Fluticasone furoate + Vilanterol (as trifenatate)

Relvar® Ellipta®

Dry Powder for Inhalation

Corticosteroid/ Selective Long-acting beta2-Adrenergic Agonist

PRODUCT DESCRIPTION

Fluticasone furoate + Vilanterol (as trifenatate) (*Relvar® Ellipta®*) Dry Powder for Inhalation 100 mcg/ 25 mcg: Each pre-dispensed dose contains 100 micrograms of fluticasone furoate and 25 micrograms of vilanterol (as trifenatate). Each single inhalation provides a delivered dose of 92 micrograms fluticasone furoate and 22 micrograms of vilanterol.
Fluticasone furoate + Vilanterol (as trifenatate) (Relvar® *Ellipta®*) Dry Powder for Inhalation 200 mcg/ 25 mcg: Each pre-dispensed dose contains 200 micrograms of fluticasone furoate and 25 micrograms of vilanterol (as trifenatate). Each single inhalation provides a delivered dose of 184 micrograms fluticasone furoate and 22 micrograms of vilanter ol.
The plastic device *Ellipta®* inhaler consists of a light grey body, a pale blue mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant packet. The tray is sealed with a peelable foil lid.
The inhaler contains two strips of 30 regularly distributed blisters, each containing a white powder.

INDICATIONS

Asthma

Fluticasone fuorate + Vilanterol (as trifenatate) (*Relvar® Ellipta®*) is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting $beta_2$-agonists.

COPD (Chronic Obstructive Pulmonary Disease)

Fluticasone fuorate + Vilanterol (as trifenatate) (*Relvar® Ellipta®*) is indicated for the symptomatic treatment of adults with COPD with a FEV_1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

DOSAGE AND ADMINISTRATION

Asthma

Adults and adolescents aged 12 years and over

One inhalation of Fluticasone fuorate + Vilanterol (as trifenatate) (*Relvar® Ellipta®*) 100 mcg / 25 mcg once daily

COPD

Adults aged 18 years and over

One inhalation of Fluticasone fuorate + Vilanterol (as trifenatate) (*Relvar® Ellipta®*) 100/25 micrograms once daily.

Special populations

Elderly patients *(>65 years)*

No dose adjustment is required in this population

Renal impairment

No dose adjustment is required in this population

Hepatic impairment

Caution should be exercised when dosing patients with hepatic impairment who may be more at risk of systemic adverse reactions associated with corticosteroids.
For patients with moderate or severe hepatic impairment the maximum dose is 100/25 micrograms

CONTRAINDICATIONS

Fluticasone fuorate + Vilanterol (as trifenatate) *(Relvar® Ellipta®)* is contraindicated in patients with severe milk-protein allergy or who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol or any of the excipients.

WARNINGS AND PRECAUTIONS

Deterioration of disease

Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.
Patients should not stop therapy with fluticasone furoate/vilanterol in asthma, without physician supervision since symptoms may recur after discontinuation.
Asthma-related adverse events and exacerbations may occur during treatment with fluticasone furoate/vilanterol. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of treatment with Fluticasone fuorate + Vilanterol (as trifenatate) (*Relvar® Ellipta®*).

Paradoxical bronchospasm

Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a short-acting inhaled bronchodilator. Fluticasone fuorate + Vilanterol (as trifenatate) (*Relvar® Ellipta®)* should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic medicinal products including Fluticasone fuorate + Vilanterol (as trifenatate) (*Relvar® Ellipta®)*. Therefore fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease.

Patients with hepatic impairment

For patients with moderate to severe hepatic impairment, the 100/25 micrograms dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions (see section 5.2).

Systemic corticosteroid effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Fluticasone furoate/vilanterol should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

Hyperglycaemia

There have been reports of increases in blood glucose levels in diabetic patients and this should be considered when prescribing to patients with a history of diabetes mellitus.

Pneumonia in patients with COPD

An increase in pneumonia has been observed in patients with COPD receiving fluticasone furoate/vilanterol. There was also an increased incidence of pneumonias resulting in hospitalisation. In some incidences these pneumonia events were fatal (see section 4.8). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD receiving fluticasone furoate/vilanterol include current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m^2 and patients with a (forced expiratory volume) FEV_1<50% predicted. These factors should be considered when fluticasone furoate/vilanterol is prescribed and treatment should be re-evaluated if pneumonia occurs.

Fluticasone fuorate + Vilanterol (as trifenatate) (*Relvar® Ellipta®)* 200/25 micrograms is not indicated for patients with COPD. There is no additional benefit of the 200/25 micrograms dose compared to the 100/25 micrograms dose and there is a potential increased risk of systemic corticosteroid-related adverse reactions (see section 4.8).

The incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma taking fluticasone furoate/vilanterol 200/25 micrograms was numerically higher compared with those receiving fluticasone furoate/vilanterol 100/25 micrograms or placebo (see section 4.8). No risk factors were identified.

Excipients

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

DRUG INTERACTIONS

Clinically significant drug interactions mediated by fluticasone furoate or vilanterol at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Interaction with beta-blockers

Beta-adrenergic blockers may weaken or antagonise the effect of $beta_2$-adrenergic agonists. Concurrent use of both non-selective and selective beta-blockers should be avoided unless there are compelling reasons for their use.

Interaction with CYP3A4 inhibitors

Fluticasone furoate and vilanterol are both rapidly cleared by extensive first-pass metabolism mediated by the liver enzyme CYP3A4.

Care is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increase in the potential for adverse reactions (see *Pharmacokinetics*).

Interaction with P-glycoprotein inhibitors

Fluticasone furoate and vilanterol are both substrates of P-glycoprotein (P-gp). A clinical pharmacology study in healthy subjects with co-administered vilanterol and the potent P-gp and moderate CYP3A4 inhibitor verapamil did not show any significant effect on the pharmacokinetics of vilanterol. Clinical pharmacology studies with a specific P-gp inhibitor and fluticasone furoate have not been conducted.

PREGNANCY AND LACTATION

Fertility

There are no fertility data in humans. Animal studies showed no effect of vilanterol or fluticasone furoate on fertility *(*see *Pre-clinical Safety Data section).*

Pregnancy

There has been limited pregnancy exposure in humans.

Animal studies have shown reproductive toxicity after administration of $beta_2$-agonists and corticosteroids (see *Pre-clinical Safety Data section*).

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.

Lactation

There is limited information on the excretion of fluticasone furoate or vilanterol or their metabolites in human milk. However, other corticosteroids and beta$_2$-agonists are detected in human milk (see *Pre-clinical Safety Data section*). A risk to breastfed newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue *Fluticasone fuorate + Vilanterol (as trifenatate) (Relvar® Ellipta®)*therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

ADVERSE EFFECTS

Very common: Headache, Nasophayngitis **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, Pyrexia, Muscle Spasm **Uncommon:** Extrasystoles **Rare:** Hypersensitivity reactions including anaphylaxis, Angioedema, Rash, Urticaria, Anxiety, Tremor, Palpitations, Tachycardia

OVERDOSAGE AND TREATMENT

Symptoms and signs
There are no data available from clinical trials on overdose with Fluticasone fuorate + Vilanterol (as trifenatate) (*Relvar® Ellipta®)*.
An overdose of *Fluticasone fuorate + Vilanterol (as trifenatate) (Relvar® Ellipta®)*may produce signs and symptoms due to the individual components' actions, including those seen with overdose of other beta$_2$-agonists and consistent with the known inhaled corticosteroid class effects (see *Warnings and Precautions*).
Treatment
There is no specific treatment for an overdose with Fluticasone fuorate + Vilanterol (as trifenatate) (*Relvar® Ellipta®)*. 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 drugs should be used with caution in patients with a history of bronchospasm.
Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

STORAGE CONDITIONS

Store at temperatures not exceeding 30^{O}C.
Following removal from the tray, the product may be stored for a maximum period of:
6 weeks: below 25°C or 1 month: below 30°C

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Full prescribing information available upon request

In case of adverse events, please report to GlaxoSmithKline using the following number: 0917 889 0640