Package Insert

RELENZA®

SCHEDULING STATUS:

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PROPRIETARY NAME AND DOSAGE FORM:

RELENZA® Powder for inhalation

COMPOSITION:

Each RELENZA Rotadisk consists of four regularly spaced double foil blisters each containing a powder mixture that contains 5 mg of zanamivir.

List of excipients: lactose (which contains milk protein).

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral Agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic Properties:

Zanamivir is a potent and highly selective *in vitro* inhibitor of neuraminidase, an influenza virus surface enzyme. Viral neuraminidase aids the release of newly formed virus particles from infected cells, and may facilitate access of virus through mucus to epithelial cell surfaces, to allow viral infection of other cells. The inhibition of this enzyme is reflected in both *in vitro* and *in vivo* activity against influenza A and B virus replication, and encompasses all of the known neuraminidase subtypes of influenza A viruses.

The activity of zanamivir is extracellular. It reduces the propagation of both influenza A and B viruses by inhibiting the release of infectious influenza virions from the epithelial cells of the respiratory tract.

Pharmacokinetic Properties:

Absorption: Pharmacokinetic studies in humans have shown that the absolute oral bioavailability of the drug is low (mean 2 %). Similar studies of orally inhaled zanamivir indicate that approximately 10-20 % of the dose is systemically absorbed, with serum concentrations generally peaking within 1-2 hours. The poor absorption of the drug results in low systemic concentrations. There is no evidence of modification in the kinetics after repeated dosing with oral inhaled administration.

Distribution: After oral inhalation, zanamivir is widely deposited throughout the respiratory tract. Zanamivir concentrations of approximately 340- and 52-fold above the median viral neuraminidase IC_{50} were measured at 12 hours and 24 hours respectively at the epithelial layer of airways. The two major sites of deposition are the oropharynx and the lungs (mean 77,6 % and 13,2 %, respectively).

Metabolism: Zanamivir has been shown to be renally excreted as unchanged drug, and does not undergo metabolism.

Elimination: The serum half-life of zanamivir following administration by oral inhalation ranges from 2,6 to 5,05 hours. It is entirely excreted unchanged in the urine. Total clearance ranges from 2,5 to 10,9 l/hour as approximated by urinary clearance. Renal elimination is completed within 24 hours.

Patients with renal impairment: At the therapeutic daily dose of 20 mg, bioavailability is low (10-20 %), and as a result there is no significant systemic exposure of patients to zanamivir.

Patients with hepatic impairment: Zanamivir is not metabolised.

Elderly patients: Any alteration of pharmacokinetics that may occur with age is unlikely to be of clinical consequence and no dose modification is recommended.

Paediatric patients: The systemic exposure in children 5-12 years of age was similar to 10 mg of inhaled powder in adults.

Clinical experience:

RELENZA, when taken as recommended for treatment of influenza in otherwise healthy and in patients at risk, mostly because of asthma or chronic obstructive pulmonary disease, alleviates the symptoms and reduces their duration.

In a pooled analysis of the principle phase III treatment studies with 1 480 patients with confirmed influenza, the median time to alleviation of influenza symptoms was reduced from 6,5 days to 5 days for patients taking RELENZA as compared to placebo ($p < 0,001$).

Complications were reduced from 208/711 (29 %) of placebo patients to 171/769 (22 %) of zanamivir patients (relative risk: 0,77; 95 % CI: 0,65 to 0,92; $p = 0,004$). Use of antibiotics for treatment of complications was reduced from 136/711 (19 %) of placebo patients to 110/769 (14 %) of zanamivir patients (relative risk: 0,76; 95 % CI: 0,60 to 0,95; $p = 0,021$). Use of antibiotics for lower respiratory tract infections was reduced from 11 % to 8 %.

Zanamivir given as prophylaxis has been shown to prevent influenza in adults and children (≥ 5 years). RELENZA given at the recommended dose for the prophylaxis of influenza provided 67-79 % protection compared to placebo.

INDICATIONS:

Treatment of Influenza:

RELENZA is indicated for treatment of both influenza A and B in adults and children (≥ 5 years).

Prophylaxis of Influenza:

RELENZA is indicated for the prophylaxis of both influenza A and B in adults and paediatric (≥ 5 years) family members of patients with influenza.

CONTRA-INDICATIONS:

Hypersensitivity to any ingredient of the preparation e.g. lactose or milk protein.

WARNINGS AND SPECIAL PRECAUTIONS:

Influenza infection can be associated with increased airways hyper-responsiveness. There have been very rare reports of patients being treated for influenza who have experienced bronchospasm and/or decline in respiratory function after the use of RELENZA, some of whom did not have any previous history of respiratory disease. Any such patients should discontinue RELENZA and seek medical evaluation. Patients with underlying respiratory disease should have a fast-acting bronchodilator available when taking RELENZA (see DOSAGE AND DIRECTIONS FOR USE).

Effects on ability to drive and use machines:

None known.

INTERACTIONS:

Zanamivir is not protein bound and not hepatically metabolised or modified. Clinically significant drug interactions are unlikely.

RELENZA, when given for 28 days, did not impair the immune response to influenza vaccine.

PREGNANCY AND LACTATION:

The safe use of RELENZA during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

RELENZA is for administration to the respiratory tract by oral inhalation only, using the Diskhaler device provided.

Patients scheduled to take inhaled medication e.g. fast-acting bronchodilators, at the same time as RELENZA should be advised to administer that medication prior to administration of RELENZA.

Treatment of Influenza:

The recommended dose of RELENZA is two inhalations (2 x 5 mg) twice daily for five days, providing a total daily inhaled dose of 20 mg.

Treatment should begin as soon as possible (within 36 hours) after onset of symptoms. Efficacy, if started more than 48 hours after onset of symptoms, has not been demonstrated.

Prophylaxis of Influenza:

The recommended dose of RELENZA is two inhalations (2 x 5 mg) once daily for 10 days, providing a total daily inhaled dose of 10 mg. This may be increased up to one month if the period of exposure risk extends beyond 10 days.

The full course of prophylaxis therapy should be completed as prescribed.

Impaired Renal or Hepatic Function: No dose modification is required (see Pharmacokinetic Properties).

Elderly patients: No dose modification is required (see Pharmacokinetic Properties).

Paediatric patients: No dose modification is required (see Pharmacokinetic Properties).

Instructions for Use/Handling:

The powdered medicine is inhaled through the mouth into the lungs. The Diskhaler device is loaded with a disk which contains the medicine in individual blisters which are opened as the device is manipulated. For detailed instructions for use refer to the Patient Information Leaflet in every pack.

SIDE EFFECTS:

Clinical trial data:

RELENZA is well tolerated by the oral inhaled route of administration. In clinical studies, including those studies with high risk patients (the elderly, and patients with certain chronic medical conditions), the adverse events reported were similar in the RELENZA and placebo groups.

Frequencies are defined as very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1 000, < 1/100), rare (> 1/10 000, < 1/1 000), very rare (< 1/10 000).

The following is a list of adverse events that occurred in treatment studies in patients receiving RELENZA 10 mg inhaled twice daily. The proportions of subjects reporting adverse events and the nature of the events were similar across the placebo and treatment groups (where placebo consisted of the same lactose vehicle used in RELENZA):

Nervous system disorders:

Common*:* headaches, dizziness

Gastrointestinal disorders:

Common*:* diarrhoea, nausea and vomiting

Uncommon: abdominal pain

Musculoskeletal & connective tissue disorders:

Uncommon*:* myalgia

Rare: arthralgia

Respiratory, thoracic and mediastinal disorders:

Common: nasal signs and symptoms, bronchitis, cough, sinusitis and ear, nose and throat infections

General disorders and administration site conditions:

Uncommon: malaise, fatigue, fever

Skin and subcutaneous tissue disorders:

Uncommon: urticaria

The most frequent laboratory abnormalities in phase 3 treatment studies included elevations of liver enzymes and CPK, lymphopaenia, and neutropaenia. These were reported in similar proportions of zanamivir and lactose vehicle placebo recipients with acute influenza-like illness.

Post-Marketing:

The following events have been identified during post-approval use of zanamivir for the treatment of influenza:

Immune system disorders:

Very rare: allergic-type reaction, including facial and oropharyngeal oedema

Respiratory, thoracic and mediastinal disorders:

Very rare: bronchospasm, dyspnoea

Skin and subcutaneous tissue disorders:

Very rare: rash, urticaria

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS:

Accidental overdose is unlikely due to the physical limitations of the presentation, the route of administration and the poor oral bioavailability (2 to 3 %) of zanamivir. Doses of zanamivir up to 64 mg/day (approximately 3 times the maximum daily recommended dose) have been administered by oral inhalation (by nebuliser) without adverse effects. Additionally, systemic exposure by intravenous administration of up to 1 200 mg/day for five days showed no adverse effect.

IDENTIFICATION:

A circular foil pack approximately 4 cm in diameter with four regularly distributed blisters each containing a small quantity of a white to off-white powder.

PRESENTATION:

RELENZA Rotadisks consist of a circular foil disk (a Rotadisk) with four regularly distributed blisters each containing 5 mg of zanamivir.

Each pack contains 5 or 7 Rotadisks (4 blisters per Rotadisk).

A Diskhaler is provided to administer the medication.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Keep out of reach of children.

REGISTRATION NUMBER:

34/20.2.8/0032

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Ave

Epping Industria 1, 7460

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