PRODUCT MONOGRAPH

Pr DUAKLIR® GENUAIR®

aclidinium bromide/formoterol fumarate dihydrate dry powder for oral inhalation

400 mcg aclidinium bromide / 12 mcg formoterol fumarate per metered dose

Bronchodilator Combination

Long-Acting Muscarinic Antagonist (LAMA) and Long-Acting Beta$_2$-Agonist (LABA)

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral inhalation	Inhalation powder/ aclidinium bromide/ formoterol fumarate dihydrate 400 mcg/12 mcg	Lactose monohydrate (which contains milk protein)

INDICATIONS AND CLINICAL USE

DUAKLIR GENUAIR (aclidinium bromide/formoterol fumarate dihydrate) is a combination of a long-acting muscarinic antagonist (LAMA) and a long-acting beta$_2$-agonist (LABA) indicated as a long-term maintenance bronchodilator treatment for airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

DUAKLIR GENUAIR is **not** indicated for the relief of an acute deterioration of COPD.

DUAKLIR GENUAIR is **not** indicated for the treatment of asthma. The safety and efficacy of DUAKLIR GENUAIR in asthma have not been established (see WARNINGS AND PRECAUTIONS).

Geriatrics (≥ 65 years of age):

DUAKLIR GENUAIR can be used at the recommended dose in patients of 65 years of age and older.

Pediatrics (< 18 years of age):

DUAKLIR GENUAIR should not be used in patients under 18 years of age. The safety and effectiveness of DUAKLIR GENUAIR in patients less than 18 years of age have not been established.

CONTRAINDICATIONS

- Patients with hypersensitivity to aclidinium bromide, formoterol fumarate dihydrate (formoterol fumarate) or to any other component of DUAKLIR GENUAIR (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

- All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to patients' usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol fumarate, one of the active ingredients in DUAKLIR GENUAIR.

DUAKLIR GENUAIR is only indicated for COPD. The safety and efficacy of DUAKLIR GENUAIR in patients with asthma have not been established. DUAKLIR GENUAIR is therefore not indicated for the treatment of asthma.

General

Not for use in asthma
DUAKLIR GENUAIR is only indicated for COPD. DUAKLIR GENUAIR should not be used in the treatment of asthma due to the absence of data in this indication, and is contraindicated in this patient population.

Acute bronchospasm

DUAKLIR GENUAIR is a twice-daily long-term maintenance treatment and is not indicated for the initial treatment of acute episodes of bronchospasm, *i.e.* as a rescue therapy.

DUAKLIR GENUAIR has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. DUAKLIR GENUAIR should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of DUAKLIR GENUAIR in this setting is inappropriate.

When beginning treatment with DUAKLIR GENUAIR, patients who have been taking inhaled, short-acting bronchodilators on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

When prescribing DUAKLIR GENUAIR, the healthcare professional should also provide the patient with an inhaled, short-acting bronchodilator for treatment of COPD symptoms that occur acutely, despite regular twice-daily use of DUAKLIR GENUAIR.

Excessive Use and Use with Other LABA and LAMA products

DUAKLIR GENUAIR should not be used more frequently than twice daily or at higher doses than recommended.

DUAKLIR GENUAIR should not be administered concomitantly with other medicines containing a long-acting beta$_2$-adrenergic agonist or a long-acting muscarinic antagonist, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Effect on ability to drive or use machines

No studies on the effects on the ability to drive and use machines have been performed. The occurrence of headache, blurred vision, or dizziness may influence the ability to drive or to use machinery.

Anticholinergic Effects

Like other anticholinergic drugs, DUAKLIR GENUAIR should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Worsening of Narrow-Angle Glaucoma

DUAKLIR GENUAIR, like other anticholinergic-containing drugs, should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. Miotic drops alone are not considered to be effective treatment.

Worsening of Urinary Retention

DUAKLIR GENUAIR, like other anticholinergic-containing drugs, should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Cardiovascular Effects

DUAKLIR GENUAIR is a combination of a long-acting beta$_2$-agonist (formoterol fumarate) and a long-acting muscarinic antagonist (aclidinium bromide). Cardiovascular effects, such as cardiac arrhythmias, e.g., atrial fibrillation and tachycardia, may be seen after the administration of sympathomimetic agents and muscarinic receptor antagonists, including DUAKLIR GENUAIR. In case such effects occur, treatment may need to be discontinued.

Cardiovascular effects such as tachycardia, arrhythmia, palpitations, myocardial ischaemia, angina pectoris, hypertension or hypotension have been associated with use of beta-adrenergic agonists. In addition, beta-adrenergic agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Therefore, DUAKLIR GENUAIR should be used with caution in patients with cardiovascular disease, especially coronary insufficiency, acute myocardial infarction, cardiac arrhythmias, severe hypertension.

Heart Rate

Like other beta$_2$-agonists, formoterol can produce clinically significant cardiovascular effects in some patients as measured by an increase in pulse rate, systolic or diastolic blood pressure or cardiac arrhythmias such as supraventricular tachycardia and extrasystoles. If such effects occur, DUAKLIR GENUAIR may need to be discontinued.

QT Interval

Like other beta$_2$-agonists, caution is recommended if DUAKLIR GENUAIR is administered to patients with a known history of QTc prolongation, risk factors for torsade de pointes (e.g., hypokalemia), or patients who are taking medications known to prolong the QTc interval (see DRUG INTERACTIONS, Drugs known to prolong the QTc interval).

Endocrine and Metabolism

DUAKLIR GENUAIR should be used with caution in patients with convulsive disorders, thyrotoxicosis and phaeochromocytoma and in those who are unusually responsive to sympathomimetic amines.

Hypokalemia and Hyperglycemia

Metabolic effects of hyperglycemia and hypokalemia may be observed with high doses of beta$_2$-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 (0%). Upon initiation of treatment with DUAKLIR GENUAIR plasma glucose should be monitored more closely in diabetic patients. DUAKLIR GENUAIR has not been investigated in patients for whom diabetes mellitus is not well controlled.

Hypokalemia is usually transient, not requiring supplementation. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment (see DRUG INTERACTIONS). Hypokalemia increases susceptibility to cardiac arrhythmias.

Immediate Hypersensitivity Reactions

As with all medications, immediate hypersensitivity reactions may occur after administration of DUAKLIR GENUAIR. If such a reaction occurs, therapy with DUAKLIR GENUAIR should be stopped at once and alternative treatments should be considered.

There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, DUAKLIR GENUAIR should be used with caution in patients with severe milk protein allergy.

Ophthalmologic

Worsening of Narrow-Angle Glaucoma (see Anticholinergic Effects).

Respiratory

Paradoxical bronchospasm

In clinical studies with DUAKLIR GENUAIR paradoxical bronchospasm was not observed. However, as with other inhalation therapies, administration of DUAKLIR GENUAIR may cause paradoxical bronchospasm. If this occurs, treatment with DUAKLIR GENUAIR should be stopped and other treatments considered.

Renal

Worsening of Urinary Retention (see Anticholinergic Effects)

Special Populations

Pregnant Women: 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 bromide and adverse effects in reproduction studies with formoterol fumarate at very high systemic exposure levels. Because animal reproduction studies are not always predictive of human response, DUAKLIR GENUAIR should only be used during pregnancy if the expected benefits outweigh the potential risks (see TOXICOLOGY).

Nursing Women: Clinical data from nursing women exposed to DUAKLIR GENUAIR are not available. Animal studies have shown excretion of small amounts of aclidinium bromide (and/or metabolites) into milk of lactating female rats and decreased pup weights. Formoterol fumarate was found to be excreted in small amounts in the milk of lactating rats after oral administration. DUAKLIR GENUAIR should be used in nursing women only if the expected benefit to the woman is greater than any possible risk to the infant (see TOXICOLOGY).

Labour and Delivery: The effect of DUAKLIR GENUAIR on labour and delivery is unknown. There are no well-controlled human studies that have investigated effects of aclidinium or formoterol fumarate on preterm labour or labour at term. Because of the potential for beta-agonist interference with uterine contractility, use of DUAKLIR GENUAIR during labour should be restricted to those patients in whom the benefits clearly outweigh the risks.

Geriatrics (≥ 65 years of age): DUAKLIR GENUAIR can be used at the recommended dose in patients of 65 years of age and older. In phase III clinical studies, 327 patients (45.4%) treated with DUAKLIR GENUAIR at the recommended dose were ≥ 65 years of age. No overall differences in safety or effectiveness were observed between elderly patients and younger patients with COPD.

Pediatrics (<18 years of age): DUAKLIR GENUAIR should not be used in patients under 18 years of age.

Hepatic Impairment: There are no data regarding the specific use of aclidinium/formoterol in patients with hepatic impairment. Aclidinium bromide is metabolised mainly by chemical and enzymatic cleavage in the plasma, hepatic dysfunction is very unlikely to alter its systemic exposure. Formoterol has not been studied in patients with hepatic impairment (see DOSAGE AND ADMINISTRATION, Dosing in special populations).

Renal Impairment: There are no data regarding the specific use of aclidinium/formoterol in patients with renal impairment. The impact of renal disease upon the pharmacokinetics of aclidinium bromide was studied in 18 subjects with mild, moderate or severe renal impairment. Systemic exposure (AUC and C_{max}) to aclidinium bromide and its main metabolites following inhalation of single doses of 400 mcg aclidinium bromide was similar between groups. Formoterol has not been studied in patients with renal impairment (see DOSAGE AND ADMINISTRATION, Dosing in special populations).

Monitoring and Laboratory Tests

Potentially serious hypokalemia has been observed with other beta-agonist therapies, which may increase susceptibility to cardiac arrhythmias. It is therefore recommended that serum potassium levels be monitored in patients predisposed to low levels of serum potassium.

Due to the hyperglycemic effect observed with other beta-agonists, additional blood glucose monitoring is recommended in diabetic patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety profile of DUAKLIR GENUAIR is based on the experience with DUAKLIR GENUAIR and the individual components. Adverse events associated with DUAKLIR GENUAIR were similar to those of the individual components. As DUAKLIR GENUAIR

contains aclidinium bromide and formoterol fumarate, the type and severity of adverse events associated with each of the components may be expected with DUAKLIR GENUAIR.

Long-acting beta$_2$-adrenergic agonists such as formoterol, one of the active ingredients of DUAKLIR GENUAIR increase the risk of asthma-related death. DUAKLIR GENUAIR is not indicated for the treatment of asthma (See INDICATIONS AND CLINICAL USE, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS).

DUAKLIR GENUAIR is a combination of a long-acting beta$_2$-agonist (LABA) and a long-acting muscarinic antagonist (LAMA). Adverse reactions to DUAKLIR GENUAIR are expected to be similar in nature to other beta$_2$-agonists and muscarinic antagonists. Adverse reactions that have been associated with muscarinic antagonists include cardiovascular effects (atrial arrhythmias and tachycardia), ocular disorders (e.g., blurred vision), urinary retention, gastrointestinal disorders (e.g. dry mouth). Adverse reactions that have been associated with beta$_2$-agonists include cardiovascular effects (tachycardia, arrhythmia, palpitations, myocardial ischaemia, hypertension or hypotension), hypokalemia, hyperglycemia, headache, nervousness, insomnia, muscle spasms and tremor.

Pooled data from two 24 week placebo-controlled clinical trials in COPD patients showed that the most commonly reported adverse reactions (>5%) with DUAKLIR GENUAIR were nasopharyngitis (6.4%) and headache (6.3%). Across these studies, 6.7% of patients who received placebo and 6.1% of patients who received DUAKLIR GENUAIR twice daily discontinued prematurely due to adverse events.

The safety profile in the long term safety trials was similar to the one observed in the placebo-controlled pivotal trials.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

A total of 1222 patients (527 females and 695 males) with moderate to severe COPD were treated with DUAKLIR GENUAIR at the recommended therapeutic dose. The incidence of adverse events associated with DUAKLIR GENUAIR is based on a pooled analysis of two placebo-controlled trials in patients with COPD of 6 months duration.

6-Month Safety Data:

In the placebo-controlled clinical trials, 720 COPD patients were treated with DUAKLIR GENUAIR at the recommended dose of 400/12 mcg twice daily. Of these, 557 patients were treated with DUAKLIR GENUAIR for at least 6 months.

Table 1 summarizes the common adverse reactions that occurred with a frequency of ≥1.0% in the DUAKLIR GENUAIR group in the two placebo-controlled clinical trials up to 6 months duration, where the rates in the DUAKLIR GENUAIR group exceeded placebo by 0.5%.

Table 1 Adverse Reactions with DUAKLIR GENUAIR occurring with ≥1.0% Frequency and ≥0.5% greater frequency than Placebo in Placebo-Controlled Clinical Trials in COPD up to 6 Months Duration

Adverse Reactions	**Treatment**			
Body System Event	**DUAKLIR GENUAIR** **(N =720) n (%)**	**Placebo** **(N =526) n (%)**	**Aclidinium bromide** **(N=722) n (%)**	**Formoterol fumarate** **(N=716) n (%)**
Respiratory, Thoracic and Mediastinal Disorders				
Nasopharyngitis	46 (6.4)	26 (4.9)	34 (4.7)	48 (6.7)
Infections and Infestations				
Influenza	11 (1.5)	2 (0.4)	6 (0.8)	6 (0.8)
Upper respiratory tract infection	18 (2.5)	8 (1.5)	18 (2.5)	19 (2.7)
Tooth abscess	10 (1.4)	2 (0.4)	3 (0.4)	2 (0.3)
Nervous System				
Headache	45 (6.3)	27 (5.1)	48 (6.6)	55 (7.7)
Tremor	7 (1.0)	1 (0.2)	2 (0.3)	6 (0.8)
Musculoskeletal and Connective Tissues				
Back pain	28 (3.9)	18 (3.4)	24 (3.3)	25 (3.5)
Muscle spasms	15 (2.1)	6 (1.1)	5 (0.7)	11 (1.5)
Musculoskeletal pain	11 (1.5)	5 (1.0)	7 (1.0)	7 (1.0)
Pain in extremity	10 (1.4)	3 (0.6)	9 (1.2)	6 (0.8)
Gastrointestinal System				
Dry Mouth	13 (1.8)	2 (0.4)	4 (0.6)	6 (0.8)
Investigations				
Blood creatine phosphokinase increased	8 (1.1)	1 (0.2)	1 (0.1)	5 (0.7)

Other less common adverse reactions that occurred in the DUAKLIR GENUAIR group at a frequency of <1.0% and at a higher frequency than placebo include:

Cardiac disorders: bundle branch block left, atrioventricular block, supraventricular extrasystoles

General disorders and administration site conditions: product taste abnormal

Musculoskeletal and connective tissue disorders: joint swelling

Psychiatric Disorders: anxiety

Respiratory, Thoracic and Mediastinal Disorders: dysphonia

Long-Term Safety Studies

DUAKLIR GENUAIR was studied in one double-blind active-controlled long-term safety trial for a duration of 52 weeks and in a 28-weeks extension trial to one of the 6-month placebo-controlled trials.

A total of 127 patients with COPD were treated with DUAKLIR GENUAIR at the recommended dose for at least 12 months in the 6-month extension study of one pivotal placebo-controlled trial.

Additionally, 233 patients with COPD were treated with DUAKLIR GENUAIR at the recommended dose for up to 12 months, in the active-controlled double-blind long term safety trial.

The adverse events reported on the long term safety trials were similar to those occurring in the placebo-controlled trials of 6 months.

Additional information on individual components

The following adverse events not already listed above were reported in clinical trials of the individual components of DUAKLIR GENUAIR:

Formoterol fumarate:

Cardiac disorders: palpitations, tachycardia;
Musculoskeletal and connective tissue disorders: muscle cramps, myalgia;
Nervous system disorders: dizziness;
Psychiatric disorders: agitation, insomnia, nervousness;
Respiratory, thoracic and mediastinal disorders: bronchospasm, coughing, oropharyngeal pain (irritation), throat irritation;
Skin and subcutaneous tissue disorders: pruritus.

Aclidinium bromide:

Cardiac disorders: cardiac failure;
Eye disorders: blurred vision;
Gastrointestinal disorders: abdominal discomfort, diarrhea, toothache, vomiting;
Infectious and infestations: candidiasis, rhinitis, sinusitis;
Injury, poisoning and procedural complications: fall;
Metabolism and nutrition disorders: diabetes mellitus;
Musculoskeletal and connective tissue disorders: osteoarthritis;
Respiratory, thoracic and mediastinal disorders: cough.

Post-Market Adverse Drug Reactions

Because adverse events are spontaneously reported in a voluntary manner from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions not already listed above have been reported during post-approval use of DUAKLIR GENUAIR:

Cardiac disorders: tachycardia;
Eye disorders: blurred vision;
Infections and infestations: urinary tract infections;
Nervous system disorders: dysgeusia;
Psychiatric disorders: insomnia;
Renal and urinary disorders: urinary retention;
Respiratory, thoracic and mediastinal disorders: bronchospasm (including paradoxical), throat irritation.

The following adverse events not already listed above were reported during post-approval use of aclidinium bromide:

Cardiac disorders: palpitations, tachycardia;
Gastrointestinal disorders: nausea, stomatitis;
Immune system disorders: anaphylactic reaction, angioedema, hypersensitivity reactions;
Nervous system disorders: dizziness;
Renal and urinary disorders: dysuria, urinary retention;
Respiratory, thoracic and mediastinal disorders: dyspnoea;
Skin and subcutaneous tissue disorders: pruritus, rash.

The following additional adverse events have been identified from post-approval use of formoterol fumarate:

Cardiac disorders: angina pectoris, blood pressure increased (including hypertension), cardiac arrhythmias (e.g. atrial fibrillation, ventricular extrasystoles, tachyarrhythmia), Electrocardiogram QT prolonged, syncope;
Immune system disorders: anaphylactic reaction, angioedema, hypersensitivity reactions;
Metabolism and nutrition disorders: hyperglycemia, hypokalemia;
Respiratory, thoracic and mediastinal disorders: cough;
Skin and subcutaneous tissue disorders: rash.

Rare reports of hypersensitivity including urticaria, pruritus, exanthema, peripheral edema and in certain cases anaphylactic reactions, such as severe hypotension and angioedema, have been received in association with the use of formoterol fumarate. Isolated cases of the following adverse events have also been reported: taste perversion, nausea.

DRUG INTERACTIONS

Overview

In vitro studies suggest limited potential for cytochrome P450 (CYP450)-related metabolic drug interactions for aclidinium bromide and formoterol fumarate.

In clinical trials, DUAKLIR GENUAIR has been used concomitantly with other COPD medicinal products including short-acting beta$_2$-adrenergic bronchodilators, methylxanthines, and oral and inhaled steroids without clinical evidence of drug interactions. However, no formal drug interaction studies have been performed with DUAKLIR GENUAIR.

Drug-Drug Interactions

Co-administration of DUAKLIR GENUAIR with other anticholinergic and/or long-acting beta2-adrenergic agonist containing medicinal products has not been studied and is not recommended.

Metabolic Interactions

In vitro studies have shown that aclidinium bromide at the therapeutic dose is not expected to cause interactions with P-glycoprotein substrate drugs or drugs metabolised by CYP450 enzymes and esterases. Formoterol fumarate does not inhibit the CYP450 enzymes at therapeutically relevant concentrations (see ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hypokalemic treatment

Concomitant treatment with methylxanthine derivatives, oral corticosteroids (e.g. prednisone), or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta$_2$-adrenergic agonists, therefore caution is advised in their concomitant use (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonize the effect of beta$_2$-adrenergic agonists. Therefore DUAKLIR GENUAIR should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers could be considered, although they should be administered with caution.

Drugs known to prolong the QTc interval

As with other drugs containing beta$_2$-adrenergic agonists, DUAKLIR GENUAIR should be administered with caution to patients treated with drugs known to prolong the QT 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. Drugs known to prolong the QT-interval may increase the risk of ventricular arrhythmia (see WARNINGS AND PRECAUTIONS, Cardiovascular Effects).

Table 2 Potential Drug-Drug Interactions

Drug Class	Ref	Effect	Clinical comment
Drugs known to prolong the QTc interval MAO inhibitors Tricyclic antidepressants Antihistamines Macrolides	T	Potential pharmacodynamics interaction (prolongation of the QTc interval and increased risk of ventricular arrhythmias)	Caution is recommended during concomitant therapy
Beta-adrenergic blockers (including ophthalmic agents)	T	Beta-adrenergic blockers may weaken or antagonize the effect of $beta_2$-adrenergic agonists	If concomitant therapy is required, cardioselective beta-adrenergic blockers could be considered, although they should be administered with caution.
Concomitant treatment with methylxanthine derivatives, oral corticosteroids (e.g. prednisone), or non-potassium-sparing diuretics	T	Potential pharmacodynamic interaction (increased risk of hypokalemia)	Caution is recommended during concomitant therapy
Sympathomimetic agents	T	Potential pharmacodynamic interaction (additive pharmacologic and adverse effects)	Caution is recommended during concomitant use with long acting sympathomimetic agents administered by any route
Anticholinergics	T	There is potential for an additive interaction with concomitantly used anticholinergic medications.	Avoid co-administration with other anticholinergic-containing drugs.

Abbreviations: T=Theoretical

Drug-Food Interactions

Interactions with food have not been established. No clinically relevant effect of food would be expected and therefore a food interaction study was not conducted.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Counseling by doctors on smoking cessation should be the first step in treating patients with COPD who smoke, independent of the clinical presentation i.e. chronic bronchitis (with or without airflow limitation) or emphysema. Cessation of smoking produces dramatic symptomatic benefits and has been shown to confer a survival advantage.

- As with other inhaled drugs containing beta$_2$-adrenergic agents, DUAKLIR GENUAIR should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing a long-acting beta-adrenergic agonist or a long-acting muscarinic antagonist, as an overdose may result.

- When beginning treatment with DUAKLIR GENUAIR, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

- Patients should be made aware that for optimum benefit, DUAKLIR GENUAIR must be used regularly, even when asymptomatic.

Recommended Dose

The recommended dose is one inhalation of DUAKLIR GENUAIR twice daily, once in the morning and once in the evening.

Dosing in special populations

Elderly patients: No dose adjustments are required for elderly patients.

Hepatic impairment: No dose adjustments are required for patients with hepatic impairment.

Renal impairment: No dose adjustments are required for patients with renal impairment.

Pediatric patients: DUAKLIR GENUAIR should not be used in patients under 18 years of age.

Administration

DUAKLIR GENUAIR should be administered twice daily, once in the morning and once in the evening via oral inhalation.

To ensure proper administration of DUAKLIR GENUAIR, the doctor or other qualified health care professional should teach the patient how to operate the GENUAIR inhalation device (see Part III CONSUMER INFORMATION; How to use DUAKLIR GENUAIR inhaler).

Missed Dose

If a dose is missed, the next dose should be taken as soon as possible. However, if it is nearly time for the next dose, the patient should not take the missed one and just go back to the regular dosing schedule. The patient should never take a double dose.

OVERDOSAGE

There is limited evidence on the management of overdose with DUAKLIR GENUAIR. High doses of DUAKLIR GENUAIR may lead to signs and symptoms that are typical of anticholinergic (e.g. dry mouth, blurred vision, ocular pain, nausea and tachycardia) and/or beta$_2$-adrenergic agents (e.g. nausea, vomiting, somnolence, hypertension, tremor, headache, tachycardia, palpitations, dizziness, ventricular arrythmias, metabolic acidosis, hypokalemia, hypoglycemia and muscle spasms).

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

DUAKLIR GENUAIR is a fixed-dose combination of two inhaled bronchodilators: aclidinium bromide is a long-acting muscarinic antagonist (LAMA, also known as a long-acting anticholinergic) and formoterol fumarate is a long-acting beta$_2$-adrenergic agonist (LABA). 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 beta$_2$-adrenoceptors in the central and peripheral airways of the lung, muscarinic antagonists should be more effective in relaxing central airways and beta$_2$-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 the individual substances is provided below.

Preclinical studies have demonstrated that aclidinium bromide is a competitive muscarinic receptor antagonist. It has a similar potency at all five human muscarinic receptors M_1 to M_5, but kinetically, shows a preference for the M_3 receptor. Aclidinium bromide has a long residence time at M_3 receptors and results of preclinical and early clinical studies in healthy subjects indicate that aclidinium bromide provides dose-dependent and long-lasting (longer than 24 hours) protection against bronchoconstriction.

Nonclinical *in vitro* and *in vivo* studies showed rapid, dose-dependent and long-lasting inhibition by aclidinium bromide of acetylcholine-induced bronchoconstriction due to its high

affinity (Ki: 0.12 nM) and long residence time (half-life of 29 hours) on human M_3 muscarinic receptors. Additionally, aclidinium bromide is rapidly hydrolyzed to two major inactive metabolites.

Formoterol fumarate is a potent selective long-acting $beta_2$-adrenoceptor agonist. The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including formoterol fumarate, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Pharmacodynamics

Clinical studies showed that DUAKLIR GENUAIR provides clinically meaningful improvements compared to placebo in lung function (as measured by the forced expiratory volume in 1 second [FEV_1]) over 12 hours following morning and evening administration from baseline.

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 $beta_2$-agonist formoterol 12 mcg. Maximal bronchodilator effects (peak FEV1) relative to baseline were evident from day one (304 ml) and were maintained over the 6-month treatment period (326 ml). The bronchodilator effects of DUAKLIR GENUAIR were maintained over a 1-year period.

Cardiac Electrophysiology

No clinically relevant effects of DUAKLIR GENUAIR on ECG parameters (including QT-interval) compared with aclidinium bromide, formoterol fumarate and placebo were seen in Phase III studies of 6 to 12 months duration conducted in approximately 4,000 patients with COPD of which 1,111 received DUAKLIR GENUAIR. In addition, no clinically significant effects of DUAKLIR GENUAIR on cardiac rhythm were observed on 24 hour Holter monitoring in a subset of 551 COPD patients, of whom 114 received DUAKLIR GENUAIR twice daily.

Pharmacokinetics

Table 3 Summary of DUAKLIR GENUAIR Pharmacokinetic Parameters

	C_{max} (pg/mL)[1]	**$AUC_{(0-12)}$ (pg*h/mL)[1]**	**t½ (h)[1]**	**Total Clearance (L/h)[2]**
Aclidinium bromide 400 mcg	128.4 (54.0)	404.3 (190.6)	19.6 (7.3)	170 (60.5)
Formoterol fumarate 12 mcg	16.7 (5.3)	85.2 (24.1)	13.6 (1.9)	NA

Data presented as arithmetic Mean (SD)

[1]Steady state value after twice daily inhaled doses of 400/12 mcg in COPD patients;
[2]Intravenous administration in healthy subjects.
NA: not available

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

Absorption: Following inhalation of a single dose of DUAKLIR GENUAIR, aclidinium bromide and formoterol fumarate 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 bromide and formoterol fumarate 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: In healthy subjects, approximately 30% of the metered dose of aclidinium bromide was deposited in the lung. Most of the dose (55%) was deposited in the gastrointestinal tract.

The plasma protein binding of aclidinium bromide determined *in vitro* most likely corresponded to the protein binding of the metabolites due to the rapid hydrolysis of aclidinium bromide in plasma; plasma protein binding was 66%-87% for the acid metabolite and 12%-26% for the alcohol metabolite. The main plasma protein that binds aclidinium bromide 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.

Metabolism: Aclidinium bromide is rapidly and extensively hydrolysed to its pharmacologically inactive alcohol- and 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. 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.

Metabolism via CYP450 enzymes plays a minor role in the total metabolic clearance of aclidinium bromide.

In vitro studies have shown that aclidinium bromide at the therapeutic dose or its metabolites do not inhibit or induce any of the cytochrome P450 (CYP450) enzymes and do not inhibit esterases (carboxylesterase, acetylcholinesterase and butyrylcholinesterase). *In vitro* studies have shown that they are not substrates or inhibitors of P-glycoprotein.

Formoterol fumarate 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 fumarate does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

Elimination: Following inhalation of DUAKLIR GENUAIR, aclidinium bromide and formoterol fumarate showed effective half-lives of approximately 10 hours.

Total clearance of aclidinium bromide was approximately 170 L/h after an intravenous dose in young healthy subjects with an inter-individual variability of 36%. Following intravenous administration of 400 mcg radiolabelled aclidinium bromide to healthy subjects, approximately 1% of the dose was excreted as unchanged aclidinium bromide in the urine. Up to 65% of the dose was eliminated as metabolites in the urine and up to 33% as metabolites in the feces.

Following inhalation of 200 mcg and 400 mcg of aclidinium bromide by healthy subjects or COPD patients, the urinary excretion of unchanged aclidinium bromide was very low at about 0.1% of the administered dose, indicating that renal clearance plays a minor role in the total clearance from plasma.

The major part of a dose of formoterol fumarate 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. The total clearance of formoterol is approximately 150 mL/min.

Special Populations and Conditions

Pediatrics: Pharmacokinetics in children was not investigated.

Geriatrics: No pharmacokinetics studies have been performed with DUAKLIR GENUAIR in elderly subjects. Since no dosage adjustments are needed for either aclidinium bromide or formoterol fumarate in elderly patients, no dosage adjustment is warranted for DUAKLIR GENUAIR in geriatric patients.

Hepatic Insufficiency: There are no data regarding the specific use of DUAKLIR GENUAIR in patients with hepatic impairment. Since no dosage adjustments are needed for either aclidinium bromide or formoterol fumarate in patients with hepatic impairment, no dosage adjustment is warranted for DUAKLIR GENUAIR.

Renal Insufficiency: There are no data regarding the specific use of DUAKLIR GENUAIR in patients with renal impairment. Since no dosage adjustments are needed for either aclidinium bromide or formoterol fumarate in patients with renal impairment, no dosage adjustment is warranted for DUAKLIR GENUAIR.

STORAGE AND STABILITY

Store between 15 to 30°C.

DUAKLIR GENUAIR should be kept protected inside the sealed bag until the administration period starts and used within 60 days of opening the bag.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each DUAKLIR GENUAIR dose contains 400 mcg aclidinium bromide and 12 mcg formoterol fumarate dihydrate. This corresponds to a delivered dose (the dose leaving the mouthpiece) of 396 mcg aclidinium bromide (equivalent to 340 mcg aclidinium) and 12 mcg formoterol fumarate dihydrate.

Each dose also contains lactose monohydrate (which contains milk protein).

DUAKLIR GENUAIR is a white or almost white powder in a white inhaler with an integral dose indicator and an orange dosage button.

The following pack type is available:

Carton containing 1 inhaler with 30 metered doses.

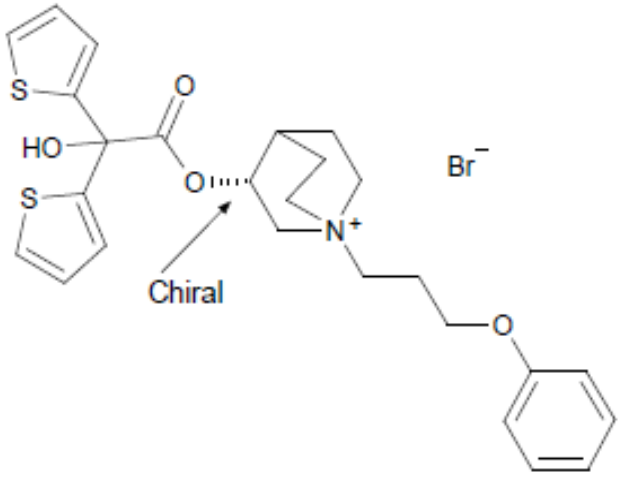
Carton containing 1 inhaler with 60 metered doses.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

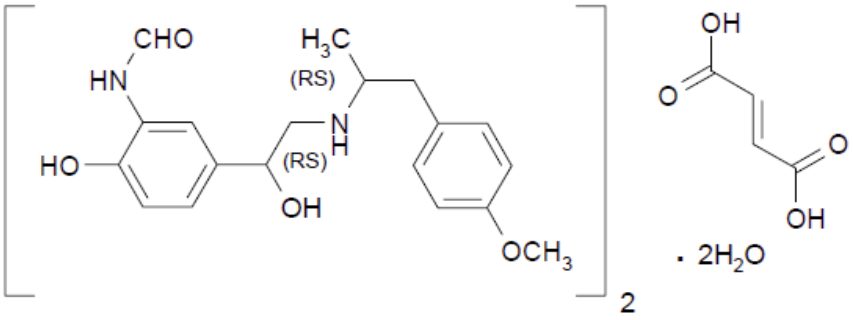
Proper Name:	aclidinium bromide
Chemical Name:	(3*R*)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1-(3-phenoxypropyl)-1λ^5-azabicyclo[2.2.2] octan-1-ylium bromide
Molecular Formula:	$C_{26}H_{30}NO_4S_2Br$
Molecular Mass:	564.56
Structural Formula:	



Physicochemical Properties:	White or almost white powder, with a melting point of 224-229°C. Aclidinium bromide is sparingly soluble in methanol, very slightly soluble in water and in ethanol, and practically insoluble in acetone, ethyl acetate, tetrahydrofuran and toluene. It is very slightly soluble (< 1 mg/ml) in weak acids (0.1 M) and in buffer solutions at acid pH values. Aclidinium bromide is slightly degraded in acid solution and totally degraded in basic solution above pH 9.

Drug Substance

Proper Name:	formoterol fumarate dihydrate
Chemical Name:	(±)-N-[2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, E-butenedioate (2:1 salt) dihydrate
Molecular Formula:	$C_{42}H_{52}N_4O_{12}$•$2H_2O$
Molecular Mass:	840.9
Structural Formula:	



Physicochemical Properties:	White or almost white or slightly yellow powder. Melts in the range between 135.0° and 142.0°C with decomposition. Formoterol fumarate dihydrate is slightly soluble in water, soluble in methanol, slightly soluble in 2-propanol, and practically insoluble in acetonitrile. The pH of a 0.1% aqueous solution of formoterol fumarate dihydrate is 5.5 – 6.5.

CLINICAL TRIALS

Study demographics and trial design

The efficacy of DUAKLIR GENUAIR (aclidinium bromide/formoterol fumarate dihydrate) was established in two 6-month randomized, double-blind, placebo and active-controlled pivotal clinical trials (M/40464/30 and LAC-MD-31).The persistence of efficacy was assessed in a 6-month extension of study LAC-MD-31 and in a further 12-month randomized controlled study, where the long-term safety was also evaluated. These studies enrolled 3986 patients aged ≥ 40 years who had a clinical diagnosis of stable moderate to severe COPD (with post bronchodilator FEV_1 of ≥ 30% to < 80% of predicted normal value) and a history of smoking of at least 10 pack-years. 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.

The study design and patient demographics for these studies is described in Table 4.

Table 4 Summary of Patient Demographics for Pivotal Clinical Trials in COPD (ITT Population)

Study #	Trial design	Dosage, route of administration and duration	Study subjects [a] (n=number)	Mean age [a] (Range)	Gender
M/40464/30	Multi-centre, placebo and active controlled, randomized, double-blind, parallel group	AB/FF, 400/12 mcg AB/FF, 400/6 mcg AB, 400 mcg FF, 12 mcg Placebo Twice daily Oral inhalation 24 weeks	AB/FF 400/12 mcg: n=385 AB/FF 400/6 mcg: n=381 AB 400 mcg: n=385 FF 12 mcg: n=384 Placebo: n=194	63 years (40-85 years)	Male: 67.6% Female: 32.4%
LAC-MD-31	Multi-centre, placebo and active controlled, randomized, double-blind, parallel group	AB/FF, 400/12 mcg AB/FF, 400/6 mcg AB, 400 mcg FF 12 mcg Placebo Twice daily Oral inhalation 24 weeks	AB/FF 400/12 mcg: n=335 AB/FF 400/6 mcg: n=333 AB 400 mcg: n=337 FF 12 mcg: n=332 Placebo: n=332	64 years (40-93 years)	Male: 53.1% Female: 46.9%

AB=aclidinium bromide; FF=formoterol fumarate; ITT=Intent-to-Treat
[a] Safety population which includes all patients who took at least one dose of IMP and counted once

In the pooled pivotal 6-month studies, the mean post-bronchodilator percent predicted FEV_1 at screening was 53.9% (range: 28.0-85.8%).

The co-primary endpoints in both pivotal studies were the changes from baseline in FEV_1 at 1 hour post-dose and in trough FEV_1 at Week 24 (compared to aclidinium bromide 400 mcg and formoterol fumarate 12 mcg, respectively) to demonstrate the bronchodilator contributions of formoterol fumarate and aclidinium bromide in DUAKLIR GENUAIR, respectively. Secondary endpoints were improvement from baseline to Week 24 in the Transition dyspnea index (TDI) focal score and the change from baseline to Week 24 in the St. George's Respiratory Questionnaire (SGRQ) total score. Other efficacy variables included rescue medication usage.

Study Results

Lung function

Inhalation of DUAKLIR GENUAIR twice daily by patients with moderate to severe COPD resulted in statistically and clinically meaningful improvements in lung function (as measured by FEV_1) relative to placebo in both M/40464/30 and LAC-MD-31.

In M/40464/30, DUAKLIR GENUAIR showed statistically significant improvements in FEV_1 at 1 hour post-dose relative to placebo and aclidinium bromide of 299 ml and 125 ml, respectively (both $p<0.0001$) and statistically significant improvements in trough FEV_1 relative to placebo

and formoterol fumarate of 143 ml and 85 ml, respectively (both p<0.0001) at Week 24. In LAC-MD-31, DUAKLIR GENUAIR showed statistically significant improvements in FEV_1 at 1 hour post-dose relative to placebo and aclidinium bromide of 284 ml and 108 ml (both p<0.0001), respectively, and improvements in trough FEV1 relative to placebo and formoterol fumarate of 130 ml (p<0.0001) and 45 ml (p=0.01), respectively.

The lung function effects of DUAKLIR GENUAIR were observed 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 (see Figure 1 and Figure 2 for representative data from M/40464/30) and one year Phase III studies.

Figure 1 **LS mean changes from baseline to time points up to Week 24 in FEV_1 (L) at 1 hour post-dose: M/40464/30**

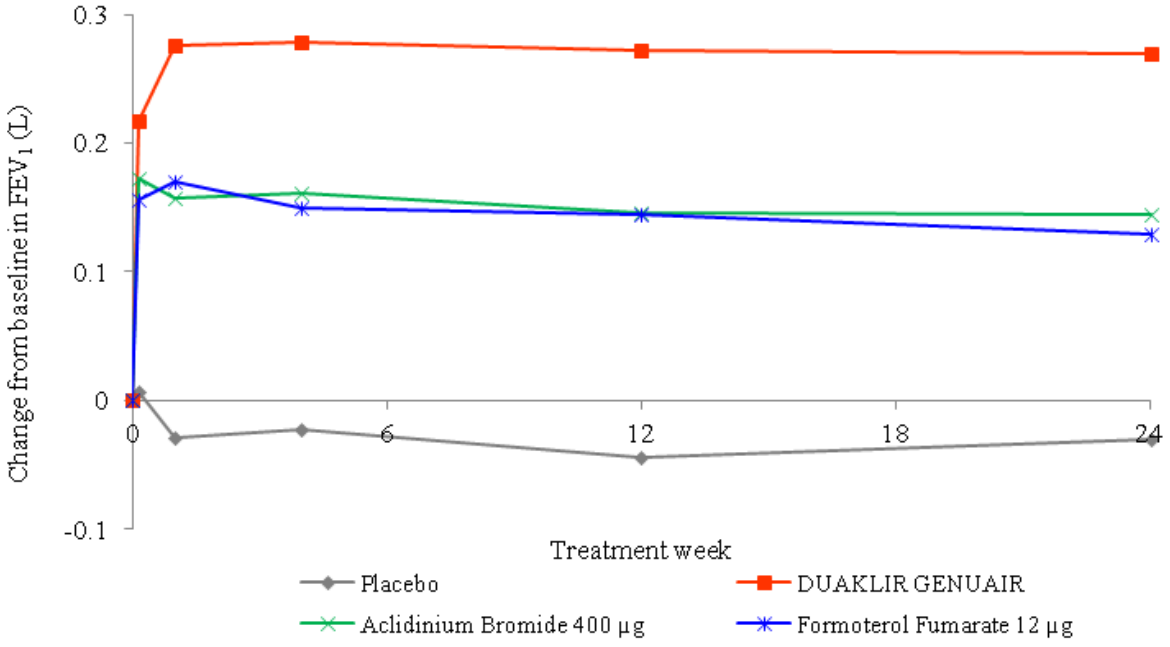
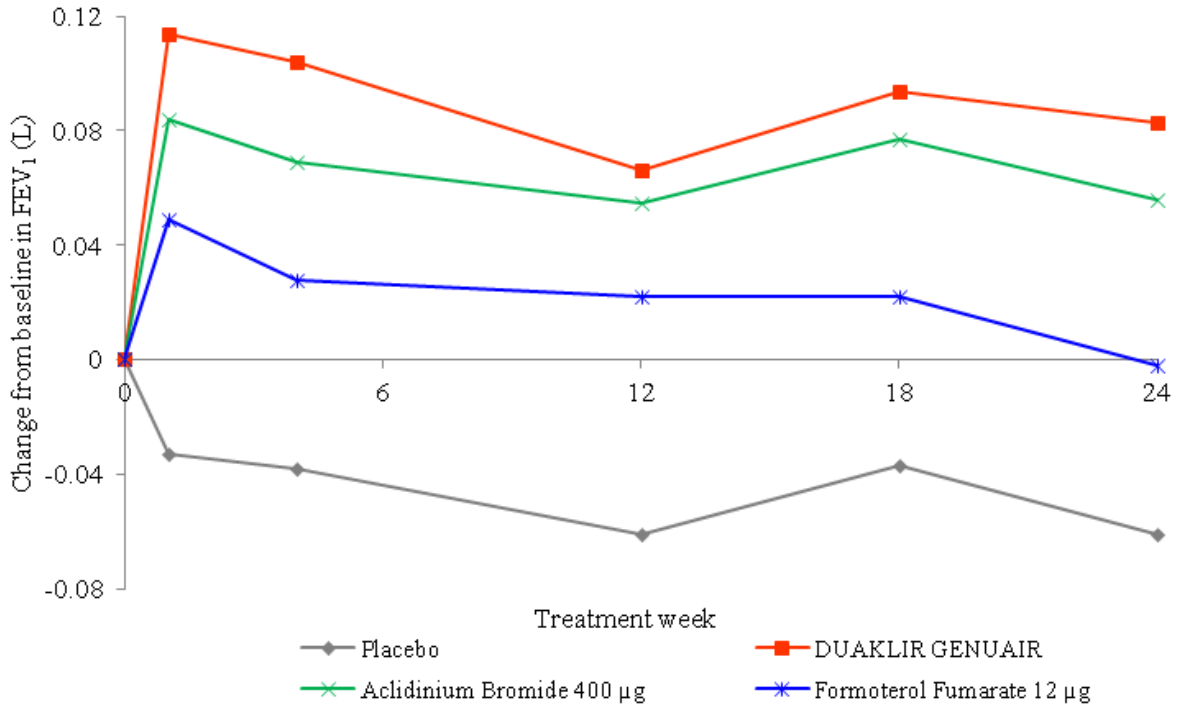


Figure 2 **LS mean changes from baseline to time points up to Week 24 in trough FEV_1 (L): M/40464/30**



Symptom related outcomes

The effects of DUAKLIR GENUAIR on dyspnea and disease-specific health status were evaluated using the Transition Dyspnea Index (TDI), and the St. George's Respiratory Questionnaire (SGRQ), respectively.

Following 24 weeks of treatment, DUAKLIR GENUAIR provided statically significant ($p<0.0001$) and clinically meaningful improvements in breathlessness (assessed by the TDI) with mean difference compared to placebo of 1.29 units (95% CI=0.73, 1.86) and 1.44 units (95% CI=0.85, 2.02) in M/40464/30 and LAC-MD-31, respectively. 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 M/40464/30 (64.8% compared to 45.5%, OR= 2.54, 95% CI:1.57, 4.10) and LAC-MD-31 (58.1% compared to 36.6%, OR= 2.8, 95% CI:1.77, 4.4).

The pooled analysis of these two studies showed DUAKLIR GENUAR to be associated with greater improvements in TDI focal score compared to aclidinium bromide (0.4 units, 95% CI: 0.1, 0.8, p=0.016) and to formoterol fumarate (0.5 units, 95% CI: 0.1, 0.8, p=0.009).

Following 24 weeks of treatment, DUAKLIR GENUAIR provided improvements in disease-specific health status (assessed by the St. George's Respiratory Questionnaire [SGRQ] total score) relative to placebo (-4.35 units, 95% CI:-6.46, -2.24, $p<0.0001$) in LAC-MD-31 only The percentage of patients 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%, OR=2.26, 95% CI: 1.41, 3.61) in LAC-MD-31 only.

In the pooled analysis of LAC-MD-31 and M/40464/30 studies, DUAKLIR GENUAIR showed greater improvements in SGRQ total score compared to formoterol fumarate (-1.7 units; 95% CI: -3.2, -0.3, p=0.018) or aclidinium bromide (-0.8 units, 95% CI: -2.2, 0.6, p=0.273).

Use of rescue medication

In the pooled analysis, DUAKLIR GENUAIR reduced the use of rescue medication over 6 months compared to placebo (by 0.9 puffs per day, 95% CI: 1.1, 0.7) [p<0.0001]).

DETAILED PHARMACOLOGY

Nonclinical Pharmacology

Preclinical studies have not been conducted to assess primary and secondary pharmacodynamics of aclidinium bromide/formoterol fumarate in animal models since both individual substances have been extensively investigated, they are known to have different mechanisms of action and no pharmacodynamic interactions have been observed.

Aclidinium bromide is a long-acting and reversible M_3 muscarinic antagonist with a rapid onset of action. The M_3 receptors on airway smooth muscle cell and submucosal glands mediate the bronchoconstriction response to acetylcholine and mucus secretion, respectively, and are critical to COPD airway pathology. Aclidinium bromide had potent affinities for all five human muscarinic receptors with affinity values of 0.09, 0.1, 0.12, 0.25 and 0.16 nM for M_1, M_2, M_3, M_4 and M_5 receptors, respectively. Residence time half-life at the M_3 receptor was 29.2 hours for aclidinium bromide. The M_3/M_2 and M_3/M_1 kinetic ratios were 6.3 and 4.2 for aclidinium bromide.

The principal therapeutic effect of formoterol fumarate is to relieve and prevent bronchoconstriction by relaxing airway smooth muscle via specific interaction with beta$_2$-adrenoreceptors. Numerous studies have confirmed that formoterol fumarate is highly potent and possesses high intrinsic activity and very high affinity at the beta$_2$-adrenoreceptor.

Safety Pharmacology

Nonclinical studies investigating the effects of aclidinium bromide/formoterol fumarate on cardiovascular parameters showed increased heart rates and arrhythmias at exposures over 286 times higher for aclidinium and 71 times higher for formoterol (based on C_{max}) compared with the maximum human exposure, and are therefore considered of little clinical relevance. These effects are known exaggerated pharmacological responses observed with beta$_2$-agonists.

Clinical Pharmacology

Pharmacokinetics

The extent to which the components of aclidinium bromide/formoterol fumarate 400/12 mcg affected each other's respective pharmacokinetic patterns was investigated in a randomised, open label, 3-way crossover study in healthy subjects. The study assessed the pharmacokinetics of a

single dose of aclidinium bromide/formoterol fumarate 400/12 mcg compared with its individual components (aclidinium bromide 400 mcg and formoterol fumarate 12 mcg).

The study showed that the overall plasma exposures (area under the concentration-time curve from time zero to time of last measurable value [AUC_{0-t}]) to aclidinium bromide or formoterol fumarate monotherapies were not significantly affected by administration in fixed combination. There was no evidence of a significant pharmacokinetic interaction between aclidinium bromide and formoterol fumarate.

Pharmacodynamics

Duration and Persistence of Effects on Lung Function

A 12-hour serial spirometry substudy, which evaluated the bronchodilation time-profile over 12 h post-dose, was performed in both the M/40464/30 (n=366) and LAC-MD-31 (n=270) clinical studies (see CLINICAL TRIALS). Statistically significant and clinically relevant adjusted mean increases from baseline in FEV1 were observed with DUAKLIR GENUAIR compared to placebo at all post-dose time points from 5 min post-dose to 12 h post-dose on Day 1 and from 0.5 h to 12 h post-dose at Week 24 (see Figure 3 and Figure 4).

Figure 3 **LS mean changes from baseline in FEV_1 (L) in the 12 hours post-dose on Day 1: M/40464/30 (Spirometry Substudy Population)**

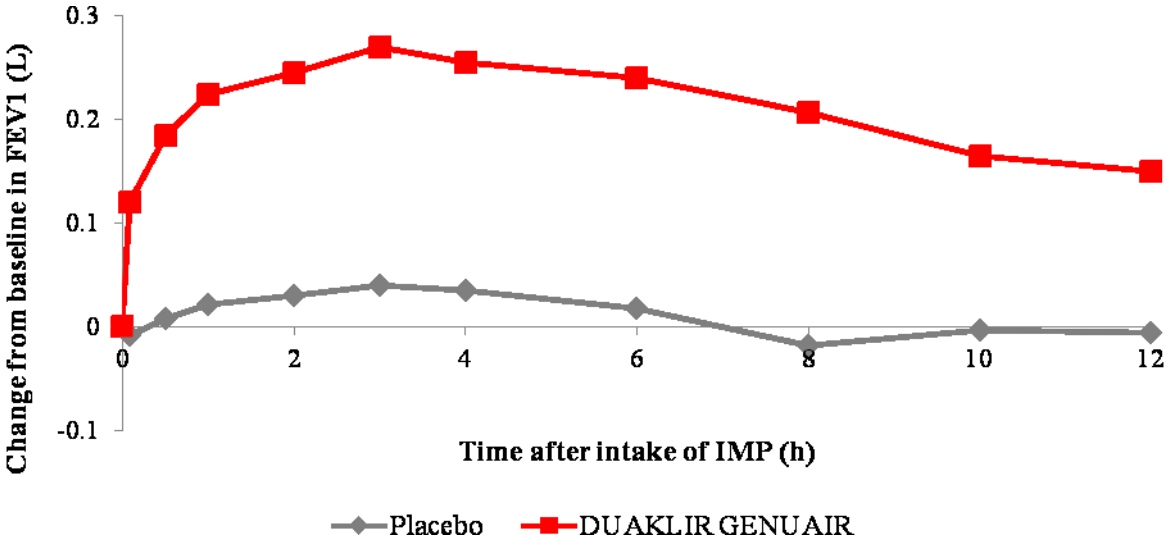
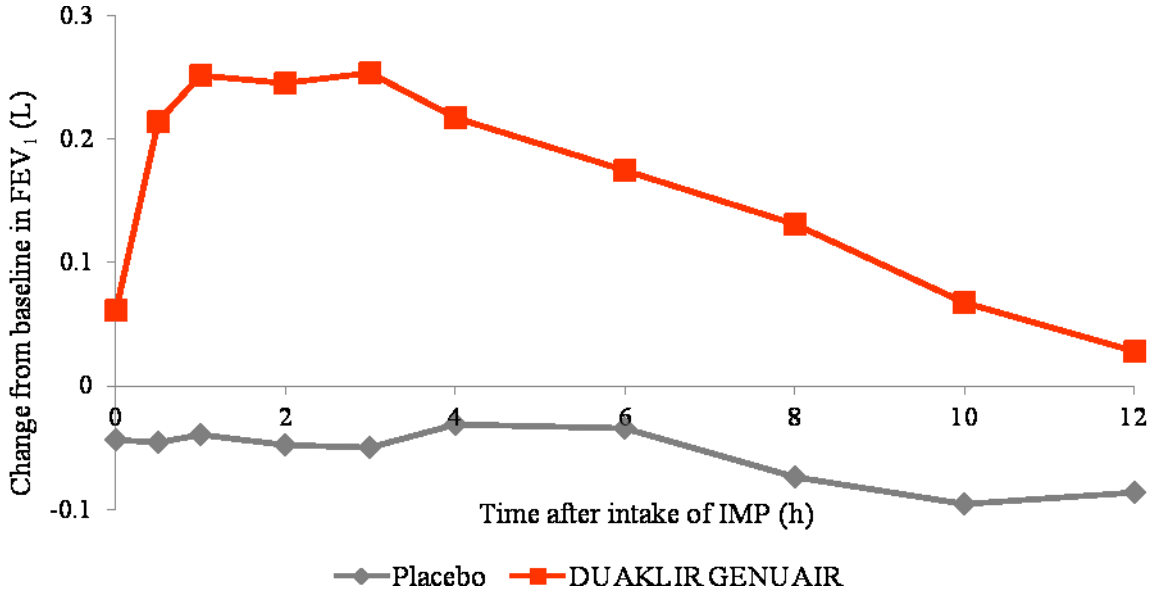


Figure 4 **LS mean changes from baseline in FEV_1 (L) in the 12 hours post-dose at Week 24: M/40464/30 (Spirometry Substudy Population)**



TOXICOLOGY

Nonclinical data reveal no clinically relevant findings for human use with aclidinium bromide and formoterol fumarate based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential and toxicity to reproduction and development.

Repeat-Dose Toxicity

The repeat dose toxicity of aclidinium bromide combined with formoterol fumarate was evaluated in 4-week and 13-week inhalation toxicity studies in dogs. Findings were consistent with systemic activity typically associated with anticholinergics and $beta_2$-agonists and are shown in Table 5.

Table 5 Repeat Dose Toxicology Studies – Aclidinium bromide/formoterol fumarate Combination

Study Type	Species	Route	Doses aclidinium bromide/ formoterol fumarate (mcg/kg/day)	Primary Findings
Repeat Dose 4 week	Beagle dog	Inhalation	0/0 (lactose), 33/2, 100/6 and 500/30	**Mortality:** All animals survived - **Aclidinium/formoterol 33/2:** Increased heart rate, increased P-amplitude with decreased PQ and QT intervals; clinical pathology revealed increased potassium (males) - **Aclidinium/formoterol 100/6:** Dry oral mucous membranes; increased heart rate, increased P amplitude with decreased PQ and QT intervals; ECG revealed ventricular arrhythmias and multifocal ventricular tachycardia during Week 1; clinical pathology revealed increased potassium (females) - **Aclidinium/formoterol 500/30:** Dry oral mucous membranes; dry eyes; swollen areas and erythema around the mouth; decreased food consumption and body weight loss in females; increased heart rate; increased P-amplitude with decreased PQ and QT intervals; 24-h heart rate values were lower at Week 4 compared with Week 1; ECG revealed ventricular arrhythmias and multifocal ventricular tachycardia during Week 1; clinical pathology revealed increased potassium (both sexes) and creatinine (females); histopathology revealed minimal to slight fibrosis of papillary muscle of the heart and moderate medial proliferation of the intramural arteries of the papillary muscle (these lesions were not noted at recovery) **NOAEL:** Aclidinium/formoterol 100/6 µg/kg/day
Repeat Dose 13 week	Beagle dog	Inhalation	0/0 (lactose), 33/2, 100/6, 300/18, 300/0 and 0/18	**Mortality:** All animals survived - **Aclidinium/formoterol 33/2 and Aclidinium/formoterol 100/6:** Increased heart rate; clinical pathology revealed increased creatinine - **Aclidinium/formoterol 300/18:** Increased heart rate; clinical pathology revealed increased creatinine; ECG revealed slight increase in P-amplitude with decreased PQ and QT intervals; persistent multifocal ventricular tachycardia or intermittent ventricular tachycardia with ventricular premature complexes were observed 24 h after the first day of dosing in two animals; no morphologic changes were noted in the heart muscle - **Aclidinium/formoterol 300/0:** Transient tachycardia; one animal had ventricular premature complexes - **Aclidinium/formoterol 0/18:** Increased heart rate; clinical pathology revealed increased creatinine. ECG revealed slight increase in P-amplitude with decreased PQ and QT interval **NOAEL:** Aclidinium/formoterol 100/6 µg/kg/day

NOAEL = no observed adverse effect level.

Since both aclidinium bromide and formoterol fumarate individual substances have previously shown to be non-genotoxic and non-carcinogenic, and the reproductive/developmental toxicity profiles of both have been sufficiently characterised individually, genotoxicity, carcinogenicity or reproductive toxicity studies of aclidinium bromide in combination with formoterol fumarate were not conducted.

Genotoxicity

Aclidinium bromide

Aclidinium bromide was positive in the *in vitro* bacterial gene mutation assay and in the *in vitro* thymidine locus mouse lymphoma assay in the presence of metabolic activation. However, aclidinium bromide was negative in the in vivo mouse micronucleus assay and the in vivo/in vitro unscheduled DNA synthesis assay with rat liver.

Formoterol fumarate

Mutagenicity tests covering a broad range of experimental endpoints have been conducted. No genotoxic effects were found in any of the in vitro or in vivo tests performed.

Carcinogenicity

Aclidinium bromide

Two-year inhalation studies were conducted in mice and rats to assess the carcinogenic potential of aclidinium bromide. No evidence of tumorigenicity was observed in rats and mice at target aclidinium bromide doses up to 0.20 mg/kg/day and 2.4 mg/kg/day, respectively (approximately 6 and 55 times the RHDD, respectively, based on the AUC of aclidinium bromide and its metabolites).

Formoterol fumarate

Two-year studies in rats and mice did not show any carcinogenic potential.

Reproductive and Developmental Toxicity

Aclidinium bromide

The effects of aclidinium bromide on fertility and embryonic development to implantation, embryo-foetal development and pre- and post-natal development were studied. Aclidinium bromide impaired several fertility and reproductive performance indices (increased number of days to mate, decreased conception rate, decreased number of corpora lutea, increased pre implantation loss with consequent decreased number of implantations and live embryos) in both male and female rats administered inhaled doses greater than or equal to 0.8 mg/kg/day (approximately 9 times the RHDD based on the AUC of aclidinium bromide and its metabolites). These adverse fertility effects were observed in the presence of paternal toxicity as evidenced by mortality and decreased body weight gain. However, there were no effects on mating index and sperm number and morphology. In the separate fertility assessments (treated males mated with untreated females; treated females mated with untreated males), no effect was observed in male

and female rats at inhaled dose of 1.9 and 0.8 mg/kg/day, respectively (approximately 20 and 9 times the RHDD, respectively, based on the AUC of aclidinium bromide and its metabolites).

Formoterol fumarate
Reproduction studies in rats revealed no impairment of fertility or effect on early embryonic development at oral doses up to 3 mg/kg (approximately 1000 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis).

In peri- and post-natal study in rats, a decreased survival rate of pups was noted. Because of this finding, a nursing study was also conducted. Litters from treated dams were nursed by untreated dams and vice-versa. The results suggest that mortality of pups was associated with maternal treatment during the peri-natal period. In this context, the proven passage of formoterol into milk of lactating rats is of importance. "Wavy ribs" were noted in fetuses in the rat teratology study and could be explained as the consequence of an incongruity between the force of (e.g. cervical and abdominal) muscular contractions and a delay in ossification. None of the pups examined on day 21 of weaning had this finding. In the rabbit teratology study with formoterol, the only finding was a decrease in the number of viable fetuses per litter at the high dose of 500 mg/kg.

REFERENCES

1. D'Urzo A.D., Rennard S.I., Kerwin E.M., et al. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. *Respir Res*. 2014;15(1):123.

2. Product Monograph: Foradil®. Long-Acting Beta$_2$-Agonist (LABA). Novartis Pharmaceuticals Canada Inc. Montreal, Canada.

3. Product Monograph: Tudorza® Genuair®. Long-Acting Muscarinic Antagonist (LAMA). AstraZeneca Canada Inc., Mississauga, Canada.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr DUAKLIR® GENUAIR®
aclidinium bromide/formoterol fumarate dihydrate dry powder for oral inhalation

This leaflet is part III of a three-part "Product Monograph" published when DUAKLIR GENUAIR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DUAKLIR GENUAIR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

What the medication is used for:
DUAKLIR GENUAIR is used long term to help open the airways in adults with breathing difficulties due to a lung disease called chronic obstructive pulmonary disease (COPD).

DUAKLIR GENUAIR is **NOT** for treating asthma or sudden, severe symptoms of COPD.

If you are a smoker, it is important to quit smoking. This will help decrease the symptoms of COPD and potentially increase your lifespan.

What it does:
DUAKLIR GENUAIR contains two active ingredients:
- Aclidinium bromide is a long-acting muscarinic antagonist (LAMA).
- Formoterol fumarate dihydrate is a long-acting beta$_2$-agonist (LABA).

Both belong to a group of medicines called bronchodilators. Bronchodilators help to open and relax the muscles of the airways. This allows more air to get in and out of the lungs. This makes it easier for patients with COPD to breathe and helps prevent shortness of breath and wheezing.

This medicine does not cure COPD but helps to control it. It is important that you take DUAKLIR GENUAIR regularly even if you feel fine.

When it should not be used:
Do not use DUAKLIR GENUAIR:
- if you are allergic to aclidinium bromide, formoterol fumarate or any of the other ingredients of this medicine;
- if you are under 18 years of age;
- to treat sudden severe symptoms of COPD (called a COPD flare-up), such as sudden shortness of breath or wheezing. If you experience this sort of attack you must use a rapid onset, short duration, inhaled bronchodilator such as salbutamol (rescue medication). Keep this rescue medication with you at all times;
- to treat asthma.

What the medicinal ingredients are:
aclidinium bromide and formoterol fumarate dihydrate

What the nonmedicinal ingredients are:
lactose monohydrate

What dosage forms it comes in:
Dry powder for oral inhalation: 400 mcg of aclidinium bromide and 12 mcg of formoterol fumarate dihydrate. Your inhaler will contain 60 metered doses.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
DUAKLIR GENUAIR should only be used to treat COPD.
DUAKLIR GENUAIR should not be used to treat asthma.

You are advised that in patients with asthma, long-acting beta$_2$-agonist (LABA) medicines may increase the chance of death from asthma problems. In a large asthma study, more patients who used another LABA medicine (salmeterol) died from asthma problems compared with patients who did not use that LABA medicine. This finding may also apply to DUAKLIR GENUAIR.

BEFORE you use DUAKLIR GENUAIR talk to your doctor or pharmacist if you:
- have heart problems, such as rapid or irregular heart beat or an abnormal electrical

signal called “prolongation of the QT interval”;
- have high blood pressure;
- have diabetes;
- have low levels of potassium in your blood;
- have seizures;
- have thyroid gland problems or disease;
- have a tumour in one of your adrenal glands (phaeochromocytoma);
- are taking similar medicines for your lung disease;
- are pregnant or planning to become pregnant;
- are breastfeeding. It is not known if DUAKLIR GENUAIR can pass into breastmilk;
- are taking any medications including eye drops, this includes medications you can buy without prescription;
- have eye problems such as glaucoma, eye pain, blurred vision, see halos around lights or coloured images;
- have an enlarged prostate, problems passing urine, or painful urination;
- have a severe allergy to milk proteins. Ask your doctor if you are not sure;
- have allergies to food or drugs.

DUAKLIR GENUAIR should not be used more frequently than twice daily. Do not exceed the prescribed dose.

Remember to tell any other doctor, dentist or pharmacist you consult that you are taking this medication.

During treatment with DUAKLIR GENUAIR, tell your doctor right away if you experience any of the following symptoms:
- **stop taking DUAKLIR GENUAIR and tell your doctor immediately** if you experience a tightness of the chest, coughing, wheezing or breathlessness immediately after inhalation of DUAKLIR GENUAIR (signs of bronchospasm);
- **stop taking DUAKLIR GENUAIR and tell your doctor immediately** if you experience difficulties in breathing or swallowing, swelling of tongue, lips and face, hives or itching, skin rash (signs of hypersensitivity reaction). Do not use DUAKLIR GENUAIR again before speaking with your doctor;
- **stop taking DUAKLIR GENUAIR and tell your doctor immediately** if you experience eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes; these may be signs of an acute attack of narrow-angle glaucoma;
- if your COPD symptoms (breathlessness, wheezing, cough) do not improve or if they worsen during your treatment.

DUAKLIR GENUAIR does not relieve sudden symptoms of COPD. Always have a short-acting bronchodilator medicine with you to treat acute symptoms. If you do not have an inhaled, short-acting bronchodilator, ask your doctor to have one prescribed for you.

Get emergency medical care if:
- breathing problems worsen quickly;
- you use your short-acting bronchodilator medicine, but it does not relieve your breathing problems.

Driving and using machines:
Avoid driving and using machines if you feel dizzy, have blurred vision or headaches.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drugs that may interact with DUAKLIR GENUAIR include:
- Any medicines that may be similar to DUAKLIR GENUAIR (contain the same or similar active ingredients, e.g. medicines containing aclidinium, tiotropium, ipratropium glycopyrronium, formoterol or salmeterol);
- Oral corticosteroids (prednisone);
- Diuretics (water pills);
- Xanthine medicines (such as theophylline) used to treat asthma;
- Beta blocker medicines used to treat high blood pressure or other heart problems (such as atenolol or propranolol) or to treat glaucoma (such as timolol eye drops);
- Medications used to treat depression or sad mood (monoamine oxidase inhibitors and tricyclic antidepressants);
- Macrolide antibiotics (such as erythromycin, azithromycin, clarithromycin);
- Antihistamines;
- Inhaled anaesthetics such as halogenated hydrocarbons (e.g. halothane), used during surgery. Inform your doctor that you use DUAKLIR GENUAIR if you are to have surgery under anaesthesia.

Other Drugs: Drugs such as quinidine, disopyramide, procainamide, phenothiazines, antihistamines, and tricyclic antidepressants may be associated with QT-interval prolongation and an increased risk of heart problems (see WARNINGS AND PRECAUTIONS).

PROPER USE OF THIS MEDICATION

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

- Use DUAKLIR GENUAIR even when you have no breathing problems or other symptoms of COPD.
- Do not use DUAKLIR GENUAIR more than twice a day or at higher doses than recommended by your doctor.
- Do not stop using the drug without consulting your doctor.
- You can use DUAKLIR GENUAIR anytime before or after food or drink.

Usual adult dose:
The recommended dose is one inhalation twice a day, once in the morning and once in the evening.

Overdose:

If you think you have taken too much DUAKLIR GENUAIR, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you forget a dose of DUAKLIR GENUAIR, inhale the dose as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

Instructions for Use

Before using the DUAKLIR GENUAIR inhaler, read the full Instructions for Use. It is important that you read this information as the GENUAIR may work differently from inhalers you have used. If you have any questions ask your doctor or pharmacist.

The Instructions for Use is divided into the following sections:

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

Getting Started

DUAKLIR GENUAIR is a multidose inhaler that uses your breath to deliver the medicine directly into your lungs. It is important that you become familiar with the parts of your GENUAIR inhaler (Figure A).

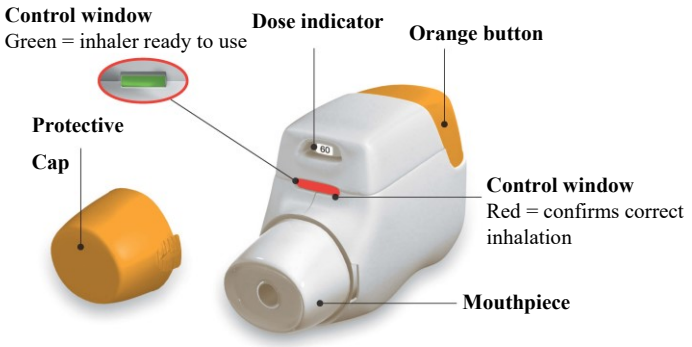


Figure A

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.
c) Pull off the protective cap by lightly squeezing the arrows marked on each side (Figure B).

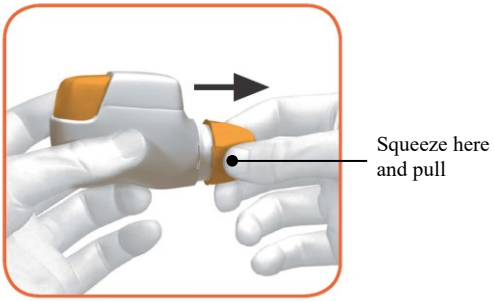


Figure B

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. It should be red (Figure C).

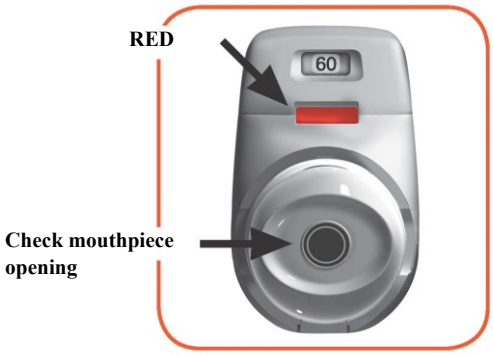


Figure C

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

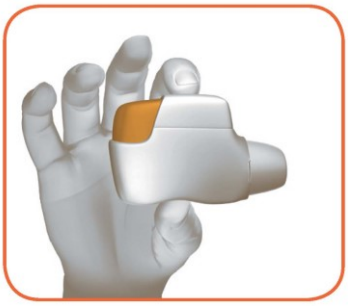


Figure D

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 the inhaler.**

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 taking your dose. **Do not tilt the inhaler**.

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

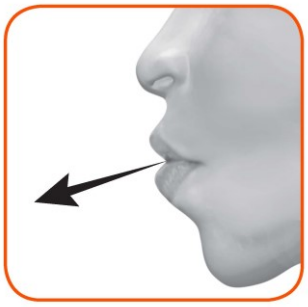


Figure I

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

Do not hold the orange button down while inhaling.

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

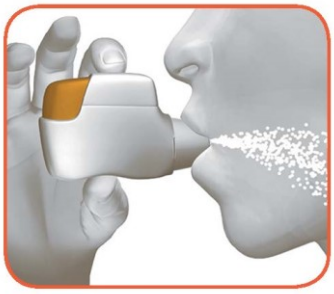


Figure J

A 'click' will let you know that you are inhaling correctly. **Keep breathing in as long as possible after you hear the 'click'.** If you do not hear the 'click', continue with Steps 2.4-2.7 and use the control window to ensure you have inhaled correctly.

2.4 Take the inhaler out of your mouth.

2.5 Hold your breath for as long as possible.

2.6 Slowly breathe out away from the inhaler.

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

Stop and Check:

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

Figure K

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

Figure L

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

If the control window still does not change to red, you may have forgotten to release the orange button before inhaling, or you may not have inhaled strongly enough. If this happens, try again. Make sure you have released the orange button, and then go back to 'STEP 2: Inhale your medicine' and repeat steps 2.1 to 2.7. Make sure that you have breathed out completely before you take a strong, deep breath through the mouthpiece.

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

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

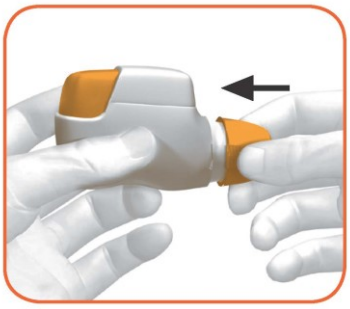


Figure M

Additional information

What should you do if you accidentally prepare a dose?

Do not tilt your inhaler. Store it with the protective cap in place until it is time to inhale your medicine, then remove the protective 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.

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).

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

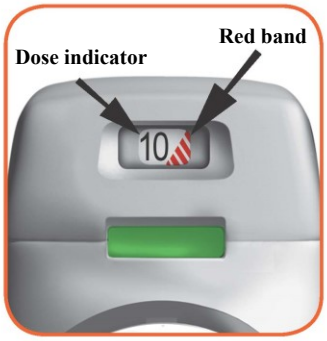


Figure N

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 protective 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 O

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.

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, DUAKLIR GENUAIR can cause side effects, although not everybody gets them.

Side effects may include:

- inflammation or irritation of the nose and throat;
- headache;
- urinary tract infection;
- throat pain;
- dizziness;
- muscle pain, cramps, spasms;
- flu;
- difficulty sleeping (insomnia);
- tooth infection;
- chest pain;
- shaking/tremor;
- cough;
- dry mouth;
- anxiety, agitation;
- rash, skin itching;
- distorted sense of taste;
- blurred vision;
- increased blood pressure;
- swelling of the hands or feet;
- inflammation of the mouth (stomatitis);
- hoarseness (dysphonia).

If any of these affects you severely, **tell your doctor or pharmacist.**

DUAKLIR GENUAIR can cause abnormal blood test results such as decreased levels of potassium, increased blood sugar, and increased creatine phosphokinase. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	
Common			
Nausea and/or diarrhea	√		
Uncommon			
Decreased levels of potassium in the blood: muscle weakness, twitching and/or irregular heartbeat		√	
Increased blood sugar: frequent urination, thirst and hunger		√	
Palpitations, unusually fast or irregular heart beat		√	
Difficulty and pain passing urine or a feeling that your bladder has not completely emptied (urinary retention)		√	
Rare			
Paradoxical Bronchospasm: tightness of the chest associated with coughing, wheezing, or breathlessness immediately after inhalation of DUAKLIR GENUAIR			√
Glaucoma: New or worsened pressure in your eyes, eye pain or discomfort, blurred vision, seeing halos of bright colours around lights, red eyes			√
Unknown			
Serious allergic reactions: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Difficulty breathing		√	

This is not a complete list of side effects. For any unexpected effects while taking DUAKLIR GENUAIR, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15 to 30°C.

Keep the DUAKLIR GENUAIR inhaler protected inside the sealed bag until you start to use it. Use the DUAKLIR GENUAIR inhaler within 60 days of opening the bag.

Keep DUAKLIR GENUAIR 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 bag after "EXP". The expiry date refers to the last day of the month.

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. You should follow local guidelines for domestic waste when throwing away the empty or unused inhaler. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Call toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This Consumer Information Leaflet provides you with the most current information at the time of printing.

The most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at: www.covispharma.com or by contacting the sponsor, Covis Pharma GmbH at: 1-833-523-3009

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