Relenza

Zanamivir

Presentation

Each Relenza Rotadisk consists of four regularly spaced double foil blisters each containing a powder mixture of zanamivir (5 mg) and lactose (20 mg).

Indications

Treatment of Influenza:
Relenza is indicated for treatment of infections due to influenza A and B viruses in adults and children 5 years and older.

Prophylaxis:
Relenza is indicated for prophylaxis of both influenza A and B in adults and juveniles 12 years and older.

Dosage and Method of Administration

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

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

Treatment of Influenza:
Adults and children 5 years and older:

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.
For maximum benefit, treatment should begin as soon as possible but no later than 48 hours after onset of symptoms.

Prophylaxis:
Adults and juveniles 12 years and older:

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. The treatment can be prolonged for up to one month at the most if the exposure risk lasts more than 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).

Contra-indications

Hypersensitivity to any ingredient of the preparation (see Pharmaceutical Particulars – List of Excipients).

Contraindicated in patients with severe milk protein allergy.

Special Warnings and Special Precautions for Use

Zanamivir is a specific treatment for infections due to Influenza A or B viruses. Use of zanamivir should be limited to patients who have characteristic symptoms of influenza when Influenza A or B virus infections have been documented locally.

Treatment of influenza in patients with severe asthma or other severe chronic respiratory diseases with zanamivir has not been adequately assessed due to the limited number of patients studied. In a placebo controlled study in patients with predominantly mild/moderate asthma and/or chronic obstructive pulmonary disease there was no evidence of a difference between zanamivir and placebo in forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEFR) measured after the end of treatment. For influenza positive patients, there were small differences in favour of zanamivir in mean morning PEFR (12.9 L/min [95% CI 3.0 to 22.9 L/min] p=0.011), and in mean evening PEFR (13.1 L/min [95% CI 3.6 to 22.7 L/min] p=0.007).

There have been some reports of patients being treated for influenza who have experienced bronchospasm and/or decline in respiratory function after the use of zanamivir. The decline in respiratory function is considered possibly related to zanamivir although the causal relationship is difficult to assess as influenza infection can be associated with increased airways hyper responsiveness, and in some patients concurrent medical conditions were present.

Decline in respiratory function should be considered as a potential risk when patients with chronic obstructive pulmonary disease or asthma are considered for treatment with zanamivir. If a decision is made to prescribe Relenza, the patient should be made aware of the risks of bronchospasm and decline in respiratory function, and should have a fast-acting bronchodilator available. Patients scheduled to take inhaled bronchodilators at the same time as Relenza should be advised to use their bronchodilators before taking Relenza (see Dosage and Method of Administration). Any patient who experiences a decline in respiratory function and/or symptoms of bronchospasm (such as worsening wheezing and shortness of breath) after use of zanamivir should discontinue the drug and seek medical evaluation.

Relenza inhalation powder must not be made into an extemporaneous solution for administration by nebulisation or mechanical ventilation. There have been reports of hospitalised patients with influenza who received a solution made with Relenza inhalation powder administered by nebulisation or mechanical ventilation, including a fatal case where it was reported that the lactose in this formulation obstructed the proper functioning of the equipment. Relenza inhalation powder must only be administered using the device provided (see Dosage and Administration).

Influenza can be associated with a variety of neurological and behavioural symptoms. There have been postmarketing reports (mostly from Japan and in paediatric subjects) of seizures, delirium, hallucination and abnormal behaviour in patients with influenza who were receiving neuraminidase inhibitors, including Relenza. The events were observed mainly early in the illness and often had an abrupt onset and rapid resolution. The contribution of Relenza to these events has not been established. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

Interaction with Other Medicinal Products and Other Forms of Interaction

In vitro, zanamivir is not a substrate of cytochrome P450 (CYP) enzymes, P-glycoprotein (Pgp) or renal transporters nor does it affect human transporters (organic anion, cation, or urate transporters) or cytochrome P450 (CYP) enzymes (CYP1A1/2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4). *In vivo*, zanamivir is excreted in urine as unchanged drug and there is no evidence that zanamivir is hepatically metabolized or modified. Clinically significant drug interactions are unlikely.

Pregnancy and Lactation

Fertility
Animal studies indicate no clinically meaningful effects of zanamivir on male or female fertility (see Pre-clinical Safety Data).

Pregnancy
There are insufficient data on the use of Relenza in pregnant women to inform drug-associated risk. Data from several studies have not found an increased risk of adverse pregnancy outcomes following *in utero* exposure to Relenza, but due to limited samples sizes, no definitely conclusions can be drawn regarding the safety of Relenza in pregnancy.

Reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs and there was no evidence of teratogenicity. Results from a rat peri- and postnatal study showed no clinically meaningful impairment of offspring development. However, there is no information on placental transfer in humans.

As experience is limited, the use of zanamivir in pregnancy should be considered only if the possible benefit to the patient is thought to outweigh any possible risk to the foetus.

Lactation
In rats zanamivir has been shown to be secreted in low amounts into milk. However, there is no information on secretion into breast milk in humans.

As experience is limited, the use of zanamivir in nursing mothers should be considered only if the possible benefit to the mother is thought to outweigh any possible risk to the child.

Undesirable Effects

Clinical trial data
Treatment studies: In clinical studies, including those studies with high risk patients (the elderly, and patients with chronic medical conditions), the adverse events reported were similar in the Relenza and placebo groups. Table 1 lists common adverse events occurring at an incidence of ≥2% reported during treatment and post-treatment in 5 major placebo-controlled influenza treatment clinical trials in adults, irrespective of the investigator's assessment of the possible relationship to study drug.

Table 1. Percentage of Patients Reporting Common Adverse Events (Incidence ≥2%): Major Treatment Studies in adults, irrespective of causality

Adverse Event	During Treatment		Post-treatment	
	Placebo (n=973)	Zanamivir (n=1703)	Placebo (n=973)	Zanamivir (n=1703)
Any event	39%	35%	26%	24%
Ear, nose and throat				
Nasal signs and symptoms	4%	3%	3%	3%
Throat and tonsil discomfort and pain	2%	2%	2%	2%
Ear, nose and throat infections	2%	2%	2%	2%
Gastrointestinal				
Nausea and vomiting	4%	4%	1%	1%
Diarrhoea	3%	2%	1%	1%
Lower respiratory				
Cough	3%	2%	3%	2%
Bronchitis	3%	1%	2%	1%
Neurology				
Headaches	3%	3%	4%	4%

Zanamivir was well tolerated. The percentage of patients reporting adverse events and the type during-treatment and post-treatment adverse events was similar for zanamivir and placebo groups. Most common adverse events were indistinguishable from signs and symptoms of influenza-like illness. Diarrhoea, dizziness, nausea and vomiting have been reported but there was no clear causal association with study treatment in the adult studies.

The nature and frequency of reports of adverse events in children (Study NAI30009) was similar to that reported in adults. 2% of both placebo and zanamivir recipients respectively reported adverse events thought to be drug-related.

Prophylaxis studies: In the two pivotal prophylaxis studies, 5% of placebo and 5-6% of zanamivir recipients reported adverse events thought to be drug-related during prophylaxis. Of these, the only event reported with an incidence ≥1.5% was headache (4% in NAI30010 and 1% in NAIA3005, compared with 1% in placebo groups for both studies). Total gastrointestinal adverse events and total lower respiratory adverse events thought to be drug-related were reported at <1.5% each in any group.

High Risk Population: In a treatment study in asthma and/or COPD patients (NAI30008), the proportion of patients reporting adverse events that were thought to be related to treatment was the same for both zanamivir and placebo recipients (9%).

The proportion of high risk patients reporting drug-related adverse events was the same for both zanamivir and placebo recipients (10%) when the data was combined for 8 major placebo-controlled influenza treatment clinical trials. There were 7 studies in adult, including NAI30008, and one study in paediatric patients.

Post-marketing data
The following events have been identified during post-approval use of zanamivir (Relenza) for the treatment of influenza.

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10,000 and <1/1000
Very rare	<1/10,000

Immune System Disorders:
Very rare: Allergic-type reactions, including anaphylactic and anaphylactoid reactions, facial and oropharyngeal oedema
Nervous systems disorders:
Very rare: Vasovagal-like reactions have been reported in patients with influenza symptoms, such as fever and dehydration, shortly following inhalation of Relenza.
Respiratory, thoracic and mediastinal disorders:
Very rare: bronchospasm, dyspnoea
Skin and subcutaneous tissue disorders:
Very rare: rash, urticaria
Very rare: severe skin reactions including Erythema Multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis

Overdosage

Signs and Symptoms
Reports of overdoses with Relenza have been received during postmarketing experience. The reported clinical signs or symptoms were similar to those observed with therapeutic doses of Relenza and the underlying disease.

Additionally, systemic exposure by intravenous administration of up to 1200 mg/day for five days showed no adverse effect.

Treatment
As zanamivir has a low molecular weight, low protein binding, and small volume of distribution, it is expected to be removed by haemodialysis. Further management should be as clinically indicated or as recommended by the national poisons centre where available.

Pharmacological Properties

Pharmacodynamic properties:
Mechanism of action: Zanamivir is a potent and highly selective inhibitor of neuraminidase, the 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. Influenza viral replication is confined to the superficial epithelium of the respiratory tract. The efficacy of topical administration of zanamivir to this site has been confirmed in clinical studies. Clinical trial data have shown that treatment of acute influenza infections with zanamivir produces reductions in virus shedding from the respiratory tract compared to placebo. Emergence of virus with reduced susceptibility to zanamivir in the clinical trials of zanamivir was rare.

Clinical experience: Relenza, when taken as recommended for treatment of influenza, alleviates the symptoms and reduces their duration. In some studies, a larger treatment benefit was observed in the ‘at risk’ patients: the elderly and patients with certain chronic medical conditions (chronic cardiac, pulmonary, renal and metabolic disorders). The efficacy of Relenza has been shown to be optimal if treatment is initiated as soon as possible after the onset of symptoms.

Zanamivir given as prophylaxis has been shown to prevent influenza. Relenza given at the recommended dose for the prophylaxis of influenza was shown to significantly reduce the incidence of symptomatic influenza by 67-79% compared to placebo.

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 4-17% 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 and therefore there is no significant systemic exposure to zanamivir after oral inhalation. There is no evidence of modification in the kinetics after repeated dosing with oral inhaled administration.

Distribution: The plasma protein binding of zanamivir is very low (< 10%). The volume of distribution of zanamivir in adults is approximately 16 L, which approximates to the volume of extracellular water.

After oral inhalation, zanamivir is widely deposited at high concentrations throughout the respiratory tract, thus delivering the drug to the site of influenza infection. The two major sites of deposition are the oropharynx and the lungs (mean 77.6% and 13.2%, respectively). Following twice daily administration of zanamivir 10 mg by oral inhalation, the median trough concentrations of zanamivir measured at the epithelial layer of the airways, (the major sites of influenza viral replication) ranged from 326 ng/mL to 891 ng/mL. These trough concentrations are multiple-fold in excess of the *in vitro* IC_{50} (<1 to 4 ng/mL) and IC_{90} (1.7 to 7.8 ng/mL) value for influenza virus neuraminidase for various influenza subtypes. The high concentrations of zanamivir in the respiratory tract will result in the rapid onset of inhibition of the viral neuraminidase.

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

Elimination: Zanamivir in the systemic circulation is eliminated entirely as unchanged drug in the urine. In adults with normal renal function, the elimination half-life is approximately 2-3 hours. The serum half-life of zanamivir increases to approximately 12-20 hours in patients with severe renal impairment (creatinine clearance < 30mL/min). Zanamivir has not been studied in patients with end-stage renal disease.

Special Patient Populations:

Elderly patients: At the therapeutic daily dose of 20 mg, bioavailability is low (4-17%), and as a result there is no significant systemic exposure of patients to zanamivir. Any alteration of pharmacokinetics that may occur with age is unlikely to be of clinical consequence and no dose modification is recommended.

Paediatric patients: In an open-label single-dose study the pharmacokinetics of zanamivir have been evaluated in 24 children aged 3 months to 12 years using nebulised (10 mg) and dry powder (10 mg) inhalation formulations. The systemic exposure in children was similar to 10 mg of inhaled powder in adults.

Patients with renal impairment: At the therapeutic daily dose of 20mg, bioavailability is low (4-17%), and as a result there is no significant systemic exposure of patients to zanamivir. Given the wide safety margin of zanamivir the possible increased exposure in patients with severe renal failure is not considered problematic and no dose adjustment is required.

Patients with hepatic impairment: Zanamivir is not metabolised, therefore dose adjustment in patients with hepatic impairment is not required.

Preclinical Safety Data

Administration of zanamivir in animal toxicity studies was not associated with any clinically relevant effects. Zanamivir was not genotoxic and showed no evidence of carcinogenic potential in long term carcinogenicity studies in rats and mice.

No drug-related malformations, maternal toxicity or embryotoxicity were observed in pregnant rats or rabbits or their foetuses following intravenous administration of zanamivir at doses up to 90 mg/kg/day.

Following subcutaneous administration of zanamivir in an additional rat embryofoetal development study, there was an increase in the incidence rates of a variety of minor skeletal and visceral alterations and variants in the exposed offspring at the highest dose 80 mg/kg, three times daily (240 mg/kg/day; total daily dose), most of which remained within the background rates of the historical occurrence in the strain studied. Based on AUC measurements, the 80 mg/kg dose (240 mg/kg/day) produced an exposure approximately 3 or 1000 times the human exposure at the clinical intravenous or inhaled dose, respectively. In the peri- and post-natal development study conducted in rats, there was no clinically meaningful impairment of development of offspring.

Intravenous doses of up to 90 mg/kg/day zanamivir produced no effect on fertility and reproductive function of the treated or subsequent generation in male and female rats.

Pharmaceutical Precautions

Relenza Rotadisks should not be stored above 30°C.

Pharmaceutical Particulars

List of Excipients:
Relenza is a white to off-white powder blend of micronised zanamivir and lactose (which contains milk protein).

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.

Please refer to the Patient Information Leaflet on the other side of this package insert for detailed instructions for use.

GlaxoSmithKline Australia Pty Ltd
Boronia, Australia

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