DUOVA Inhaler (Tiotropium bromide monohydrate + Formoterol fumarate)

**Composition**

DUOVA Inhaler
Each actuation delivers:
Tiotropium Bromide Monohydrate, equivalent to Tiotropium ............ 9 mcg
Formoterol Fumarate Dihydrate IP..........................6 mcg

**Dosage Form**

Inhalation aerosol

**Description**

Tiotropium bromide monohydrate is a long-acting, anticholinergic agent, which binds to the muscarinic receptors in the bronchial smooth musculature. Tiotropium inhibits the cholinergic (bronchoconstrictive) effects of acetylcholine, released from parasympathetic nerve endings. The long duration is due to the slow dissociation from the M₃-receptor, exhibiting a significantly longer dissociation half-life than ipratropium.

Formoterol fumarate is a potent, long-acting, selective beta₂-receptor agonist, which exhibits a bronchodilator effect by binding to the beta₂-receptors in the airways. The combination of tiotropium and formoterol produces additive effects since they target different receptors in the airways.

**Pharmacology**

- **Pharmacodynamics**

  Tiotropium:
  Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M₁ to M₅. In the airways, it exhibits pharmacological effects through the inhibition of M₁-receptors at the smooth muscle, leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In pre-clinical *in vitro* as well as *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects was dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

  Electrophysiology:
  In a dedicated QT study involving 53 healthy volunteers, tiotropium 18 mcg and 54 mcg (i.e. three times the therapeutic dose) over 12 days did not significantly prolong QT intervals of the ECG.

Formoterol:
Formoterol fumarate is a long-acting, selective beta₂-adrenergic receptor agonist (beta₂-agonist). Inhaled formoterol
Fumarate acts locally in the lungs as a bronchodilator. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at \( \beta_2 \)-receptors than at \( \beta_1 \)-receptors. Although \( \beta_2 \)-receptors are the predominant adrenergic receptors in bronchial smooth muscle and \( \beta_1 \)-receptors are the predominant receptors in the heart, there are also \( \beta_2 \)-receptors in the human heart, comprising 10-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective \( \beta_2 \)-agonists may have cardiac effects.

The pharmacological effects of \( \beta_2 \)-adrenoceptor agonist drugs, including formoterol, are, at least in part, attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses 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 inhibit the release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lungs. Formoterol also inhibits histamine-induced plasma albumin extravasation in anaesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

Pharmacokinetics

Tiotropium:
In common with other inhaled drugs, the majority of the delivered dose of tiotropium is deposited in the gastrointestinal tract and, to a lesser extent, in the lungs, the intended organ. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption:
Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lungs is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastrointestinal tract (10-15%). For the same reason, food is not expected to influence the absorption of tiotropium. Oral solutions of tiotropium have an absolute bioavailability of 2–3%. Maximum tiotropium plasma concentrations were observed 5 minutes after inhalation. At steady state, peak tiotropium plasma levels in COPD patients were 12.9 pg/ml and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.71 pg/ml.

Distribution:
Tiotropium shows a volume of distribution of 32 L/kg, indicating that the drug binds extensively to tissues. The drug is bound by 72% to plasma proteins. At steady state, peak tiotropium plasma levels in chronic obstructive pulmonary disease (COPD) patients were 17–19 pg/mL, when measured 5 minutes after dry powder inhalation of an 18 mcg dose, and decreased rapidly in a multi-compartmental manner. Steady-state trough plasma concentrations were 3–4 pg/mL. Local concentrations in the lungs are not known, but the mode of administration suggests substantially higher concentrations in the lungs. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Metabolism:
The extent of biotransformation appears to be small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is non-enzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, neither of which binds to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene.
Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. In vitro studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

**Elimination:**
The effective half-life of tiotropium ranges between 27-45 hours in COPD patients. After an intravenous dose in young healthy volunteers, total clearance was 880 mL/min. Intravenously administered tiotropium is mainly excreted unchanged in the urine (74%). After inhalation by COPD patients to steady-state, urinary excretion is 7% (1.3 mcg) of the unchanged drug over 24 hours, the remainder being mainly non-absorbed drug in the gut, which is eliminated via the faeces. The renal clearance of tiotropium exceeds the creatinine clearance (CrCl), indicating active secretion into the urine. After continual once-daily inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

**Drug Interactions:**
An interaction study was conducted with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once daily. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC$_{0-4h}$, a 28% decrease in the renal clearance of tiotropium, and no significant change in the C$_{max}$ and amount excreted in the urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium. Therefore, no clinically significant interaction occurred between tiotropium and cimetidine or ranitidine.

**Special Populations:**

**Elderly Patients:**
As expected for drugs predominantly excreted renally, advanced age was associated with a decrease of tiotropium renal clearance (326 mL/min in COPD patients <58 years to 163 mL/min in COPD patients >70 years), which may be explained by decreased renal function. After inhalation, tiotropium excretion in the urine decreased from 14% (young healthy volunteers) to about 7% (COPD patients). Plasma concentrations were numerically increased with advancing age within COPD patients (43% increase in AUC$_{0-4h}$ after dry powder inhalation), which was not significant when considered in relation to inter- and intra-individual variability.

**Hepatically-impaired Patients:**
The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

**Renally-impaired Patients:**
Since tiotropium is, predominantly, renally excreted, renal impairment was associated with increased plasma drug concentrations and reduced drug clearance after both intravenous infusion and dry powder inhalation. Mild renal impairment (CrCl 50-80 mL/min), which is often seen in elderly patients, increased tiotropium plasma concentrations (39% increase in AUC$_{0-4h}$ after intravenous infusion). In COPD patients with moderate to severe renal impairment (CrCl <50 mL/min), the intravenous administration of tiotropium resulted in the doubling of the plasma concentrations (82% increase in AUC$_{0-4h}$), which was confirmed by plasma concentrations after dry powder inhalation.

**Formoterol:**

**Absorption:**
Following inhalation of a single 120 mcg dose of formoterol fumarate by 12 healthy subjects, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 92 pg/mL within 5 minutes of dosing. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 mcg b.i.d., the mean plasma concentrations of formoterol ranged between 4.0 and 8.8 pg/mL and 8.0 and 17.3 pg/mL, respectively, at 10 min, 2 h and 6 h post inhalation. Studies in 10 healthy males investigating the cumulative urinary excretion of formoterol and/or its (R, R) and (S, S)-enantiomers, after inhalation of dry powder (12-96 mcg) or aerosol formulations (12-96 mcg), showed that absorption
increased linearly with the dose.

After 12 weeks administration of 12 mcg or 24 mcg formoterol powder b.i.d., the urinary excretion of unchanged formoterol increased by 63-73% in adult patients with asthma, by 19-38% in adult patients with COPD and by 18-84% in children, suggesting a modest and self-limiting accumulation of formoterol in plasma after repeated dosing. As reported for other inhaled drugs, it is likely that about 90% of formoterol administered from an inhaler will be swallowed and then absorbed from the gastrointestinal tract. This means that the pharmacokinetic characteristics of the oral formulation largely apply also to the inhalation powder. When 80 mcg of 3H-labelled formoterol fumarate was orally administered to two healthy volunteers, at least 65% of the drug was absorbed. The excreted amounts of formoterol at steady-state were close to those predicted based on single-dose kinetics.

Oral doses of up to 300 mcg of formoterol are rapidly absorbed from the gastrointestinal tract. The peak plasma concentration of the unchanged substance is reached after 30 minutes to 1 hour.

Repeated daily administration of 40 micrograms to 160 micrograms per day does not result in accumulation because of the short half-life. The pharmacokinetics of formoterol does not differ significantly between men and women.

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

Metabolism:
Formoterol is eliminated primarily by metabolism, direct glucuronidation being the major pathway of biotransformation, with O-demethylation followed by further glucuronidation being another pathway. Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Multiple isoforms catalyze the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP2D6, 2C19, 2C9, and 2A6) of formoterol, and so consequently the potential for metabolic drug-drug interaction is low. Formoterol did not inhibit cytochrome P450 3A4 at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isoforms results in elevated systemic exposure to formoterol or systemic adverse effects, has not been adequately explored. The kinetics of formoterol are similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism.

Elimination:
Elimination of formoterol from the circulation seems to be polyphasic; the apparent half-life depends on the time interval considered. On the basis of plasma or blood concentrations up to 6, 8 or 12 hours after oral administration, elimination half-life of about 2–3 hours was determined. From urinary excretion rates between 3 and 16 hours after inhalation, a half-life of about 5 hours was calculated.

Following oral administration of 80 mcg of radiolabeled formoterol fumarate to 2 healthy subjects, 59%-62% of the radioactivity was eliminated in the urine and 32%-34% in the feces over a period of 104 hours. Renal clearance of formoterol from blood in these subjects was about 150 mL/min. Following inhalation of a 12 mcg or 24 mcg dose by 16 patients with asthma, about 10% and 15%-18% of the total dose was excreted in the urine as unchanged formoterol and direct conjugates of formoterol, respectively. Following inhalation of 12 mcg or 24 mcg dose by 18 patients with COPD the corresponding values were 7% and 6-9% of the dose, respectively.

Based on plasma concentrations measured following inhalation of a single 120 mcg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. From urinary excretion rates measured in these subjects, the mean terminal elimination half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 13.9 and 12.3 hours, respectively. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively, following single inhaled doses between 12 and 120 mcg in healthy volunteers and single and repeated doses of 12 and 24 mcg in patients with asthma. Thus, the relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the
other after repeated dosing.

Special Populations:

Gender:

After correction for body weight, formoterol pharmacokinetics did not differ significantly between males and females.

Geriatrics and Paediatrics:

The pharmacokinetics of formoterol has not been studied in the elderly population, and limited data are available in paediatric patients.

In a study of children with asthma who were 5 to 12 years of age, when formoterol fumarate 12 mcg or 24 mcg was given twice daily by oral inhalation for 12 weeks, the accumulation index ranged from 1.18-1.84 based on urinary excretion of unchanged formoterol. Hence, the accumulation in children did not exceed that in adults, where the accumulation index ranged from 1.63-2.08 (see above). Approximately 6% and 6.5-9% of the dose was recovered in the urine of the children as unchanged and conjugated formoterol, respectively.

Hepatic/Renal Impairment:

The pharmacokinetics of formoterol has not been studied in subjects with hepatic or renal impairment.

Indications

DUOVA Inhaler is indicated in the maintenance treatment of COPD (chronic obstructive pulmonary disease).

Dosage And Administration

The recommended dosage is the inhalation of two puffs, once daily. It is recommended to use DUOVA Inhaler with the Cipla Zerostat/Zerostat VT Spacer.

Contraindications

DUOVA Inhaler is contraindicated in patients with a hypersensitivity to atropine or its derivatives (e.g., ipratropium and oxitropium), formoterol, tiotropium or any other component of the product.

Warnings And Precautions

Since DUOVA Inhaler contains a combination of tiotropium and formoterol, the warnings and precautions for both drugs should be observed.

DUOVA Inhaler is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy. In the event of an acute attack, a rapid-acting beta₂-agonist should be used.

Tiotropium:

Consistent with its anticholinergic activity, tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination), urinary retention or prostatic hyperplasia. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia. Patients should consult a physician immediately should any of these signs or symptoms develop.

As plasma concentration increases with decreased renal function in patients with moderate to severe renal impairment (creatinine clearance \( \times 50 \) ml/min) tiotropium bromide should be used only if the expected benefit outweighs the potential risk. There is no long term experience in patients with severe renal impairment.

Patients should be cautioned to avoid getting the drug powder into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision,
visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema. Should any combination of these eye symptoms develop, patients should stop using DUOVA Inhaler and consult a specialist immediately. Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental caries.

Tiotropium bromide should not be used more frequently than once daily.

Immediate hypersensitivity reactions, including angio-oedema, may occur after administration of tiotropium. If such a reaction occurs, therapy with DUOVA Inhaler should be stopped at once and alternative treatments should be considered.

Inhaled medicines, including tiotropium, may cause paradoxical bronchospasm. If this occurs, treatment with DUOVA Inhaler should be stopped and other treatments considered.

As plasma concentration increases with decreased renal function in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min) Tiotropium should be used only if the expected benefit outweighs the potential risk. There is no long term experience in patients with severe renal impairment. Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental caries.

Formoterol:

It should not be initiated in patients with significantly worsening, acutely deteriorating, or potentially life-threatening episodes of COPD. The use of formoterol in this setting is not appropriate.

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, aneurysm, pheochromocytoma, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

When beginning treatment with formoterol, patients who have been taking inhaled, short-acting beta-2-agonists 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 symptoms.

Formoterol fumarate, like other beta-2-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure and/or symptoms.

Special care and supervision, with particular emphasis on dosage limits, is required in patients receiving formoterol when the following conditions may exist: Ischaemic heart disease, cardiac arrhythmias, especially third degree atrioventricular block, severe cardiac decompensation, idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, thyrotoxicosis, coronary insufficiency, known or suspected prolongation of the QT interval (QTc> 0.44 sec), flattening of T wave, ST segment depression and in patients treated with drugs affecting the QT interval. Formoterol itself may induce prolongation of QT interval.

Caution should be used when co-administering theophylline and formoterol in patients with pre-existing cardiac conditions. Due to the hyperglycaemic effect of beta-2-stimulants, additional blood glucose controls are recommended in diabetic patients.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

As with other inhalation therapy there is a risk of paradoxical bronchospasm. If paradoxical bronchospasm occurs, formoterol should be discontinued immediately and alternative therapy instituted.

Immediate hypersensitivity reactions may occur after administration of formoterol, as demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm.

Because beta-agonists may potentially interfere with uterine contractility, Formoterol should be used during labor only if
the potential benefit justifies the potential risk.

Drug Interactions

There has been no clinical trial performed to study the interactions of various drugs with DUOVA Inhaler, however the interactions of the individual components of the combination should be kept in mind before prescribing DUOVA Inhaler.

Tiotropium:
Although no formal drug interaction studies have been performed, tiotropium bromide has been used concomitantly with other drugs without clinical evidence of drug interactions. These include sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leukotriene modifiers, cromones, anti-IgE treatment. Use of LABA or ICS was not found to alter the exposure to tiotropium. The co-administration of tiotropium bromide with other anticholinergic-containing drugs has not been studied and is therefore not recommended.

Formoterol:
If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of Formoterol may be potentiated.
Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists. The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonist with non-potassium sparing diuretics. Formoterol, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta₂-agonists, such as formoterol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardio selective beta-blockers could be considered, although they should be administered with caution.
There is an elevated risk of arrhythmias in patients receiving concomitant anesthesia with halogenated hydrocarbons.

Use In Special Population

Renal Impairment
As Tiotropium bromide is a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of <50 mL/min) treated with DUOVA Inhaler should be monitored closely.

Hepatic Impairment
The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. However, hepatic impairment is not expected to have relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors. The pharmacokinetics of formoterol has not been studied in subjects with hepatic or renal impairment.
Pregnancy

There are no adequate and well-controlled studies of formoterol in pregnant women. Animal reproduction studies of formoterol fumarate in rats and rabbits revealed evidence of teratogenicity as well as other developmental toxic effects. Use of DUOVA Inhaler during pregnancy should be considered only if the expected benefit to the mother is greater than the risk to the foetus.

Lactation

There are no well-controlled human studies of the use of formoterol in nursing mothers. Since it is not known whether the active substances pass into breast milk, DUOVA Inhaler is not recommended for use during lactation.

Paediatric Use

The safety and effectiveness of the combination of tiotropium and formoterol in paediatric patients has not been established and, therefore, DUOVA Inhaler should not be used in patients under 18 years of age.

Undesirable Effects

As DUOVA Inhaler is a combination of tiotropium and formoterol, the type and severity of side effects associated with each of the components may be expected.

Tiotropium:
Several organ systems and functions are under the control of the parasympathetic nervous system and, therefore, can be affected by anticholinergic agents. Possible adverse events attributable to systemic anticholinergic effects include dry mouth, dry throat, increased heart rate, blurred vision, glaucoma, urinary difficulty, urinary retention, and constipation. The most common anticholinergic adverse reaction reported by COPD patients was dry mouth, which was mild in the majority of cases. In general, dry mouth had an onset of 3 and 5 weeks, which resolved while patients continued to receive tiotropium bromide. Serious undesirable effects consistent with anticholinergic effects include glaucoma, constipation and intestinal obstruction including ileus paralytic as well as urinary retention. The adverse events seen include body as a whole: chest pain (non-specific), and edema (dependent), allergic reaction, leg pain; gastrointestinal system disorders: abdominal pain, constipation, dry mouth, dyspepsia, vomiting, gastroesophageal reflux disease, gastrointestinal disorder not otherwise specified (NOS), oropharyngeal candidiasis, intestinal obstruction, including ileus paralytic, gingivitis, glossitis, dysphagia, stomatitis (including ulcerative stomatitis), nausea, dental caries; musculoskeletal and connective tissue disorders: myalgia, skeletal pain, joint swelling; resistance mechanism disorders: infection (herpes zoster), moniliasis; respiratory, thoracic and mediastinal disorders: oral candidiasis, throat irritation, dysphonia, cough, bronchospasm, laryngitis, epistaxis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection; skin and subcutaneous tissue disorders, immune system disorders: rash, urticaria, pruritus, hypersensitivity (including immediate reactions), angioedema, skin infection, skin ulcer, dry skin; renal and urinary disorders: dysuria, urinary retention, urinary tract infection; eye disorders: vision blurred, glaucoma, intraocular pressure increased, cataract; metabolism and nutrition disorders: dehydration; nervous system disorders: dizziness, headache, insomnia, paresthesia, taste disorders; cardiac disorders: tachycardia, palpitations, supraventricular tachycardia, atrial fibrillation, angina pectoris (including aggravated angina pectoris); psychiatric disorder: depression.

In addition, the following adverse reactions have also been identified during worldwide post-approval use of tiotropium bromide: mouth ulceration, and pharyngolaryngeal pain, dysphagia, and hoarseness.

Formoterol:

An increase in anticholinergic effects may occur with increasing age.
Adverse events that occurred in ≥1% of patients with COPD in two clinical trials with formoterol fumarate 12 mcg twice daily: upper respiratory tract infection, back pain, pharyngitis, chest pain, sinusitis, fever, cramps in muscles and leg, anxiety, pruritus, increased sputum and dry mouth. The two clinical trials included doses of 12 mcg and 24 mcg, administered twice daily. Seven treatment-emergent adverse reactions showed dose ordering among tested doses of 12 and 24 mcg administered twice daily; pharyngitis, fever, muscle cramps, increased sputum, dysphonia, myalgia, and tremor. Overall, the frequency of all cardiovascular treatment-emergent adverse reactions in the two pivotal studies was 6.4% for formoterol fumarate 12 mcg twice daily, and 6.0% for placebo.

There were no frequently-occurring specific cardiovascular treatment emergent adverse reactions for formoterol fumarate (frequency greater than or equal to 1% and greater than placebo).

Rare reports of anaphylactic reactions, including severe hypotension and angioedema, have also been received in association with the use of formoterol fumarate inhalation powder. Other adverse reactions to formoterol are similar in nature to other selective beta₂-adrenoceptor agonists; e.g., angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, nausea, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis, agitation, anxiety, restlessness, palpitations, supraventricular tachycardia, increased and variations in blood pressure, muscle cramp, myalgia, acute asthma exacerbation and insomnia.

The following adverse reactions have been identified during post approval use of formoterol fumarate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare reports of anaphylactic reactions, including severe hypotension and angioedema, hypokalemia, hyperglycemia, cough, rash, angina pectoris, cardiac arrhythmias, e.g., atrial fibrillation, ventricular extra systoles, tachyarrhythmia, electrocardiogram QT prolonged, blood pressure increased (including hypertension) have been reported.

Overdosage

There is no data on overdosage with the combination of tiotropium and formoterol.

Tiotropium:
High doses of tiotropium bromide may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 mcg tiotropium bromide in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth, were observed following seven-day dosing of up to 170 mcg tiotropium bromide in healthy volunteers. In a multiple-dose study in COPD patients with a maximum daily dose of 43 mcg of tiotropium bromide over 4 weeks, no significant undesirable effect has been observed. Acute intoxication by inadvertent oral ingestion of Tiotropium bromide is unlikely due to low oral bioavailability.

Formoterol:
The expected signs and symptoms with overdosage of formoterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of formoterol. The preferred antidotes are other cardioselective beta₂-blocking agents, but these should be used with caution in patients with a history of bronchospasm.

Packaging Information

DUOVA Inhaler with Dose Counter......Each canister contains 200 metered doses

Last updated: July 2015
Last reviewed: July 2015

DUOVA Inhaler

Source URL: https://ciplamed.com/content/duova-inhaler