NEW ZEALAND DATA SHEET

1. PRODUCT NAME

RELENZA ROTADISK 5 mg/blister inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect:

Lactose monohydrate 20 mg (which contains milk protein).

For full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Inhalation powder, white to off-white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Influenza

RELENZA is indicated for treatment of both influenza A and B in adults and children (≥ 5 years) who present with symptoms typical of influenza when influenza is circulating in the community.

Prophylaxis of Influenza

Vaccination remains the primary method of preventing and controlling influenza.

RELENZA is indicated for prophylaxis of influenza A and B in adults and children (≥ 5 years) to reduce transmission among individuals in households with an infected person.

RELENZA is indicated for prophylaxis of influenza A and B during community outbreaks only in circumstances where such prophylaxis is justified (such as when vaccine that antigenically matches circulating influenza is not available or there is a pandemic).

It is not recommended for routine prophylaxis against influenza infection.

4.2 Dose and method of administration

Dose

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.

For maximum benefit, treatment should begin as soon as possible (preferably within two days) after onset of symptoms.

Prophylaxis of Influenza:

The recommended dose of RELENZA is two inhalations (2 x 5 mg) once daily, providing a total daily inhaled dose of 10 mg, for 10 days. This may be increased up to 28 days if the period of exposure risk extends beyond 10 days.

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

Special populations

Elderly patients

No dose modification is required (see section 5.2 Pharmacokinetic properties).

Impaired renal or hepatic function

No dose modification is required (see section 5.2 Pharmacokinetic properties).

Patients on asthma medication

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

Zanamivir has not been evaluated in immunocompromised patients.

Paediatric population

No dose modification is required (see section 5.2 Pharmacokinetic properties).

4.3 Contraindications

Hypersensitivity to any ingredient of the preparation (see section 6.1 List of excipients).

RELENZA is contraindicated in patients with severe milk protein allergy.

4.4 Special warnings and precautions for use

Influenza can be associated with a variety of neurological and behavioural symptoms.

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

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 zanamivir, some of whom did not have any previous history of respiratory disease. Any such patients should discontinue inhaled zanamivir and seek medical evaluation.

Patients with underlying respiratory disease should have a fast acting bronchodilator available when taking zanamivir (see section 4.2 Dose and method of administration).

Should zanamivir be considered appropriate for patients with asthma or chronic obstructive pulmonary disease, the patient should be informed of the potential risk of bronchospasm with RELENZA and should have a fast acting bronchodilator available. Patients on maintenance inhaled bronchodilating therapy should be advised to use their bronchodilators before taking RELENZA.

Inhaled zanamivir had an acceptable safety profile in prophylactic use in high risk subjects in Study NAI30034. In general, the frequency and nature of adverse events was similar across treatment groups for subjects with each category of underlying high-risk condition.

Zanamivir 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 zanamivir 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. Zanamivir inhalation powder must only be administered using the device provided (see section 4.2 Dose and method of administration, and section 6.6 Special precautions for disposal and other handling).

4.5 Interaction with other medicines 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 metabolised or modified. Clinically significant drug interactions are unlikely.

4.6 Fertility, pregnancy and lactation

Fertility

Animal studies indicate no clinically meaningful effects of zanamivir on male or female fertility (see section 5.3 Preclinical safety data).

Pregnancy

There are insufficient data on the use of zanamivir 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 inhaled zanamivir, but due to limited sample sizes, no definitive conclusions can be drawn regarding the safety of zanamivir 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 RELENZA in pregnancy should be considered only if the possible benefit to the patient is thought to outweigh any possible risk to the foetus.

Breast-feeding

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.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Clinical trial data

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 zanamivir inhalation powder and placebo groups.

Post-marketing data

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

The following events have been identified during post-approval use of inhaled zanamivir (RELENZA).

Immune system disorders:

Very rare: Allergic-type reactions, including anaphylactic and anaphylactoid reactions, facial and oropharyngeal oedema

Nervous system disorders:

Very rare: Vasovagal-like reactions, have been reported in patients with influenza symptoms, such as fever and dehydration shortly following inhalation of zanamivir.

Respiratory, thoracic and mediastinal disorders:

Very rare: bronchospasm, dyspnoea

Skin and subcutaneous tissue disorder:

Very rare: rash, urticaria, severe skin reactions including Erythema Multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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

Doses of an investigational (lactose-free) aqueous solution 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 1200 mg/day for five days showed no adverse effect.

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Antiviral, neuraminidase inhibitor, ATC code J05AH01.

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 inhaled 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 in otherwise healthy and high risk patients, alleviates the symptoms and reduces their duration. In a pooled analysis of the principal phase III treatment studies (NAIB3001, NAIA3002, NAIB3002 and NAI30008) the median time to alleviation of influenza symptoms was reduced by 1.5 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; $p=0.021$).

The efficacy of RELENZA has been shown to be optimal if treatment is initiated as soon as possible after the onset of symptoms.

The efficacy of RELENZA in preventing naturally occurring influenza illness has been demonstrated in two post-exposure prophylaxis studies in households and two seasonal prophylaxis studies during community outbreaks of influenza.

Two studies assessed post-exposure prophylaxis in household contacts once a member of the household (the index case) developed an influenza-like illness. Within 1.5 days of onset of symptoms in an index case, each household (including all family members 5 years of age) was randomized to RELENZA 10 mg inhaled once daily or placebo inhaled once daily for 10 days. In the first study only, each index case was randomized to the same treatment (RELENZA or placebo) as the other household members. In this study, the proportion of households with at least one new case of symptomatic influenza was reduced from 19% (32 of 168 households) with placebo to 4% (7 of 169 households) with RELENZA (79% protective efficacy). In the second study, index cases were provided with relief medication for supportive care. In this study and the incidence of symptomatic influenza was reduced from 19% (46 of 242 households) with placebo to 4% (10 of 245 households) with RELENZA (81% protective efficacy). Results were similar in the subgroups with influenza A or B.

Two seasonal prophylaxis studies assessed RELENZA 10 mg inhaled once daily versus placebo inhaled once daily for 28 days during community outbreaks. In one study, the incidence of symptomatic influenza was reduced from 6.1% (34 of 554) with placebo to 2.0% (11 of 553) with RELENZA (67% protective efficacy). In the second study, the incidence of symptomatic influenza was reduced from 1.4% (23 of 1,685) with placebo to 0.2% (4 of 1,678) with RELENZA (83% protective efficacy).

5.2 Pharmacokinetic properties

Absorption

Pharmacokinetic studies in humans have shown that the absolute bioavailability of zanamivir from an oral solution 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

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) values 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

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/h as approximated by urinary clearance. Renal elimination is completed within 24 hours.

Patients with renal impairment

At the therapeutic daily dose of inhaled zanamivir of 20 mg, bioavailabilty 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.

Elderly patients

At the therapeutic daily dose of 20 mg, bioavailabilty 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.

5.3 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 developmental 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose (which contains milk protein).

6.2 Incompatibilities

None known.

6.3 Shelf life

10 years.

6.4 Special precautions for storage

RELENZA ROTADISKS should not be stored above 30°C.

6.5 Nature and contents of container

RELENZA ROTADISKS consists of a circular foil disk (a ROTADISK) with four regularly distributed blisters each containing 5 mg of zanamivir and 20 mg of lactose. A DISKHALER is provided to administer the medication.

6.6 Special precautions for disposal and other handling

The DISKHALER device is loaded with a disk that contains the medicine in individual blisters which are opened as the device is manipulated.

For detailed instructions for use refer to the Patient Instruction Leaflet in every pack.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Instructions for use:

A RELENZA ROTADISK may be kept in the DISKHALER at all times but a blister should only be pierced immediately prior to use. Failure to observe this instruction will affect operation of the DISKHALER.

The DISKHALER is a device which is used together with a ROTADISK for inhaling medication.

The DISKHALER consists of:

- an outer coloured body with a hinged lid and piercing needle
- a dark mouthpiece cover
- a white sliding tray with mouthpiece
- a dark wheel to support the ROTADISK

The ROTADISK consists of 4 blisters. Each blister contains a measured dose of dry powder medication.

WARNING:

Do not puncture any ROTADISK blister until loaded into the DISKHALER.

<u>To load the ROTADISK into the DISKHALER</u>

1. Remove the mouthpiece cover and check inside and outside to ensure that the mouthpiece is clean.
2. Hold the corners of the white tray and pull out gently until you can see all the plastic ridges on the sides of the tray.
3. Put your finger and thumb on the ridges, squeeze inwards and gently pull the tray out of the DISKHALER body.
4. Place the ROTADISK on the dark wheel with the blisters facing down. Then slide the tray back fully into the DISKHALER body.

<u>To pierce the blister in the ROTADISK</u>

5. Raise the lid as far as it will go into the fully upright position. Both surfaces of the blister must be pierced. Some resistance will be felt as the upper and especially the lower surfaces of the blister are pierced. Then close the lid.

WARNING:

Do not try to lift the lid unless the tray is positioned fully within the body of the DISKHALER or is completely removed.

<u>To inhale from the DISKHALER</u>

6. Breathe out as far as is comfortable. Keeping the DISKHALER level, raise the DISKHALER to your mouth and gently place the mouthpiece between your teeth and lips but do not bite the mouthpiece. Do not cover the air holes on

either side of the mouthpiece. Breathe in through your mouth steadily and as deeply as you can. Hold this breath in for several seconds and remove the DISKHALER from your mouth. Continue to hold your breath for as long as is comfortable.

To prepare for the next inhalation

7. Rotate the ROTADISK to the next blister by gently pulling the tray once out and in. Do not pierce the blister until immediately before inhalation. When you take another inhalation pierce the blister and inhale as shown in steps 5 and 6.

8. Always replace the mouthpiece cover after use.

To replace the ROTADISK

9. Each ROTADISK consists of 4 blisters containing medication. When the ROTADISK is empty, it should be replaced with a new ROTADISK by repeating steps 2 to 4.

WARNING:

Do not throw the wheel away with the empty ROTADISK.

7. MEDICINE SCHEDULE

Prescription only medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland 1143
NEW ZEALAND

Telephone: (09) 367 2900
Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 24 June 1999

10. DATE OF REVISION OF THE TEXT

5 April 2018

Summary table of changes:

Section changed	**Summary of new information**
All	Minor editorial and formatting changes

4.4	Relocation of existing information
4.5	Addition of information regarding interactions
4.6	Addition of fertility information and updates to information regarding use in pregnancy and breast-feeding
4.8	Deletion of text
4.9	Update to information regarding reports of overdose
5.1	Clarification of text
5.2	Update to absorption and distribution information
5.3	Addition of preclinical safety information

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