT TO CONTINUE TO HOLD THE TURQUOISE BUTTON DOWN.

Patients should check that the control window is green. It means the inhaler is ready to use (image 3).

IMAGE 1 IMAGE 2 IMAGE 3

IF THE COLOURED CONTROL WINDOW IS RED, PATIENTS SHOULD REPEAT PRESS AND RELEASE ACTIONS (SEE STEP 1).

STEP 2: Patients should inhale **STRONGLY** and **DEEPLY** through the mouthpiece (image 4). Patients should keep breathing in, even after they have heard the inhaler "click".

• Patients should check that the control window has turned to red from green, which indicates they have inhaled correctly (image 5).

IMAGE 4

IMAGE 5

IF THE COLOURED CONTROL WINDOW IS STILL GREEN, PATIENTS SHOULD REPEAT INHALING STRONGLY AND DEEPLY THROUGH THE MOUTHPIECE (SEE STEP 2).

Remind patients that after removing the Genuair inhaler from their mouth they should hold their breath for as long as is comfortable, then breathe out slowly through their nose.

After inhalation, patients should remember to replace the protective cap. Some patients may experience a mild sweet or slightly bitter taste, depending on the patient, when inhaling the medicinal product. The patient should not take an extra dose if they do not taste anything after inhaling.

The Genuair inhaler has a dose indicator to show approximately how many doses are left in the inhaler. Every Genuair inhaler will deliver at least 60 doses. When a red striped band appears in the dose indicator, this means the last dose is coming up and a new Genuair inhaler should be obtained. When the last dose has been prepared for inhalation, the turquoise button will not return to its full upper position, but will be locked in a middle position. The last dose may still be inhaled, but after that the Genuair inhaler cannot be used again and the patient should start using a new Genuair inhaler.

The Genuair inhaler does not require cleaning but if necessary the outside of the mouthpiece may be wiped with a dry tissue or paper towel. Remind the patient NEVER to use water to clean the Genuair inhaler, as this may damage the medicinal product.

4.3 Contraindications

Hypersensitivity to the active substances or to the excipient listed in section 6.1.

4.4 Special warnings and precautions for use

Asthma
Duaklir Genuair should not be used in asthma; clinical studies of Duaklir Genuair in asthma have not been conducted.

Paradoxical bronchospasm
In clinical studies, paradoxical bronchospasm was not observed with Duaklir Genuair at its recommended dose. However, paradoxical bronchospasm has been observed with other inhalation therapies. If this occurs, medicinal product should be stopped and other treatment will be considered.

Not for acute use
Duaklir Genuair is not indicated for the treatment of acute episodes of bronchospasm.

Cardiovascular effects
Patients with a myocardial infarction during the previous 6 months, unstable angina, newly diagnosed arrhythmia within the previous 3 months, QTc (Bazett's method) above 470 msec, or hospitalisation within the previous 12 months for heart failure functional classes III and IV as per the "New York Heart Association" were excluded from the clinical studies, therefore Duaklir Genuair should be used with caution in these patients groups.

β_2-adrenergic agonists may produce increases in pulse rate and blood pressure, electrocardiogram (ECG) changes such as T wave flattening, ST segment depression and prolongation of the QTc-interval in some patients. In case such effects occur, treatment may need to be discontinued. Long-acting β_2-adrenergic agonists should be used with caution in patients with history of or known prolongation of the QTc-interval or treated with medicinal products affecting the QTc interval (see section 4.5).

Systemic effects
Duaklir Genuair should be used with caution in patients with severe cardiovascular disorders, convulsive disorders, thyrotoxicosis and phaeochromocytoma.

Metabolic effects of hyperglycaemia and hypokalaemia may be observed with high doses of β_2-adrenergic agonists. In Phase III clinical studies, the frequency of notable increases in blood glucose with Duaklir Genuair was low (0.1%) and similar to placebo. Hypokalaemia is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see section 4.5). Hypokalaemia increases susceptibility to cardiac arrhythmias.

Due to its anticholinergic activity, Duaklir Genuair should be used with caution in patients with symptomatic prostatic hyperplasia, urinary retention or narrow-angle glaucoma (even though direct contact of the product with the eyes is very unlikely). Dry mouth, which has been observed with anticholinergic treatment, may in the long term be associated with dental caries.

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

4.5 Interaction with other medicinal products and other forms of interaction

COPD medicinal products
Co-administration of Duaklir Genuair with other anticholinergic and/or long-acting β_2-adrenergic agonist containing medicinal products has not been studied and is not recommended.

Although no formal *in vivo* drug interaction studies have been performed with Duaklir Genuair, it has been used concomitantly with other COPD medicinal products including short-acting β_2-adrenergic bronchodilators, methylxanthines, and oral and inhaled steroids without clinical evidence of drug interactions.

Metabolic interactions
In vitro studies have shown that aclidinium or its metabolites at the therapeutic dose are not expected to cause interactions with P-glycoprotein (P-gp) substrate drugs or drugs metabolised by cytochrome P450 (CYP450) enzymes and esterases. Formoterol does not inhibit the CYP450 enzymes at therapeutically relevant concentrations (see section 5.2).

Hypokalaemic treatment
Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of β_2-adrenergic agonists, therefore caution is advised in their concomitant use (see section 4.4).

β-adrenergic blockers
β -adrenergic blockers may weaken or antagonise the effect of β_2-adrenergic agonists. If β-adrenergic blockers are required (including eye drops), cardioselective beta-adrenergic blockers are preferred, although they should also be administered with caution.

Other pharmacodynamic interactions
Duaklir Genuair should be administered with caution to patients being treated with medicinal products known to prolong the QTc interval such as monoamine oxidase inhibitors, tricyclic antidepressants, antihistamines or macrolides because the action of formoterol, a component of Duaklir Genuair, on the

cardiovascular system may be potentiated by these medicinal products. Medicinal products that are known to prolong the QTc interval are associated with an increased risk of ventricular arrhythmias.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data available on the use of Duaklir Genuair in pregnant women.

Studies in animals have shown fetotoxicity only at dose levels much higher than the maximum human exposure to aclidinium and adverse effects in reproduction studies with formoterol at very high systemic exposure levels (see section 5.3).

Duaklir Genuair should only be used during pregnancy if the expected benefits outweigh the potential risks.

Breast-feeding
It is unknown whether aclidinium (and/or its metabolites) or formoterol are excreted in human milk. As studies in rats have shown excretion of small amounts of aclidinium (and/or its metabolites) and formoterol into milk, the use of Duaklir Genuair by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

Fertility
Studies in rats have shown slight reductions in fertility only at dose levels much higher than the maximum human exposure to aclidinium and formoterol (see section 5.3). Nevertheless, it is considered unlikely that Duaklir Genuair administered at the recommended dose will affect fertility in humans.

4.7 Effects on ability to drive and use machines

Duaklir Genuair has no or negligible influence on the ability to drive and use machines. The occurrence of blurred vision or dizziness may influence the ability to drive or to use machines.

4.8 Undesirable effects

The presentation of the safety profile is based on the experience with Duaklir Genuair and the individual components.

Summary of the safety profile
The safety experience with Duaklir Genuair comprised exposure at the recommended therapeutic dose for up to 12 months.

Adverse reactions associated with Duaklir Genuair were similar to those of the individual components. As Duaklir Genuair contains aclidinium and formoterol, the type and severity of adverse reactions associated with each of the components may be expected with Duaklir Genuair.

The most frequently reported adverse reactions with Duaklir Genuair were nasopharyngitis (7.9%) and headache (6.8%).

Tabulated summary of adverse reactions
The Duaklir Genuair clinical development programme was conducted in patients with moderate or severe COPD. A total of 1222 patients were treated with Duaklir Genuair 340 micrograms /12 micrograms. The frequencies assigned to the adverse reactions are based on crude incidence rates observed with Duaklir Genuair 340 micrograms /12 micrograms in the pooled analysis of randomised, placebo-controlled Phase III clinical studies of at least six months duration.

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

System organ class	Preferred term	Frequency
Infectious and infestations	Nasopharyngitis[3] Urinary tract infection[1] Sinusitis[2] Tooth abscess[1]	Common
Immune system disorders	Hypersensitivity[4]	Rare
	Angioedema[4]	Not known
Metabolism and nutrition disorders	Hypokalaemia[3]	Uncommon
	Hyperglycaemia[3]	Uncommon
Psychiatric disorders	Insomnia[2] Anxiety[2]	Common
	Agitation[3]	Uncommon
Nervous system disorders	Headache[3] Dizziness[3] Tremor[2]	Common
	Dysgeusia[3]	Uncommon
Eye disorders	Blurred vision[2]	Uncommon
Cardiac disorders	Tachycardia[2] Electrocardiogram QTc prolonged[2] Palpitations[3]	Uncommon
Respiratory, Thoracic and mediastinal disorders	Cough[3]	Common
	Dysphonia[2] Throat irritation[3]	Uncommon
	Bronchospasm, including paradoxical[4]	Rare
Gastrointestinal disorders	Diarrhoea[3] Nausea[3] Dry mouth[2]	Common
Skin and subcutaneous tissue disorders	Rash[3] Pruritus[3]	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia[2] Muscle spasms[2]	Common
Renal and urinary disorders	Urinary retention[3]	Uncommon
General disorders and administration site conditions	Oedema peripheral[3]	Common
Investigations	Blood creatine phosphokinase increased[1]	Common
	Blood pressure increased[3]	Uncommon

[1] Adverse reactions observed with Duaklir Genuair, but not reported in the SmPC of the individual components

[2] Adverse reactions observed with Duaklir Genuair and reported in the SmPC of at least one of the individual components

[3] Adverse reactions reported in the SmPC of at least one of the individual components, but reported with Duaklir Genuair 340/12 micrograms at an incidence lower than or comparable to that of placebo.

[4] Adverse reactions reported in the SmPC of at least one of the individual components, but not observed with Duaklir Genuair 340/12 micrograms; frequency category according to section 4.8 of Summary of Product Characteristics of the individual components.

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

There is limited evidence on the management of overdose with Duaklir Genuair. High doses of Duaklir Genuair may lead to exaggerated anticholinergic and/or β_2-adrenergic signs and symptoms; the most frequent of which include blurred vision, dry mouth, nausea, muscle spasm, tremor, headache, palpitations and hypertension.

DUAKLIR Genuair should be discontinued in case of overdose. Supportive and symptomatic treatment is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics, ATC code: R03AL05

Mechanism of action
Duaklir Genuair contains two bronchodilators: aclidinium is a long-acting muscarinic antagonist (also known as an anticholinergic) and formoterol is a long-acting β_2-adrenergic agonist. The combination of these substances with different mechanisms of action results in additive efficacy compared to that achieved with either component alone. As a consequence of the differential density of muscarinic receptors and β_2-adrenoceptors in the central and peripheral airways of the lung, muscarinic antagonists should be more effective in relaxing central airways and β_2-adrenergic agonists should be more effective in relaxing peripheral airways; relaxation of both central and peripheral airways with combination treatment may contribute to its beneficial effects on lung function. Further information regarding these two substances is provided below.

Aclidinium is a competitive, selective muscarinic receptor antagonist, 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. Aclidinium has also been shown to provide benefits to patients with COPD in terms of symptoms reduction, improvement in disease-specific health status, reduction in exacerbation rates and improvements in exercise tolerance. Since aclidinium bromide is quickly broken down in plasma, the level of systemic anticholinergic undesirable effects is low.

Formoterol is a potent selective β_2-adrenoceptor agonist. Bronchodilation is induced by causing direct relaxation of airway smooth muscle as a consequence of the increase in cyclic AMP through activation of adenylate cyclase. In addition to improving pulmonary function, formoterol has been shown to improve symptoms and quality of life in patients with COPD.

Pharmacodynamic effects
Clinical efficacy studies showed that Duaklir Genuair provides clinically meaningful improvements in lung function (as measured by the forced expiratory volume in 1 second [FEV_1]) over 12 hours following administration.

Duaklir Genuair demonstrated a rapid onset of action within 5 minutes of the first inhalation relative to placebo ($p<0.0001$). The onset of action of Duaklir Genuair was comparable to the effect of the fast-acting

β_2-agonist formoterol 12 micrograms. Maximal bronchodilator effects (peak FEV_1) relative to baseline were evident from day one (304 ml) and were maintained over the 6-month treatment period (326 ml).

Cardiac electrophysiology
No clinically relevant effects of Duaklir Genuair on ECG parameters (including QT-interval) compared with aclidinium, formoterol and placebo were seen in Phase III studies of 6 to 12 months duration conducted in approximately 4,000 patients with COPD. No clinically significant effects of Duaklir Genuair on cardiac rhythm were observed on 24-hour Holter monitoring in a subset of 551 patients, of whom 114 received Duaklir Genuair twice daily.

Clinical Efficacy and Safety
The Phase III clinical development programme included approximately 4,000 patients with a clinical diagnosis of COPD and comprised two 6-month randomised, placebo- and active-controlled studies (ACLIFORM-COPD and AUGMENT), a 6-month extension of the AUGMENT study and a further 12-month randomised controlled study. During these studies, patients were permitted to continue their stable treatment with inhaled corticosteroids, low doses of oral corticosteroids, oxygen therapy (if less than 15h/day) or methylxanthines and to use salbutamol as rescue medication.

Efficacy was assessed by measures of lung function, symptomatic outcomes, disease-specific health status, rescue medication use, and exacerbations. In long-term safety studies, Duaklir Genuair was associated with sustained efficacy when administered over a one-year treatment period with no evidence of tachyphylaxis.

Effects on lung function
Duaklir Genuair 340/12 micrograms twice daily consistently provided clinically meaningful improvements in lung function (as assessed by FEV_1, forced vital capacity and inspiratory capacity) compared with placebo. In Phase III studies, clinically meaningful bronchodilator effects were seen within 5 minutes of the first dose and were maintained over the dosing interval. There was a sustained effect over time in the six months and one year Phase III studies.

FEV_1 at 1 hour post-dose and trough FEV_1 (compared to aclidinium 400 micrograms and formoterol 12 micrograms, respectively) were defined as co-primary endpoints in both 6-month pivotal Phase III studies to demonstrate the bronchodilator contributions of formoterol and aclidinium in Duaklir Genuair, respectively.

In study ACLIFORM-COPD, Duaklir Genuair showed improvements in FEV_1 at 1 hour post-dose relative to placebo and aclidinium of 299 ml and 125 ml, respectively (both $p<0.0001$) and improvements in trough FEV_1 relative to placebo and formoterol of 143 ml and 85 ml, respectively (both $p<0.0001$). In study AUGMENT, Duaklir Genuair showed improvements in FEV_1 at 1 hour post-dose relative to placebo and aclidinium of 284 ml and 108 ml (both $p<0.0001$), respectively, and improvements in trough FEV_1 relative to placebo and formoterol of 130 ml ($p<0.0001$) and 45 ml ($p=0.01$), respectively.

Symptom relief and disease-specific health status benefits

Breathlessness and other symptomatic outcomes:
Duaklir Genuair provided a clinically meaningful improvement in breathlessness (assessed by the Transition Dyspnoea Index [TDI]) with an improvement in the TDI focal score at 6 months compared to placebo of 1.29 units in study ACLIFORM-COPD ($p<0.0001$) and 1.44 units in study AUGMENT ($p<0.0001$). The percentages of patients with clinically meaningful improvements in TDI focal score (defined as an increase of at least 1 unit) were higher with Duaklir Genuair than with placebo in ACLIFORM-COPD (64.8% compared to 45.5%; $p<0.001$) and AUGMENT (58.1% compared to 36.6%; $p<0.0001$).

The pooled analysis of these two studies showed Duaklir Genuair to be associated with statistically significantly greater improvements in TDI focal score compared to aclidinium (0.4 units, $p=0.016$) or formoterol (0.5 units, $p=0.009$). In addition, a higher percentage of patients receiving Duaklir Genuair responded with a clinically meaningful improvement in TDI focal score compared to either aclidinium or formoterol (61.9% compared to 55.7% and 57.0%, respectively; $p=0.056$ and $p=0.100$, respectively).

Duaklir Genuair improved daily symptoms of COPD such as 'breathlessness', 'chest symptoms', 'cough and sputum' (assessed by E-RS total score) as well as overall night-time symptoms, overall early morning symptoms and symptoms limiting early morning activities compared to placebo, aclidinium and formoterol but the improvements were not always statistically significant. Aclidinium/formoterol did not statistically significantly reduce the average number of night-time awakenings due to COPD compared with placebo or formoterol.

Health-related quality of life:
Duaklir Genuair provided a clinically meaningful improvement in disease-specific health status (as assessed by the St. George's Respiratory Questionnaire [SGRQ]) in study AUGMENT, with an improvement in the SGRQ total score compared to placebo of -4.35 units ($p<0.0001$). The percentage of patients in AUGMENT who achieved a clinically meaningful improvement from baseline in SGRQ total score (defined as a decrease of at least 4 units) was higher with Duaklir Genuair than with placebo (58.2% compared to 38.7%, respectively; $p<0.001$). In study ACLIFORM-COPD, only a small decrease in SGRQ total score compared to placebo was observed due to an unexpectedly large placebo response ($p=0.598$) and the percentages of patients who achieved clinically meaningful improvements from baseline were 55.3% with Duaklir Genuair and 53.2% with placebo ($p=0.669$).

In the pooled analysis of these two studies, Duaklir Genuair showed greater improvements in SGRQ total score compared to formoterol (-1.7 units; $p=0.018$) or aclidinium (-0.79 units, $p=0.273$). In addition, a higher percentage of patients receiving Duaklir Genuair responded with a clinically meaningful improvement in SGRQ total score compared to aclidinium and formoterol (56.6% compared to 53.9% and 52.2%, respectively; $p=0.603$ and $p=0.270$, respectively).

COPD exacerbation reductions
Pooled efficacy analysis of the two 6-month Phase III studies demonstrated a statistically significant reduction of 29% in the rate of moderate or severe exacerbations (requiring treatment with antibiotics or corticosteroids or resulting in hospitalisations) with Duaklir Genuair compared to placebo (rates per patient per year: 0.29 vs. 0.42, respectively; $p=0.036$).

In addition, Duaklir Genuair statistically significantly delayed the time to first moderate or severe exacerbation compared to placebo (hazard ratio=0.70; $p=0.027$).

Use of rescue medication
Duaklir Genuair reduced the use of rescue medication over 6 months compared to placebo (by 0.9 puffs per day [$p<0.0001$]), aclidinium (by 0.4 puffs/day [$p<0.001$]) and formoterol (by 0.2 puffs/day [$p=0.062$]).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Duaklir Genuair in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

When aclidinium and formoterol were administered in combination by the inhaled route, the pharmacokinetics of each component showed no relevant differences from those observed when the medicinal products were administered separately.

Absorption
Following inhalation of a single dose of Duaklir Genuair 340/12 micrograms, aclidinium and formoterol were rapidly absorbed into plasma, reaching peak plasma concentrations within 5 minutes of inhalation in healthy subjects and within 24 minutes of inhalation in patients with COPD. The peak plasma concentrations at steady state of aclidinium and formoterol observed in patients with COPD treated with Duaklir Genuair twice daily for 5 days were reached within 5 minutes post-inhalation and were 128 pg/ml and 17 pg/ml, respectively.

Distribution
Whole lung deposition of inhaled aclidinium via Genuair averaged approximately 30% of the metered dose. The plasma protein binding of aclidinium determined *in vitro* most likely corresponded to the protein binding of the metabolites due to the rapid hydrolysis of aclidinium 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 is albumin.

The plasma protein binding of formoterol is 61% to 64% (34% primarily to albumin). There is no saturation of binding sites in the concentration range reached with therapeutic doses.

Biotransformation
Aclidinium is rapidly and extensively hydrolysed to its pharmacologically inactive alcohol- and carboxylic acid-derivatives. 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 hydrolysis occurs both chemically (non-enzymatically) and enzymatically by esterases, butyrylcholinesterase being the main human esterase involved in the hydrolysis. The low absolute bioavailability of inhaled aclidinium (<5%) is because aclidinium 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. *In vitro* studies have shown that aclidinium 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 or its metabolites are not substrates or inhibitors of P-glycoprotein.

Formoterol is eliminated primarily by metabolism. The prominent pathway involves direct glucuronidation, with O-demethylation followed by glucuronide conjugation being a further metabolic pathway. Cytochrome P450 isoenzymes CYP2D6, CYP2C19, CYP2C9 and CYP2A6 are involved in the O-demethylation of formoterol. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

Elimination
Following inhalation of Duaklir Genuair 340/12 micrograms , aclidinium and formoterol showed terminal elimination half-lives of approximately 5 h and 8 h, respectively.

Following intravenous administration of radiolabelled aclidinium 400 micrograms 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 aclidinium 200 micrograms and 400 micrograms by healthy subjects or patients with COPD, 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.

The major part of a dose of formoterol is transformed by liver metabolism followed by renal elimination. After inhalation, 6% to 9% of the delivered dose of formoterol is excreted in the urine unchanged or as direct conjugates of formoterol.

Special populations
Elderly patients
No pharmacokinetics studies have been performed with aclidinium/formoterol in elderly subjects. Since no dosage adjustments are needed for either aclidinium or formoterol medicinal products in elderly patients, no dosage adjustment is warranted for aclidinium/formoterol in geriatric patients.

Renally and hepatically impaired patients
There are no data regarding the specific use of aclidinium/formoterol in patients with renal or hepatic impairment. Since no dosage adjustments are needed for either aclidinium or formoterol medicinal products in patients with renal or hepatic impairment, no dosage adjustment is warranted for aclidinium/formoterol.

5.3 Preclinical safety data

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

Effects of aclidinium in nonclinical studies with respect to reproductive toxicity (fetotoxic effects) and fertility (slight decreases in conception rate, number of corpora lutea, and pre- and post-implantation losses) were observed only at exposures considered sufficiently in excess of the maximum human exposure indication to be of little relevance to clinical use.

Formoterol showed reduced fertility (implantation losses) in rats, as well as decreased early postnatal survival and birth weight with high systemic exposure to formoterol. A slight increase in the incidence of uterine leiomyomas has been observed in rats and mice; an effect which is considered to be a class-effect in rodents after long-term exposure to high doses of β_2-adrenoreceptor agonists.

Nonclinical studies investigating the effects of aclidinium/formoterol on cardiovascular parameters showed increased heart rates and arrhythmias at exposures sufficiently in excess of the maximum human exposure indication to be of little relevance to clinical use. These effects are known exaggerated pharmacological responses observed with β_2-agonists.

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 60 days of opening the pouch.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

The Genuair inhaler is a multicomponent device made of plastic (polycarbonate, acrylonitrile-butadiene-styrene, polyoxymethylene, polyester-butylene-terephthalate, polypropylene, polystyrene) and stainless steel. It is white-coloured with an integral dose indicator and a turquoise dosage button. The mouthpiece is covered with a removable turquoise protective cap. The inhaler is supplied sealed in a protective aluminium laminate pouch containing a desiccant sachet, placed in a cardboard carton.

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.

For instructions for use please see section 4.2.

7. MARKETING AUTHORISATION HOLDER

Almirall, S.A.
Ronda General Mitre, 151
E-08022 Barcelona
Spain
Tel. +34 93 291 30 00
Fax +34 93 291 31 80

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/964/001
EU/1/14/964/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer 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

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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

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

Description	Due date
Submission of the results of the agreed drug utilisation study (DUS) and post-authorisation safety study (PASS) for aclidinium bromide to evaluate the overall mortality and the proposed cardiovascular safety endpoints (with an additional endpoint of cardiac arrhythmia) among patients with COPD using aclidinium/formoterol, according to a protocol agreed by the PRAC.	Q3 2018

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Duaklir Genuair 340/12 micrograms inhalation powder
Aclidinium/Formoterol fumarate dihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 396 micrograms aclidinium bromide (equivalent to 340 micrograms of aclidinium) and 11.8 micrograms of formoterol fumarate dihydrate.

3. LIST OF EXCIPIENTS

Also contains: Lactose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

1 inhaler containing 60 doses
3 inhalers each containing 60 doses

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before 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 60 days of opening pouch.

9. SPECIAL STORAGE CONDITIONS

Keep the Genuair inhaler protected inside the sealed 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

Almirall, S.A.
Ronda General Mitre, 151
E-08022 Barcelona
Spain
(logo)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/964/001	1 inhaler with 60 doses
EU/1/14/964/002	3 inhalers each with 60 doses

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

duaklir genuair

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ALUMINIUM POUCH

1. NAME OF THE MEDICINAL PRODUCT

Duaklir Genuair 340/12 micrograms inhalation powder
Aclidinium/Formoterol fumarate dihydrate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Almirall, S.A. (logo)

3. EXPIRY DATE

EXP

To be used within 60 days of opening the pouch.

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

5. OTHER

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

[arrow] Tear here

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INHALER LABEL

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

Duaklir Genuair 340/12 mcg inhalation powder
Aclidinium/Formoterol fumarate dihydrate

2. METHOD OF ADMINISTRATION

Inhalation use

3. EXPIRY DATE

To be used within 60 days of opening the pouch.
EXP

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 doses

6. OTHER

Almirall, S.A. (logo)

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Duaklir Genuair 340 micrograms /12 micrograms inhalation powder
aclidinium/formoterol fumarate dihydrate

▼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 Duaklir Genuair is and what it is used for

What Duaklir Genuair is
This medicine contains two active ingredients called aclidinium and formoterol fumarate dihydrate. Both belong to a group of medicines called bronchodilators. Bronchodilators relax the muscles in your airways, which allows the airways to open more widely and helps you to breathe more easily. The Genuair inhaler delivers the active ingredients directly into your lungs as you breathe in.

What Duaklir Genuair is used for
Duaklir Genuair is used for adult patients who have breathing difficulties due to a lung disease called chronic obstructive pulmonary disease (COPD), in which the airways and air sacs in the lungs become damaged or blocked. By opening the airways, the medicine helps relieve symptoms such as shortness of breath. Taking Duaklir Genuair regularly will help to minimise the effects of COPD on your everyday life.

2. What you need to know before you use Duaklir Genuair

Do not use Duaklir Genuair:
- if you are allergic to aclidinium, formoterol fumarate dihydrate or to the other ingredient of this medicine, lactose (see section 2 under “Duaklir Genuair contains lactose”).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Duaklir Genuair, if you have any of the following conditions/symptoms:
- If you have asthma. This medicine should not be used for the treatment of asthma.
- If you have heart problems.
- If you have epilepsy.
- If you have thyroid gland problems (thyrotoxicosis).
- If you have a tumour in one of your adrenal glands (phaeochromocytoma).

- If you have difficulty passing urine or problems due to an enlarged prostate.
- If you have an eye condition called narrow angle glaucoma, which results in high pressure in the eye.

Stop taking Duaklir Genuair and seek medical help immediately if you experience any of the following:
- If you have sudden difficulty in breathing or swallowing, if you have swelling of the tongue, throat, lips or face, or a skin rash and/or itching. These may be signs of an allergic reaction.
- If you get sudden tightness of the chest, coughing, wheezing or breathlessness immediately after using the medicine. These may be signs of a condition called " paradoxical bronchospasm", which is an excessive and prolonged contraction of the airway muscles immediately following treatment with a bronchodilator.

Duaklir Genuair is used as a maintenance (long-term) treatment for COPD. You should not use this medicine to treat a sudden attack of breathlessness or wheezing.

If your usual COPD symptoms (breathlessness, wheezing, cough) do not improve or get worse while you are using Duaklir Genuair you should continue to use it, but go to see your doctor as soon as possible because you may need another medicine.

If you see halos around lights or coloured images, have eye pain or discomfort or suffer temporary blurring of vision, go to see your doctor for advice as soon as possible.

Dry mouth has been observed with medicines like Duaklir Genuair. In the long-term, dry mouth can be associated with tooth decay, so it is important to pay attention to oral hygiene.

Children and adolescents
Duaklir Genuair is not for use in children or adolescents below 18 years of age.

Other medicines and Duaklir Genuair
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines,. If you use Duaklir Genuair with some other medicines, the effect of Duaklir Genuair or the other medicines may be altered.

Tell your doctor or pharmacist if you are taking:
- Any medicines that may be similar to Duaklir Genuair to treat breathing difficulties.
- Medicines that lower the amount of potassium in your blood. These include:
    - corticosteroids that you take by mouth (such as prednisolone),
    - diuretics (such as furosemide or hydrochlorothiazide),
    - certain medicines used to treat breathing conditions (such as theophylline).
- Medicines called beta blockers that may be used to treat high blood pressure or other heart problems (such as atenolol or propranolol) or to treat glaucoma (such as timolol).
- Medicines which can cause a type of change in the electrical activity of the heart known as QT interval prolongation (observed in an electrocardiogram). These include medicines for the treatment of:
    - depression (such as monoamine oxidase inhibitors or tricyclic antidepressants),
    - bacterial infections (such as erythromycin, clarithromycin, telithromycin),
    - allergic reactions (anti-histamines).

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, nurse or pharmacist for advice before using this medicine. You should not use Duaklir Genuair if you are pregnant or are breast-feeding unless your doctor tells you to do so.

Driving and using machines
Duaklir Genuair is unlikely to affect your ability to drive or use machines. In some patients, this medicine may cause blurred vision or dizziness. If you are affected by either of these side effects, do not drive or use machines until the dizziness has cleared or your vision has returned to normal.

Duaklir Genuair contains lactose
This medicine 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 Duaklir 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 Duaklir Genuair last for 12 hours; therefore, you should try to use Duaklir Genuair at the same time each morning and evening as this will ensure that there is always enough medicine in your body to help you breathe more easily throughout the day and night. Taking your medicine at regular times will also help you to remember to use it.
- **Instructions for use:** Refer to section 7 at the end of the package leaflet for instructions on how to use the Genuair inhaler. If you are not sure of how to use Duaklir Genuair, contact your doctor or pharmacist.
- You can use Duaklir Genuair anytime before or after food or drink.

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

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

If you use more Duaklir Genuair than you should
If you think you may have used more Duaklir Genuair than you should, you are more likely to experience some of its side effects, such as blurred vision, dry mouth, feeling sick, shaking/tremor, headache, palpitations or an increase in blood pressure , therefore you must immediately contact your doctor or go to the nearest emergency unit. Show the packaging of Duaklir Genuair. Medical attention may be needed.

If you forget to use Duaklir Genuair
If you forget a dose of Duaklir Genuair, just take it as soon as possible and take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop using Duaklir 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.

Some side effects may be serious: if you get any of these side effects, tell your doctor immediately.

Uncommon: may affect up to 1 in 100 people
- Muscle weakness, twitching and/or abnormal heart rhythm, as these may be signs of a decrease in the amount of potassium in your blood
- Tiredness, increased thirst and/or a need to pass urine more frequently than usual, as these may be signs of an increase in the amount of sugar in your blood
- Palpitations, as these may be a sign of an unusually fast heart beat or an abnormal heart rhythm

Rare: may affect up to 1 in 1,000 people

- Tightness of the chest, coughing, wheezing or breathlessness immediately after using the medicine
- Sudden difficulty in breathing or swallowing, swelling of the tongue, throat, lips or face, skin rash and/or itching - these may be signs of an allergic reaction

Not known:frequency cannot be estimated from the available data
Swelling of the face, throat, lips or tongue (with or without difficulty breathing or swallowing), severe itchy bumps on the skin (hives) as these may be symptoms of an allergic reaction.

Other side effects which may occur while using Duaklir Genuair:

Common: may affect up to 1 in 10 people
- Combination of sore throat and runny nose – these may be signs of nasopharyngitis
- Headache
- Painful and/or frequent urination – these may be signs of a urinary tract infection
- Cough
- Diarrhoea
- A blocked, runny or stuffy nose and/or pain or a feeling of pressure in the cheeks or forehead – these may be symptoms of sinusitis
- Dizziness
- Muscle cramps
- Nausea (feeling sick)
- Difficulty sleeping
- Dry mouth
- Muscle pain
- Swelling of hands, ankles or feet
- Abscess (infection) in the tissues at the base of a tooth
- Increased blood levels of a protein found in muscle called creatine phosphokinase.
- Shaking/tremor
- Anxiety

Uncommon:
- Fast heart beat (tachycardia)
- Blurred vision
- Changes in the sound of the voice (dysphonia)
- Difficulty passing urine or a feeling that your bladder has not completely emptied (urinary retention)
- An abnormal heart trace (QT interval prolongation) potentially leading to an abnormal heart rhythm
- Distorted sense of taste (dysgeusia)
- Throat irritation
- Increased blood pressure
- Agitation
- 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 Duaklir 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, carton and inhaler pouch after “EXP”. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

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

To be used within 60 days of opening the pouch.

Do not use Duaklir 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 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 Duaklir Genuair contains
- The active substances are aclidinium bromide and formoterol fumarate dihydrate. Each delivered dose contains 396 micrograms aclidinium bromide equivalent to 340 micrograms of aclidinium and 11.8 micrograms of formoterol fumarate dihydrate.
- The other ingredient is lactose monohydrate.

What Duaklir Genuair looks like and contents of the pack
Duaklir Genuair is a white or almost white powder.
The Genuair inhaler is a white device fitted with an integral dose indicator and a turquoise dosage button. The mouthpiece is covered with a removable turquoise protective cap. It is supplied in a sealed protective aluminium pouch containing a desiccant sachet.

Pack sizes supplied:

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 and Manufacturer
Marketing Authorisation Holder:
Almirall, S.A.
Ronda General Mitre, 151
E-08022 Barcelona
Spain

Manufacturer:
Industrias Farmacéuticas Almirall, S.A.
Ctra. Nacional II, Km. 593
08740 Sant Andreu de la Barca, Barcelona
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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

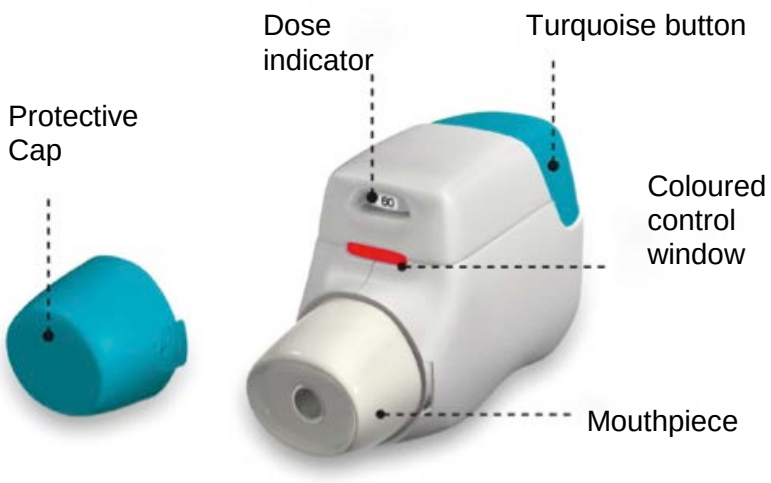
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

7. The Genuair inhaler: instructions for use

This section contains information on how to use your Genuair inhaler. A video demonstration on how to use the Genuair inhaler is also available on www.genuair.com and through the code below. If you have any questions about how to use your inhaler, please ask your doctor, pharmacist or nurse for assistance.

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

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



How to Use Duaklir Genuair

Summary

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

Step 1: Press and **RELEASE** the turquoise button and breathe out completely, away from the inhaler.
Step 2: Place your lips tightly around the mouthpiece and inhale **STRONGLY** and **DEEPLY** through the inhaler.

After inhalation, remember to replace the protective cap.

Getting Started

- Before first use, tear the sealed pouch along the notch and remove the Genuair inhaler. The pouch and desiccant should be discarded.

- When you are about to take your dose of medicine, remove the protective cap by **lightly squeezing the arrows** marked on each side and pulling outwards (see image 1).

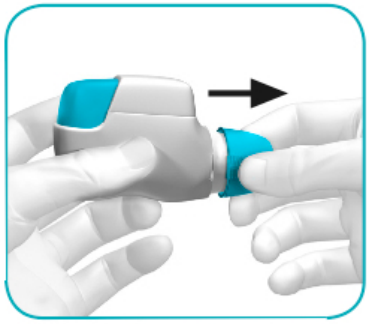


IMAGE 1

- Look to see that nothing is blocking the mouthpiece.

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

Hold with the turquoise button facing straight up. DO NOT TILT.

IMAGE 2

STEP 1: <u>PRESS</u> the turquoise button all the way down and then **RELEASE** it (see images 3 and 4).

<u>DO NOT CONTINUE TO HOLD THE TURQUOISE BUTTON DOWN.</u>

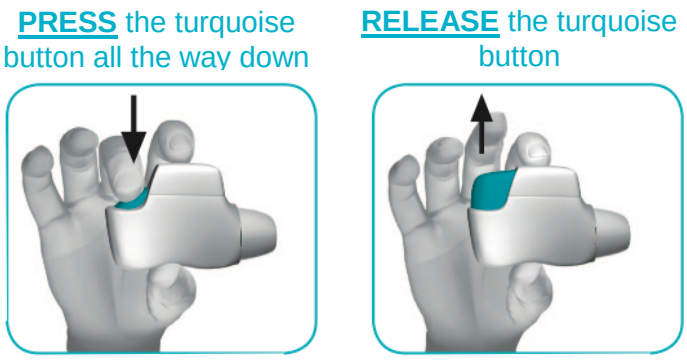


IMAGE 3 IMAGE 4

Stop and Check: Make sure dose is ready for inhalation

- Make sure the coloured control window has changed to **green** (see image 5).
- The green control window confirms that your medicine is ready for inhalation.

IMAGE 5

IF THE COLOURED CONTROL WINDOW STAYS RED, PLEASE REPEAT PRESS AND RELEASE ACTIONS (SEE STEP 1).

- Before bringing the inhaler to your mouth, breathe out completely. Do not breathe out into the inhaler.

STEP 2:

- Put your lips tightly around the mouthpiece of the Genuair inhaler and breathe in **STRONGLY** and **DEEPLY** through the mouthpiece (see image 6).
  - This strong, deep breath pulls the medicine through the inhaler into your lungs.

ATTENTION: DO NOT HOLD THE TURQUOISE BUTTON DOWN WHILE YOU ARE INHALING.

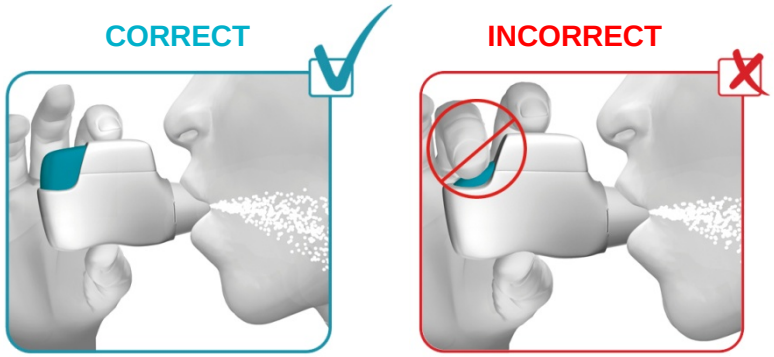


IMAGE 6

- While you breathe in you will hear a "**CLICK**" which signals that you are using the Genuair inhaler correctly.

- Keep breathing in even after you have heard the inhaler **"CLICK"** to be sure you get the full dose.

- Remove the Genuair inhaler from your mouth and hold your breath for as long as is comfortable, then breathe out slowly through your nose.

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

Stop and Check: Make sure you have inhaled correctly

- Make sure the control window has turned to **red** (see image 7). This confirms that you have inhaled your full dose correctly.

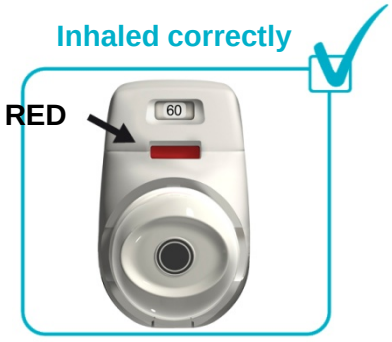


IMAGE 7

IF THE COLOURED CONTROL WINDOW IS STILL GREEN, PLEASE REPEAT INHALING STRONGLY AND DEEPLY THROUGH THE MOUTHPIECE (SEE STEP 2).

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

Make sure you have <u>RELEASED</u> the turquoise button and take a <u>STRONG</u> deep breath in through the mouthpiece.

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

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

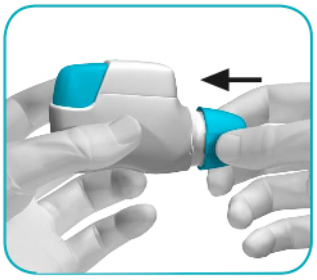


IMAGE 8

When should you get a new Genuair inhaler?

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

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

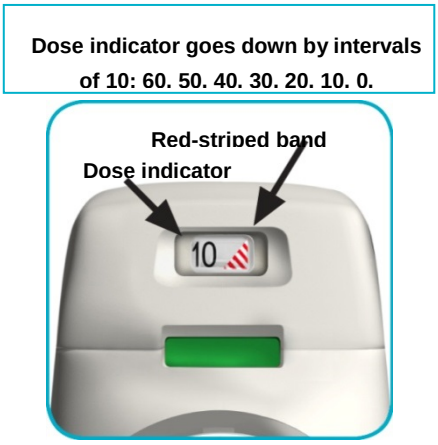


IMAGE A

Note: If your Genuair inhaler appears to be damaged or if you lose the cap, your inhaler should be replaced. You DO NOT NEED to clean your Genuair inhaler. However, if you wish to clean it you should do so by wiping the outside of the mouthpiece with a dry tissue or paper towel.

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

How do you know that your Genuair inhaler is empty?

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

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

IMAGE B