Vilanto™-UF

(Fluticasone Furoate + Umeclidinium + Vilanterol)

ویلینٹو-یوایف

Dry Powder Inhaler Capsules

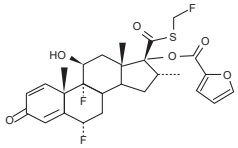
100mcg + 62.5mcg + 25mcg

DESCRIPTION

Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) is an oral inhalation powder drug product for delivery of a combination of Fluticasone Furoate (an ICS), Umeclidinium (an anticholinergic), and Vilanterol (a LABA (Long Acting beta Agonist)).

Fluticasone Furoate

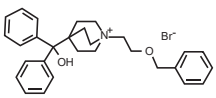
Fluticasone Furoate has the chemical name (6α,11β,16α,17α)-6,9-difluoro-17-[(fluoro-methyl)thio]carbonyl]-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furancarboxylate. Its molecular formula is $C_{27}H_{29}F_3O_6S$ and the structural formula is:



Fluticasone Furoate

Umeclidinium Bromide

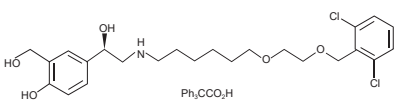
Umeclidinium bromide has the chemical name 1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide. Its molecular formula is $C_{29}H_{34}NO_2$•Br (as a quaternary ammonium bromide compound) and the structural formula is:



Umeclidinium Bromide

Vilanterol Trifenatate

Vilanterol Trifenatate has the chemical name triphenylacetic acid-4-{(1R)-2-[(6-{2-[2,6-dicholorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1:1). Its molecular formula is $C_{24}H_{33}Cl_2NO_5$•$C_{20}H_{16}O_2$ and the structural formula is:



Vilanterol Trifenatate

QUALITATIVE & QUANTITATIVE COMPOSITION

Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) 100mcg + 62.5mcg + 25mcg is available for administration as:

Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) DPI Capsules 100mcg + 62.5mcg + 25mcg
Each capsule contains:
Fluticasone Furoate…100mcg
Umeclidinium Bromide equivalent to Umeclidinium…62.5mcg
Vilanterol Trifenatate equivalent to Vilanterol…25mcg

CLINICAL PHARMACOLOGY

Mechanism of Action

Fluticasone Furoate

Fluticasone Furoate is a corticosteroid with potent anti-inflammatory activity. The precise mechanism through which Fluticasone Furoate affects COPD symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g. eosinophils, macrophages, lymphocytes) and mediators (e.g. cytokines and chemokines) involved in inflammation.

Umeclidinium

Umeclidinium is a long-acting muscarinic receptor antagonist (also referred to as an anticholinergic). Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic receptors on airway smooth muscle. It demonstrates slow reversibility at the human M3 muscarinic receptor subtype in vitro and a long duration of action in vivo when administered directly to the lungs in pre-clinical models.

Vilanterol

Vilanterol is a selective long-acting, $beta_2$-adrenergic receptor agonist (LABA). The pharmacologic effects of $beta_2$- adrenergic agonists, including Vilanterol, are at least in part attributable to stimulation of intracellular adenylate 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 inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Pharmacokinetics

Absorption

Fluticasone Furoate

Following inhaled administration of Fluticasone Furoate + Umeclidinium + Vilanterol in healthy subjects, Fluticasone Furoate C_{max} occurred at 15 minutes. The absolute bioavailability of Fluticasone Furoate when administrated as Fluticasone Furoate + Vilanterol by inhalation was 15.2%, primarily due to absorption of the inhaled portion of the dose delivered to the lung, with negligible contribution from oral absorption. Following repeat dosing steady state was achieved within 6 days with up to 1.6-fold accumulation.

Umeclidinium

Following inhaled administration of Fluticasone Furoate + Umeclidinium + Vilanterol in healthy subjects, Umeclidinium C_{max} occurred at 5-15 minutes. The absolute bioavailability of inhaled Umeclidinium was on average 13%, with negligible contribution from oral absorption. Following repeat dosing of inhaled Umeclidinium, steady state was achieved within 7 to 10 days with 1.5 to 2-fold accumulation.

Vilanterol

Following inhaled administration of Fluticasone Furoate + Umeclidinium + Vilanterol in healthy subjects, Vilanterol C_{max} occurred at 5-15 minutes. The absolute bioavailability of inhaled Vilanterol was 27%, with negligible contribution from oral absorption, steady state was achieved within 6 days with up to 1.5-fold accumulation.

Distribution

Fluticasone Furoate

Following intravenous dosing of Fluticasone Furoate to healthy volunteers, the mean volume of distribution at steady state of 661 liters. Fluticasone Furoate has a low association with red blood cells. In vitro plasma protein binding in human plasma of Fluticasone Furoate was high, on average >99.6%.

Umeclidinium

Following intravenous administration of Umeclidinium to healthy volunteers, the mean volume of distribution was 86 liters. In vitro plasma protein binding in human plasma was on average 89%.

Vilanterol

Following intravenous administration of Vilanterol to healthy volunteers, the mean volume of distribution at steady state was 165 liters. Vilanterol has a low association with red blood cells. In vitro plasma protein binding in human plasma was on average 94%.

Metabolism

Fluticasone Furoate

Fluticasone Furoate is primarily metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate for the P-gp transporter. The primary metabolic route for Fluticasone Furoate is hydrolysis of the S-fluoromethyl carbothioate group to metabolites with significantly reduced corticosteroid activity. Systemic exposure to the metabolites is low.

Umeclidinium

Umeclidinium is primarily metabolised by cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-gp transporter. The primary metabolic routes for Umeclidinium are oxidative (hydroxylation, O-dealkylation) followed by conjugation (glucuronidation, etc), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low.

Vilanterol

Vilanterol is primarily metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate for the P-gp transporter. The primary metabolic routes for Vilanterol are O-dealkylation to a range of metabolites with significantly reduced $beta_1$- and $beta_2$-adrenergic agonist activity. Plasma metabolic profiles following oral administration of Vilanterol in a human radiolabel study were consistent with high first-pass metabolism. Systemic exposure to the metabolites is low.

Elimination

Fluticasone Furoate

The apparent plasma elimination half-life of Fluticasone Furoate was, on average, 24 hours. Following intravenous administration, the elimination phase half-life averaged 15.1 hours. Plasma clearance following intravenous administration was 65.4 liters/hour. Urinary excretion accounted for approximately 2% of the intravenously administered dose. Following oral administration, Fluticasone Furoate was eliminated in humans mainly by metabolism with metabolites being excreted almost exclusively in feces, with <1% of the recovered radioactive dose eliminated in the urine.

Umeclidinium

Umeclidinium plasma elimination half-life following inhaled dosing for 10 days averaged 19 hours, with 3% to 4% active substance excreted unchanged in urine at steady-state. Plasma clearance following intravenous administration was 151 liters/hour. Following intravenous administration, approximately 58% of the administered radiolabeled dose was excreted in feces and approximately 22% of the administered radiolabeled dose was excreted in urine. The excretion of the drug-related material in the feces following intravenous dosing indicated secretion into the bile. Following oral administration, 92% of the administered radiolabeled dose was excreted primarily in feces. Less than 1% of the orally administered dose (1% of recovered radioactivity) was excreted in urine, suggesting negligible absorption following oral administration.

Vilanterol

Vilanterol plasma elimination half-life following inhaled dosing for 10 days averaged 11 hours. Plasma clearance of Vilanterol following intravenous administration was 108 liters/hour. Following oral administration of radiolabeled Vilanterol, 70% of the radiolabel was excreted in urine and 30% in feces. Primary elimination of Vilanterol was by metabolism followed by excretion of metabolites in urine and feces.

Special Population

Patients with Hepatic Impairment

For Fluticasone Furoate, patients with moderate hepatic impairment showed up to three times higher systemic exposure therefore, patients with severe hepatic impairment received half the dose. Caution is advised in moderate to severe hepatic impairment.

THERAPEUTIC INDICATIONS

Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) DPI Capsule is indicated:

- As a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long acting $beta_2$-agonist or a combination of a long-acting $beta_2$-agonist and a long-acting muscarinic antagonist.
- For the maintenance treatment of asthma in patients aged 18 years and older.

DOSAGE AND ADMINISTRATION

Recommended Dosage for Maintenance Treatment of Chronic Obstructive Pulmonary Disease

The recommended dosage of Vilanto-UF for maintenance treatment of COPD is 1 actuation of Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) 100mcg + 62.5mcg + 25mcg once daily by oral inhalation, each day at the same time.

If shortness of breath occurs in the period between doses, an inhaled, short-acting $beta_2$-agonist (rescue medicine, e.g., salbutamol) should be used for immediate relief.

Recommended Dosage for Maintenance Treatment of Asthma

The recommended starting dosage of Vilanto-UF for maintenance treatment of asthma is 1 actuation of Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) 100mcg + 62.5mcg + 25mcg once daily by oral inhalation, each day at the same time.

When choosing the starting dosage strength of Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol), consider the patient's disease severity; their previous asthma therapy, including the inhaled corticosteroid (ICS) dosage; as well as the patient's current control of asthma symptoms and risk of future exacerbation.

If asthma symptoms arise in the period between doses, an inhaled, short-acting $beta_2$-agonist (rescue medicine, e.g., salbutamol) should be used for immediate relief.

Special Population

Elderly

No dose adjustment is required in patients 65 years of age or older.

Patients with Renal Impairment

No dose adjustment is required in patients with renal impairment.

Patients with Hepatic Impairment

No dose adjustment is required in patients with mild, moderate or severe hepatic impairment. Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) should be used with caution in patients with moderate to severe hepatic impairment.

Pediatric Patients

Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) is not indicated for use in pediatric patients.

Dosage and Administration Overview

Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) is for oral inhalation only. Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) should be administered once daily, either morning or evening, but at the same time each day. Do not use Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) more than 1 time every 24 hours. After inhalation, the patient should rinse their mouth with water without swallowing. If a dose is missed the next dose should be inhaled at the usual time the next day.

Read the instructions for the use of Prohaler (DPI Device) before you start to use Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) Dry Powder Inhaler Capsules.

Do not store Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) Dry Powder Inhaler Capsules in the Prohaler (DPI Device). Discard the Prohaler (DPI Device) 06 months after first use.

ADVERSE REACTIONS

Common: Pneumonia, upper respiratory tract infection, bronchitis, pharyngitis, rhinitis, sinusitis, influenza, nasopharyngitis, candidiasis of mouth and throat, urinary tract infection, headache, cough, oropharyngeal pain, constipation, arthralgia and back pain.

Uncommon: Viral respiratory tract infection, fractures, dysgeusia, vision blurred, glaucoma, eye pain, supraventricular tachyarrhythmia, tachycardia, atrial fibrillation, dysphonia and dry mouth.

Rare: Hypersensitivity reactions including anaphylaxis, angioedema, urticaria, and rash, hyperglycemia, anxiety, tremor, intraocular pressure increased, palpitations, muscle spasms urinary retention and dysuria.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS

The use of Fluticasone Furoate + Umeclidinium + Vilanterol is contraindicated in following conditions:

- In patients with hypersensitivity to active substance(s) and to any of the excipient of the product.

- In patients with severe hypersensitivity to milk proteins.
- Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required.

PRECAUTIONS

Serious Asthma-Related Events-Hospitalizations, Intubations, Death

Use of long-acting beta$_2$-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroid (ICS)] for asthma is associated with an increased risk of asthma-related death.

Deterioration of Disease and Acute Episodes

Fluticasone Furoate + Umeclidinium + Vilanterol should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. Fluticasone Furoate + Umeclidinium + Vilanterol has not been studied in subjects with acutely deteriorating COPD or asthma. The initiation of Fluticasone Furoate + Umeclidinium + Vilanterol in this setting is not appropriate.

Fluticasone Furoate + Umeclidinium + Vilanterol should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. When beginning treatment with Fluticasone Furoate + Umeclidinium + Vilanterol, 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 to use them only for symptomatic relief of acute respiratory symptoms.

Avoid Excessive Use and Avoid Use with Other Long-acting Beta$_2$-agonists

Fluticasone Furoate + Umeclidinium + Vilanterol should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using Fluticasone Furoate + Umeclidinium + Vilanterol should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

Oropharyngeal Candidiasis

Fluticasone Furoate + Umeclidinium + Vilanterol contains Fluticasone Furoate, an ICS. Localized infections of the mouth and pharynx with *Candida albicans* have occurred in subjects treated with orally inhaled drug products containing Fluticasone Furoate. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with Umeclidinium Bromide + Vilanterol Trifenatate + Fluticasone Furoate continues, but at times therapy with Umeclidinium Bromide + Vilanterol Trifenatate + Fluticasone Furoate may need to be interrupted. Advise the patient to rinse mouth with water without swallowing following administration to help reduce the risk of oropharyngeal candidiasis.

Pneumonia

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as clinical features of pneumonia and exacerbations frequently overlap.

Immunosuppression and Risk of Infection

Patients who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure.

ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

During periods of stress or a severe COPD exacerbation or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to Fluticasone Furoate + Umeclidinium + Vilanterol. Lung function (forced expiratory volume in 1 second [FEV1]), beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids

Transfer of patients from systemic corticosteroid therapy to Fluticasone Furoate + Umeclidinium + Vilanterol may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

Corticosteroid Withdrawal Symptoms

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression

Inhaled Fluticasone Furoate is absorbed into the circulation and can be systemically active or Fluticasone Furoate exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction. Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with Fluticasone Furoate + Umeclidinium + Vilanterol should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, reduce the dose of Umeclidinium Bromide + Vilanterol Trifenatate + Fluticasone Furoate slowly, consistent with accepted procedures for reducing systemic corticosteroids, and consider other treatments for management of COPD or asthma symptoms.

Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of Fluticasone Furoate + Umeclidinium + Vilanterol with ketoconazole and other known strong CYP3A4 inhibitors (including, but not limited to, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

Paradoxical Bronchospasm

As with other inhaled medicines, Fluticasone Furoate + Umeclidinium + Vilanterol can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with Fluticasone Furoate + Umeclidinium + Vilanterol, it should be treated immediately with an inhaled, short-acting bronchodilator; Fluticasone Furoate + Umeclidinium + Vilanterol should be discontinued immediately; and alternative therapy should be instituted.

Hypersensitivity Reactions, including Anaphylaxis

Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of Fluticasone Furoate + Umeclidinium + Vilanterol. Discontinue Fluticasone Furoate + Umeclidinium + Vilanterol if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use Fluticasone Furoate + Umeclidinium + Vilanterol.

Cardiovascular Effects

Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, Fluticasone Furoate + Umeclidinium + Vilanterol may need to be discontinued.

Fluticasone Furoate + Umeclidinium + Vilanterol, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating Fluticasone Furoate + Umeclidinium + Vilanterol and periodically thereafter. If significant reductions in BMD are seen and Fluticasone Furoate + Umeclidinium + Vilanterol is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

Glaucoma and Cataracts, Worsening of Narrow- Angle Glaucoma

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of ICS or with use of inhaled anticholinergics.

Fluticasone Furoate + Umeclidinium + Vilanterol should be used with caution in patients with narrow-angle glaucoma. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use Fluticasone Furoate + Umeclidinium + Vilanterol long term.

Worsening of Urinary Retention

Fluticasone Furoate + Umeclidinium + Vilanterol, like all medicines containing an anticholinergic, should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Consult a healthcare provider immediately if any of these signs or symptoms develop.

Coexisting Conditions

Fluticasone Furoate + Umeclidinium + Vilanterol, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist salbutamol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines 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. Beta-agonist medications may produce transient hyperglycemia in some patients.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. Fluticasone Furoate + Umeclidinium + Vilanterol is not indicated for use in this population.

Pregnancy

Administration of Fluticasone Furoate + Umeclidinium + Vilanterol to pregnant women should only be considered if the expected benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

It is unknown whether Fluticasone Furoate, Umeclidinium, Vilanterol or their metabolites are excreted in human milk. However, other corticosteroids, muscarinic antagonists and beta$_2$- agonists are detected in human milk. A risk to breast-fed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue Fluticasone Furoate + Umeclidinium + Vilanterol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

DRUG INTERACTIONS

Inhibitors of Cytochrome P450 3A4

Fluticasone Furoate and Vilanterol are substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to Fluticasone Furoate and Vilanterol. Caution should be exercised when considering the coadministration of Fluticasone Furoate + Umeclidinium + Vilanterol with ketoconazole and other known strong CYP3A4 inhibitors.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, and QTc Prolonging Drugs

Vilanterol, like other beta$_2$-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 or within 2 weeks of discontinuation of such agents, because the effect 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 Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as Vilanterol, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

Non–Potassium-Sparing Diuretics

The electrocardiographic 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 coadministration of beta-agonists with non–potassium-sparing diuretics.

Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of Fluticasone Furoate + Umeclidinium + Vilanterol with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Other long acting antimuscarinics and long acting beta$_2$ - adrenergic agonists

Co-administration of Fluticasone Furoate + Umeclidinium + Vilanterol with other long-acting muscarinic antagonists or long-acting beta$_2$ - adrenergic agonists is not recommended as it may potentiate the adverse reactions.

OVERDOSAGE

Symptoms

An overdose will likely produce signs, symptoms or adverse effects associated with the individual components' pharmacological actions (e.g. Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, dry mouth, visual accommodation disturbances, tachycardia, arrhythmias, tremor, headache, palpitations, nausea, hyperglycemia and hypokalemia).

Treatment

There is no specific treatment for an overdose with Fluticasone Furoate + Umeclidinium + Vilanterol. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Cardioselective beta-blockade should only be considered for profound Vilanterol overdose effects that are clinically concerning and unresponsive to supportive measures. Cardioselective beta-blocking medicinal products should be used with caution in patients with a history of bronchospasm. Further management should be as clinically indicated.

STORAGE

Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Vilanto-UF (Fluticasone Furoate + Umeclidinium + Vilanterol) Dry Powder Inhaler Capsules are available in blister pack of 30 capsules.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan

PAK-200019767