Vilanto™-F

(Fluticasone Furoate + Vilanterol)

ویلینٹو-ایف

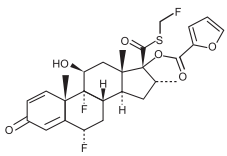
Dry Powder Inhaler Capsules
100mcg + 25mcg & 200mcg + 25mcg

DESCRIPTION

Vilanto-F DPI Capsule is an inhalation powder drug product for delivery of a combination of Fluticasone Furoate (an ICS) and Vilanterol (a LABA) to patients by oral inhalation.

Fluticasone Furoate:

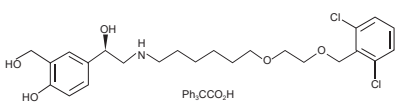
Fluticasone furoate, a synthetic trifluorinated corticosteroid, has the chemical name (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoro-methyl)thio]carbonyl}-11-hydroxy-16-methyl-3- oxoandrosta-1,4-dien-17-yl 2-furancarboxylate. Its molecular formula is $C_{27}H_{29}F_3O_6S$ and the structural formula is:



Fluticasone Furoate

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 $C_{24}H_{33}Cl_2NO_5 \cdot C_{20}H_{16}O_2$ and the structural formula is:



Vilanterol Trifenatate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Vilanto-F (Fluticasone Furoate + Vilanterol) is available for administration as:

Vilanto-F DPI Capsules 100mcg + 25mcg
Each capsule contains:
Fluticasone Furoate…100mcg
Vilanterol Trifenatate equivalent to Vilanterol…25mcg

Vilanto-F DPI Capsules 200mcg + 25mcg
Each capsule contains:
Fluticasone Furoate…200mcg
Vilanterol Trifenatate equivalent to Vilanterol…25mcg

CLINICAL PHARMACOLOGY

Mechanism of Action

Fluticasone Furoate

Fluticasone Furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity.

The precise mechanism through which fluticasone furoate affects COPD and asthma symptoms is not known. Inflammation is an important component in the pathogenesis of COPD and asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation.

Vilanterol

Vilanterol trifenatate is a selective long-acting, $beta_2$-adrenergic agonist (LABA). The pharmacologic effects of $beta_2$-adrenergic agonist drugs, including Vilanterol, 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.

Pharmacokinetics

Absorption

Fluticasone Furoate

Fluticasone Furoate plasma levels may not predict therapeutic effect. Peak plasma concentrations are reached within 0.5 to 1 hour. Absolute bioavailability of Fluticasone Furoate when administered by inhalation was 15.2%, primarily due to absorption of the inhaled portion of the dose delivered to the lung. Oral bioavailability from the swallowed portion of the dose is low (approximately 1.3%) due to extensive first-pass metabolism. Systemic exposure (AUC) in patients with COPD or asthma was 46% or 7% lower, respectively, than observed in healthy subjects.

Vilanterol

Vilanterol plasma levels may not predict therapeutic effect. Peak plasma concentrations are reached within 10 minutes following inhalation. Absolute bioavailability of Vilanterol when administered by inhalation was 27.3%, primarily due to absorption of the inhaled portion of the dose delivered to the lung. Oral bioavailability from the swallowed portion of the dose of Vilanterol is low (<2%) due to extensive first-pass metabolism. Systemic exposure (AUC) in patients with COPD was 24% higher than observed in healthy subjects. Systemic exposure (AUC) in patients with asthma was 21% lower than observed in healthy subjects.

Distribution

Fluticasone Furoate

Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 661L. Binding of Fluticasone Furoate to human plasma proteins was high (>99%).

Vilanterol

Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 165L. Binding of Vilanterol to human plasma proteins was on average 94%.

Metabolism

Fluticasone Furoate

Fluticasone Furoate is cleared from systemic circulation principally by hepatic metabolism via CYP3A4 to metabolites with significantly reduced corticosteroid activity. There was no in vivo evidence for cleavage of the furoate moiety resulting in the formation of fluticasone.

Vilanterol

Vilanterol is mainly metabolized, principally via CYP3A4, to a range of metabolites with significantly reduced $Beta_1$ and $beta_2$ agonist activity.

Elimination

Fluticasone Furoate

Fluticasone Furoate and its metabolites are eliminated primarily in the feces, accounting for approximately 101% and 90% of the orally and intravenously administered doses, respectively. Urinary excretion accounted for approximately 1% and 2% of the orally and intravenously administered doses, respectively. Following repeat-dose inhaled administration, the plasma elimination phase half-life averaged 24 hours.

Vilanterol

Following oral administration, Vilanterol was eliminated mainly by metabolism followed by excretion of metabolites in urine and feces (approximately 70% and 30%, respectively, of the recovered radioactive dose). The plasma elimination half-life of Vilanterol, as determined from inhalation administration of multiple doses of Vilanterol 25mcg, is 21.3 hours in patients with COPD and 16.0 hours in patients with asthma.

Special Population

Patients with hepatic Impairment

Fluticasone Furoate

Following repeat dosing of Fluticasone Furoate + Vilanterol 200mcg + 25mcg (100mcg + 12.5mcg in the severe impairment group) for 7 days, there was an increase of 34%, 83%, and 75% in Fluticasone Furoate systemic exposure (AUC) in patients with mild, moderate, and severe hepatic impairment, respectively, compared with healthy subjects.

In patients with moderate hepatic impairment receiving Fluticasone Furoate + Vilanterol 200mcg + 25mcg, mean serum cortisol (0 to 24 hours) was reduced by 34% (90% CI: 11%, 51%) compared with healthy subjects. In patients with severe hepatic impairment receiving Fluticasone Furoate + Vilanterol 100mcg + 12.5mcg, mean serum cortisol (0 to 24 hours) was increased by 14% (90% CI: -16%, 55%) compared with healthy subjects. Patients with moderate to severe hepatic disease should be closely monitored.

THERAPEUTIC INDICATIONS

Vilanto-F (Fluticasone Furoate + Vilanterol) DPI capsules are indicated for:

- The maintenance treatment of chronic obstructive pulmonary disease (COPD) in adults and adolescents aged 12 years and older.
- The maintenance treatment of asthma in patients aged 12 years and older.

DOSAGE & ADMINISTRATION

Recommended Dosage for Maintenance Treatment of Chronic Obstructive Pulmonary Disease

The recommended dosage of Vilanto-F DPI Capaule 100mcg + 25mcg (containing Fluticasone Furoate 100mcg and Vilanterol 25mcg) is 1 actuation once daily by oral inhalation.

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

<u>*Adult Patients Aged 18 Years and Older*</u>

The recommended dosage of Vilanto-F DPI Capsule 100mcg + 25mcg (containing Fluticasone Furoate 100mcg and Vilanterol 25mcg) is 1 actuation once daily by oral inhalation or Vilanto-F DPI 200mcg + 25mcg (containing Fluticasone Furoate 200mcg and Vilanterol 25mcg) is 1 actuation once daily by oral inhalation.

- When choosing the starting dosage strength of Vilanto-F DPI, consider the patients' disease severity; their previous asthma therapy, including the inhaled corticosteroid (ICS) dosage; as well as the patients' current control of asthma symptoms and risk of future exacerbation.
- The median time to onset, defined as a 100-mL increase from baseline in mean forced expiratory volume in 1 second (FEV1), was approximately 15 minutes after beginning treatment. Individual patients will experience a variable time to onset and degree of symptom relief.
- For patients who do not respond adequately to Vilanto-F DPI 100mcg + 12.5mcg once daily, increasing the dose to Vilanto-F DPI 200mcg + 25mcg once daily may provide additional improvement in asthma control. For patients who do not respond adequately to Vilanto-F DPI 200mcg + 25mcg once daily, re-evaluate and consider other therapeutic regimens and additional therapeutic options.
- The maximum recommended dosage is 1 inhalation of Vilanto-F DPI 200mcg + 25mcg once daily.
- If asthma symptoms arise in the period between doses, an inhaled, short-acting $beta_2$-agonist (rescue medicine, e.g., albuterol) should be used for immediate relief.

<u>*Pediatric Patients Aged 12 and older*</u>

The recommended dosage of Vilanto-F DPI 100mcg + 25mcg (containing Fluticasone Furoate 100mcg and Vilanterol 25mcg) is 1 actuation once daily by oral inhalation.

Administration Instruction

After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

Vilanto-F DPI should be used at the same time every day. Do not use Vilanto-F DPI more than 1 time every 24 hours.

More frequent administration or a greater number of inhalations (more than 1 inhalation daily) of the prescribed strength of Vialnto F DPI is not recommended as some patients are more likely to experience adverse effects with higher doses.

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

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

ADVERSE REACTIONS

Very common: Headache and nasopharyngitis.

Common: Pneumonia, upper respiratory tract infection, bronchitis, influenza, candidiasis of mouth and throat, oropharyngeal pain, sinusitis, pharyngitis, rhinitis, cough, dysphonia, abdominal pain, arthralgia back pain, fractures, muscle spasms and pyrexia.

Uncommon: Hyperglycaemia, vision blurred and extrasystoles.

Rare: Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, tremor, anxiety, tachycardia, palpitation and paradoxical bronchospasm.

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

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

Oropharyngeal Candidiasis
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 Fluticasone Furoate + Vilanterol Trifenatate continues, but at times therapy with Fluticasone Furoate + Vilanterol Trifenatate 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 + 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 + 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 + 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 Fluticasone Furoate + Vilanterol 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 + 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 + Vilanterol can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with Fluticasone Furoate + Vilanterol, it should be treated immediately with an inhaled, short-acting bronchodilator; Fluticasone Furoate + 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 + Vilanterol. Discontinue Fluticasone Furoate + 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 + 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 + Vilanterol may need to be discontinued.
Fluticasone Furoate + 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 + Vilanterol and periodically thereafter. If significant reductions in BMD are seen and Fluticasone Furoate + 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
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 + 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 + Vilanterol long term.

Coexisting Conditions
Fluticasone Furoate + 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 + Vilanterol is not indicated for use in this population.

Excipients
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 or limited data from the use of Fluticasone Furoate and Vilanterol in pregnant women. Administration of Fluticasone Furoate + Vilanterol to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Nursing Mothers
There is insufficient information on the excretion of Fluticasone Furoate or Vilanterol trifenatate and/or metabolites in human milk. However, other corticosteroids and beta$_2$-agonists are detected in human milk. A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Fluticasone Furoate + Vilanterol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Effects on ability to drive and use machines
This medicinal product has no or negligible influence on the ability to drive and use machines. However, the occurrence of dizziness may influence the ability to drive and use machines.

DRUG INTERACTIONS
Inhibitors of Cytochrome P450 3A4
Fluticasone Furoate and Vilanterol are both 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 Vilanto-F DPI 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.

OVERDOSAGE
Symptoms
Fluticasone Furoate
If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur.

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 Fluticasone Furoate + 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-F DPI Capsules 100mcg + 25mcg is available in pack of 30's.
Vilanto-F DPI Capsules 200mcg + 25mcg is available in pack of 30's.

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:

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