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

SUMMARY OF PRODUCT CHARACTERISTICS

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 an orange 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

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) 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 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 the active substances or to the excipients 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 in clinical trials at the recommended therapeutic dose for up to 12 months, and in post-marketing experience. 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 patient 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, or on experience with individual components.

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] Anaphylactic reaction[2]	Not known
Metabolism and nutrition disorders	Hypokalaemia[3]	Uncommon
	Hyperglycaemia[3]	Uncommon
Psychiatric disorders	Insomnia[2]	Common

	Anxiety[2]	
	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] Angina pectoris[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
	Stomatitis[3]	Uncommon
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

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 http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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 [$p=0.062$]).

Lung volumes, exercise endurance and physical activity

The effect of Duaklir Genuair on lung volumes, exercise endurance and physical activity was investigated in an 8-week parallel, randomised, placebo-controlled clinical study in COPD patients with hyperinflation (functional residual capacity [FRC] >120%).

After 4 weeks of treatment Duaklir Genuair implied improvement versus placebo in change

from baseline in morning pre-dose (trough) FRC, the primary endpoint, but the difference was not statistically significant (-0.125 L; 95% CI=(-0.259, 0.010); p=0.069*).

Duaklir Genuair showed improvements compared to placebo in lung volumes at 2-3h post dose (FRC=-0.366 L [95% CI=-0.515, -0.216; p<0.0001]; residual volume [RV]=-0.465 L [95% CI=-0.648, -0.281; p<0.0001] and inspiratory capacity [IC]= 0.293 L [95% CI=0.208, 0.378; p<0.0001]).

Duaklir Genuair also showed improvements in exercise endurance time compared to placebo after 8 weeks of treatment (55 seconds [95% CI=5.6, 104.8; p=0.0292]; baseline value: 456 seconds).

After 4 weeks of treatment, Duaklir Genuair improved the number of steps per day compared to placebo (731 steps/day; 95% CI=279, 1181; p=0.0016) and reduced the percentage of inactive patients (<6000 steps per day) [40.8% compared to 54.5%; p<0.0001]. Improvements in the PROactive total score were observed in patients treated with Duaklir Genuair compared with placebo (p=0.0002).

A behavioural intervention program was added to both treatment groups for an additional 4 weeks. The number of steps/day in the Duaklir Genuair treatment group was maintained resulting in a treatment effect compared to placebo of 510 steps/day (p=0.1588) and a reduction versus placebo in the percentage of inactive patients (<6000 steps per day) (41.5% compared to 50.4%; p=0.1134).

*As the primary endpoint did not achieve statistical significance, all p-values for secondary endpoints are tested at a nominal significance level of 0.05, and no formal statistical inference can be drawn.

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, with plasma sampling up to 24 hours post-dose, the terminal elimination half-life observed for aclidinium bromide ranged from 11-33 hours and for formoterol from 12-18 hours

Mean effective half-lives* observed for both aclidinium and formoterol (based on the accumulation ratio) are approximately 10 hours.
**Half-life consistent with product accumulation based on a known dose regimen.*

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.

Race
Following repeated inhalations of Duaklir Genuair 340/12 micrograms, the systemic exposure of aclidinium and formoterol, as measured by AUC, is similar in Japanese and Caucasian patients

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

The expiry date of the product is indicated on the packaging materials
To be used within 60 days of opening the pouch.

6.4 Special precautions for storage

Store below 30 °C
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 an orange dosage button. The mouthpiece is covered with a removable orange 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.

Instructions for Use

Getting Started

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

Become familiar with the parts of Genuair inhaler.

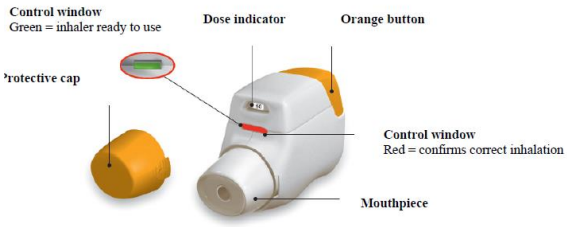

Figure A

Before use:

a) Before first use, tear open the sealed bag and remove the inhaler. Throw away the bag and the desiccant.

b) Do not press the orange 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).

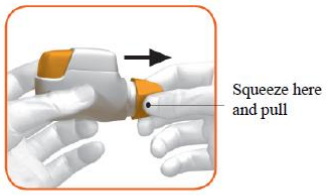

Figure B

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).

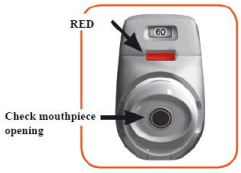

Figure C

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

Figure D

1.4 Press the orange 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 orange button is on top. **Do not tilt.**

1.5 Release the orange 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 orange 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.

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

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 orange button before inhaling, or you may not have strongly enough. If that happens, try again. Make sure you have released the orange button, and you have breathed out completely. Then take a strong, deep breath through the mouthpiece.

Please contact your doctor if 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 and other materials. You should discard your inhaler if you lose the cap.

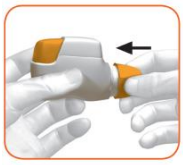

Figure M

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 orange 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).

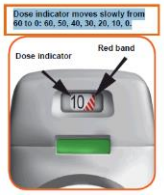

Figure N

How do you know that your inhaler is empty?

When the orange 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 orange button is locked, your last dose may still be inhaled. After that, the inhaler cannot be used again and you should start using a new inhaler.

Figure O

How should you clean the inhaler?

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

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

7. Marketing authorisation holder

AstraZeneca (Israel) Ltd.,

PO Box 1455 Hod Hasharon 4524075

8. Manufacturer

Industrias Farmaceuticas Almirall, S.A.,

Barcelona, Spain.