Vilanto-U™

(Umeclidinium + Vilanterol)

ویلینٹو-یو

Dry Powder Inhaler Capsules

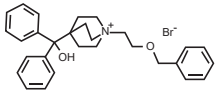
62.5mcg+25mcg

DESCRIPTION

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

Umeclidinium Bromide

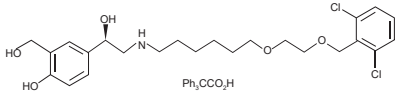
Umeclidinium bromide has the chemical name 1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide. Its molecular formula is $C_{29}H_{34}NO_2$•Br (as a quaternary ammonium bromide compound) and the structural formula is:



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 $C_{24}H_{33}Cl_2NO_5$•$C_{29}H_{16}O_2$ and the structural formula is:



Vilanterol Trifenatate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Vilanto-U (Umeclidinium + Vilanterol) is available for administration as:

Vilanto-U DPI Capsules 62.5mcg + 25mcg
Each capsule contains:
Umeclidinium Bromide equivalent to Umeclidinium…62.5mcg
Vilanterol Trifenatate equivalent to Vilanterol…25mcg

CLINICAL PHARMACOLOGY

Mechanism of Action

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.
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 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.

Pharmacokinetics

Absorption

Umeclidinium

Following inhaled administration of Umeclidinium in healthy volunteers, C_{max} occurred at 5 to 15 minutes. The absolute bioavailability of inhaled Umeclidinium was on average 13% of the dose, 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 1.8-fold accumulation.

Vilanterol

Following inhaled administration of Vilanterol in healthy volunteers, C_{max} occurred at 5 to 15 minutes. The absolute bioavailability of inhaled Vilanterol was 27%, with negligible contribution from oral absorption. Following repeat dosing of inhaled Vilanterol, steady state was achieved within 6 days with up to 2.4-fold accumulation.

Distribution

Umeclidinium

Following intravenous administration 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 to healthy volunteers, the mean volume of distribution at steady state was 165 liters. In vitro plasma protein binding in human plasma was on average 94%.

Metabolism

Umeclidinium

In vitro studies showed that Umeclidinium is primarily metabolised by cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-glycoprotein (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

In vitro studies showed that 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

Umeclidinium

Plasma clearance following intravenous administration was 151 liters/hour. Following intravenous administration, approximately 58% of the administered radiolabeled dose (or 73% of the recovered radioactivity) was excreted in feces by 192 hours post-dose. Urinary elimination accounted for 22% of the administered radiolabeled dose by 168 hours (27% of recovered radioactivity). The excretion of the drug-related material in the feces following intravenous dosing indicated secretion into the bile. Following oral administration to healthy male volunteers, total radioactivity was excreted primarily in feces (92% of the administered radiolabeled dose or 99% of the recovered radioactivity) by 168 hours post dose. Less than 1% of the orally administered dose (1% of recovered radioactivity) was excreted in urine, suggesting negligible absorption following oral administration. Umeclidinium plasma elimination half-life following inhaled dosing for 10 days averaged 19 hours in healthy volunteers, with 3% to 4% excreted unchanged in urine at steady-state.

Vilanterol

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

THERAPEUTIC INDICATIONS

Vilanto-U (Umeclidinium + Vilanterol) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema.

DOSAGE AND ADMINISTRATION

The recommended dosage of Vilanto-U (Umeclidinium + Vilanterol) for maintenance treatment of COPD is 1 actuation of Vilanto-U (Umeclidinium + Vilanterol) DPI Capsules 62.5mcg+25mcg once daily by oral inhalation.

Vilanto-U (Umeclidinium + Vilanterol) should be used at the same time every day. Do not use Vilanto-U (Umeclidinium + Vilanterol) more than 1 time every 24 hours.

Special Population

Elderly patients

No dose adjustment is required in patients over 65 years.

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 or moderate hepatic impairment. The use of Vilanto-U (Umeclidinium + Vilanterol) has not been studied in patients with severe hepatic impairment and should be used with caution.

Pediatric population

There is no relevant use of Vilanto-U (Umeclidinium + Vilanterol) in the pediatric population (under 18 years of age) for the indication of COPD.

Read the instructions for the use of Prohaler (DPI Device) before you start to use Vilanto-U (Umeclidinium + Vilanterol) Dry Powder Inhaler Capsules.
Do not store Vilanto-U (Umeclidinium + Vilanterol) Dry Powder Inhaler Capsules in the Prohaler (DPI Device). Discard the Prohaler (DPI Device) 06 months after first use.

CONTRAINDICATIONS

The use of 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.
- Use of a long-acting beta$_2$-adrenergic agonist (LABA), including Vilanterol, without an inhaled corticosteroid (ICS), in patients with asthma. Umeclidinium + Vilanterol is not indicated for the treatment of asthma.

ADVERSE REACTIONS

Common:

Urinary tract infection, sinusitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, headache, cough, oropharyngeal pain, constipation and dry mouth.

Uncommon:

Rash, tremor, dysgeusia, atrial fibrillation, supraventricular tachycardia, rhythm idioventricular, tachycardia, supraventricular extrasystoles, palpitations, dysphonia and muscle spasms.

Rare:

Anaphylaxis, angioedema, urticarial, vision blurred, glaucoma, intraocular pressure increased, eye pain, paradoxical bronchospasm, urinary retention, dysuria and bladder outlet obstruction.

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

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

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

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 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

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 Umeclidinium + Vilanterol should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of 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, Umeclidinium + Vilanterol can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with Umeclidinium + Vilanterol, it should be treated immediately with an inhaled, short-acting bronchodilator; 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 Umeclidinium + Vilanterol. Discontinue 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 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, Umeclidinium + Vilanterol may need to be discontinued.

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

Coexisting Conditions

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.

Worsening of Narrow-Angle Glaucoma

Umeclidinium + Vilanterol should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should also be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop.

Worsening of Urinary Retention

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.

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.

Excipient

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

Pregnancy

There are no data from the use of Umeclidinium + Vilanterol in pregnant women. Studies in animals have shown reproductive toxicity at exposures which are not clinically relevant after administration of Vilanterol. Umeclidinium + Vilanterol should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

It is unknown whether Umeclidinium or Vilanterol are excreted in human milk. However, other beta$_2$ -adrenergic agonists are detected in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Umeclidinium + Vilanterol therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

DRUG INTERACTIONS

Inhibitors of Cytochrome P450 3A4

Vilanterol is substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to Vilanterol. Caution should be exercised when considering the coadministration of 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. Therefore, patients with COPD 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 Umeclidinium + Vilanterol with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Methylxanthine derivatives and steroids

Concomitant hypokalemic treatment with methylxanthine derivatives or steroids may potentiate the possible hypokalemic effect of beta$_2$-adrenergic agonists, therefore use with caution.

OVERDOSAGE

Umeclidinium

High doses of Umeclidinium may lead to anticholinergic signs and symptoms.

Vilanterol

The expected signs and symptoms with overdosage of Vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of Vilanterol.

Treatment

Treatment of overdosage consists of discontinuation of Umeclidinium + Vilanterol together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

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-U (Umeclidinium + Vilanterol) Dry Powder Inhaler Capsules 62.5mcg + 25mcg 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
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