AUSTRALIAN PRODUCT INFORMATION

RELENZA ROTADISK (zanamivir)

1 NAME OF THE MEDICINE

Zanamivir

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each RELENZA ROTADISK blister contains 5 mg of zanamivir.

Excipients with known effect

Lactose monohydrate 20 mg (which contains milk protein).

For a 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

RELENZA (zanamivir) is indicated for the treatment of infections due to Influenza A and B viruses in adults and children aged 5 years and older. Treatment should commence as soon as possible but no later than forty-eight hours after the onset of the initial symptoms of infection (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Prophylaxis

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

The recommended dose of RELENZA is two oral 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 after onset of symptoms for maximum benefit, and at the latest should commence within 48 hours of symptom onset. Administration is by oral inhalation.

Prophylaxis

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.

RELENZA ROTADISKS are for pulmonary administration by oral inhalation only, using the DISKHALER device provided. Patients scheduled to take inhaled drugs, for example fast acting bronchodilators, at the same time as RELENZA, should be advised to administer that drug prior to administration of RELENZA (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Special populations

Renal Impairment

No alteration of dosage or frequency of administration is required (see Section 5.2 PHARMACOKINETIC PROPERTIES, Pharmacokinetics in Renal Impairment).

Hepatic Impairment

There is currently no experience in this patient population. Zanamivir is not hepatically metabolised and no dose modification is required (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in the elderly

Experience with zanamivir in the elderly (≥65 years) is limited. However based on the pharmacokinetic properties of zanamivir no dose modification is required (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric use

No dose modification is required (see Section 5.2 PHARMACOKINETIC PROPERTIES, Pharmacokinetics in Paediatric Patients). When zanamivir is prescribed for children, it should be used only under adult supervision.

Method of administration

Each RELENZA ROTADISK is inserted in the accompanying DISKHALER device. The medication is then inhaled through the mouth using the DISKHALER.

For instructions on preparation of the medicine before administration, see the Patient Instruction Leaflet in every pack.

4.3 CONTRAINDICATIONS

The use of RELENZA is contraindicated in patients with known 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

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).

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. RELENZA ROTADISKS must only be administered using the DISKHALER device provided.

Bronchospasm

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 Section 4.2 DOSE 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.

Neuropsychiatric Events

Influenza can be associated with a variety of neurological and behavioural symptoms which can include events such as seizures, hallucinations, delirium and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

There have been postmarketing reports (mostly from Japan and in paediatric patients) of delirium and abnormal behaviour leading to injury in patients with influenza who were receiving neuroaminidase inhibitors, including RELENZA. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made, but they appear to be uncommon based on usage data of RELENZA. These events were reported primarily among paediatric patients and often had an abrupt onset and rapid resolution. The contribution of

RELENZA to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behaviour. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

Use in the elderly

Please refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Use in the elderly.

Paediatric use

Please refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Paediatric use.

Effects on laboratory tests

No data available.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The potential for clinically significant drug-drug interactions resulting from zanamivir co-administration has been evaluated in a number of *in vitro* screens for effects on antiviral activity and pharmacokinetic disposition. These evaluations have found that the antiviral activity of zanamivir (e.g. with aspirin, ibuprofen, paracetamol, codeine, oxymetazoline, phenylephrine, diphenhydramine, promethazine or AUGMENTIN) as well as the renal excretion of zanamivir (e.g. with cimetidine, ibuprofen, cefuroxime, pseudoephedrine and paracetamol) is unlikely to be affected by drugs administered in influenza patients.

In vivo, zanamivir is excreted in urine as unchanged drug and zanamivir clearance closely approximates the glomerular filtration rate. Therefore, there is no evidence that zanamivir is hepatically metabolised or actively transported by renal transporters. *In vitro*, zanamivir is not a substrate of P-glycoprotein (Pgp) nor does it affect human transporters (organic anion, cation, or urate transporters) or cytochrome P450 (CYP) enzymes (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4). Clinically significant interactions involving these enzymes and transporters are therefore unlikely.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Zanamivir had no adverse effects on fertility, reproductive performance or development of the F_1 generation in the rat. Minor behavioural effects seen in F_1 males at 9 and 90 mg/kg/day in the fertility study were not seen in an additional study using the same dosages and dosing throughout embryo/foetal development. There were no changes seen which were considered to be clinically relevant.

Use in Pregnancy

(Pregnancy Category B1)

There is limited experience with the use of zanamivir during pregnancy reported during clinical trials and post marketing experience. The safe use of zanamivir during pregnancy has not been established.

Zanamivir should not be used in pregnancy, especially during the first trimester, unless the possible benefit to the patient is thought to outweigh any possible risk to the foetus.

There is no information on placental transfer of zanamivir in humans. Zanamivir crosses the placenta in rats and rabbits. Thirty minutes following intravenous administration of radiolabelled zanamivir (10 mg/kg) to rats on day 12 and 19 of pregnancy, low levels of placental transfer were noted (0.04% and 0.02%, respectively). Studies of embryofetal development showed no evidence of malformations in rats or rabbits with repeated intravenous doses up to 90 mg/kg/day, nor in rats administered subcutaneous doses up to 80 mg/kg/day, three times daily, resulting in total daily systemic exposures (AUCs) in the latter study of up to 1050 times the clinical exposure.

Use in lactation

There is no information on secretion of zanamivir in milk in humans. In rats, the drug has been found to be secreted into milk, although this did not appear to affect the peri- and post-natal development of the offspring.

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 infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no reported effects of zanamivir on driving performance or the ability to operate machinery. Detrimental effect on such activities is not predicted from the pharmacology of the drug.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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%

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

Adverse events that occurred with an incidence of ≥1.5% in the 4 prophylaxis studies are listed in Table 2.

Table 2. Summary of Adverse Events ≥1.5% Incidence During Prophylaxis Studies in Adults, Adolescents, and Children*

Adverse Event	Household Studies NAI30010, NAI30031		Community Studies NAIA3005, NAI30034	
	RELENZA contacts (n = 1,068)	Placebo† contacts (n = 1,059)	RELENZA (n = 2,231)	Placebo† (n = 2,239)
Lower respiratory				
Viral respiratory infections	13%	19%	3%	4%
Cough	7%	9%	17%	18%
Bronchospasm-like events	<1%	1%	2%	3%
Neurologic				
Headaches	13%	14%	24%	26%
Ear, nose, and throat				
Nasal signs and symptoms	12%	12%	12%	13%
Throat and tonsil discomfort and pain	8%	9%	19%	20%

Adverse Event	Household Studies NAI30010, NAI30031		Community Studies NAIA3005, NAI30034	
	RELENZA contacts (n = 1,068)	Placebo† contacts (n = 1,059)	RELENZA (n = 2,231)	Placebo† (n = 2,239)
Nasal inflammation	1%	2%		
Ear, nose, throat infections			2%	2%
Musculoskeletal				
Muscle pain	3%	3%	8%	8%
Musculoskeletal pain			6%	6%
Arthralgia and articular rheumatism			2%	<1%
Endocrine and metabolic				
Feeding problems (decreased or increased appetite and anorexia)	2%	2%	4%	4%
Gastrointestinal				
Nausea and vomiting	1%	2%	2%	3%
Diarrhoea			2%	2%
Non-site specific				
Malaise and fatigue	5%	5%	8%	8%
Temperature regulation disturbances (fever and/or chills)	5%	4%	9%	10%

* In prophylaxis studies symptoms associated with influenza-like illness were captured as adverse events; subjects were enrolled during a winter respiratory season during which time any symptoms that occurred were captured as adverse events.

† Because the placebo consisted of inhaled lactose powder, which is also the vehicle for the active drug, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation.

The frequency and nature of adverse events reported during prophylaxis for all four studies were very similar between the placebo and zanamivir groups. The most commonly reported adverse events during prophylaxis were headaches, throat and tonsil discomfort and pain, cough, and nasal signs and symptoms, which are typical of the signs and symptoms of influenza and other viral respiratory infections.

There were no notable differences in the frequency and nature of adverse events between placebo and zanamivir in paediatric subgroups (ages 5 to 11 and 12 to 16 years).

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.

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.

Post-marketing experience

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

General

Very rare (<1/10,000): allergic-type reactions, including anaphylactic and anaphylactoid reactions, facial and oropharyngeal oedema

Nervous systems disorders

Very rare (<1/10,000): vasovagal-like reactions have been reported in patients with influenza symptoms, such as fever and dehydration, shortly following inhalation of zanamivir

Respiratory

Very rare (<1/10,000): bronchospasm, dyspnea

Skin and subcutaneous tissue disorders

Very rare (<1/10,000): rash, urticaria, severe skin reactions including Erythema Multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Reports of overdoses with inhaled zanamivir have been received during post-marketing experience. The reported clinical signs or symptoms were similar to those observed with therapeutic doses of inhaled zanamivir and the underlying disease. Doses up to 96 mg/day (approximately 5 times the maximum recommended daily dose) have been administered intranasally without adverse effects. Additionally, systemic exposure following intravenous administration of up to 1200 mg/day for five days showed no adverse effect.

No specific action is required in the event of an overdose.

Further management should be as clinically indicated or as recommended by the national poisons centre. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacodynamics

Zanamivir is a potent and highly selective inhibitor of the influenza virus surface enzyme, neuraminidase. Viral neuraminidase may facilitate access of virus to cell surfaces and aid the release of newly formed virus particles from infected cells, to allow viral infection of other cells.

The inhibition of this enzyme is demonstrated by both *in vitro* and *in vivo* activity against influenza A and B virus replication and encompasses all known neuraminidase subtypes of influenza A viruses.

Influenza viral replication is confined to the superficial epithelium of the respiratory tract. The activity of zanamivir is extracellular; it inhibits the release of infective influenza virions from the epithelial cells of the respiratory tract, thereby reducing the propagation of both influenza A and B viruses. The efficacy of zanamivir following oral inhalation to the respiratory tract has been confirmed in clinical studies. Clinical trial data have shown that treatment of acute influenza 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.

When taken as recommended for the treatment of influenza, zanamivir alleviates and reduces duration of influenza symptoms in patients aged 5 years and older. The efficacy of zanamivir is optimal if treatment is initiated as early as possible after symptom onset**.** The efficacy of zanamivir administered more than 48 hours after the onset of symptoms has not been demonstrated. When taken as recommended for the prophylaxis of influenza, it reduces the incidence of symptomatic influenza in the same population.

Drug Resistance

Influenza viruses with reduced susceptibility to zanamivir have been recovered *in vitro* by passage of the virus in the presence of increasing concentrations of the drug. Genetic analysis of these viruses showed that the reduced susceptibility *in vitro* to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral haemagglutinin or both. Even though exhibiting a drug resistant phenotype *in vitro*, based on *in vivo* studies to date, a virus with such combinations of mutations would be expected to have reduced pathogenicity and transmissibility in the clinical setting.

There has been no detectable emergence of virus to date with reduced susceptibility to zanamivir during the clinical development programme. Data obtained from *in vitro* studies and from clinical treatment and prophylaxis studies suggests that the potential for the development of reduced clinical susceptibility to zanamivir in the future is low.

Clinical trials

Treatment

Five Phase III randomised, placebo-controlled, parallel-group, multicentre studies were conducted with zanamivir in the treatment of naturally acquired influenza A and B in adults and adolescents (NAIB3001, NAIA3002, NAIB3002 and NAI30008) and in children aged 5-12 years (NAI30009). The Intent-to-Treat population of the four adult studies and the paediatric study comprised of 2113 and 471 patients respectively; of whom 1075 adults and 224 children received 10 mg zanamivir twice daily by oral inhalation. The proportion of influenza-positive patients across the five studies, ranges from 60% to 78%. Of these, 88-91% had influenza A and 9-11% had influenza B in the adult studies. In the paediatric study, there were 65% and 35% influenza A and B cases respectively.

In the adult studies, patients aged 65 years and over, or patients with concurrent cardiovascular conditions (excluding uncomplicated hypertension), respiratory conditions, metabolic conditions, endocrine conditions or who were immunocompromised were considered more vulnerable to complications of influenza and were therefore categorised as ‘High Risk’ patients.

Protocols for the five studies were similar. Patients were recruited into studies when influenza was known to be circulating in the community. Eligibility of entry into study was based on the presence of feverishness (NAIB3001) or fever (NAIA3002, NAIB3002 and NAI30008) and at least two of the following: headache, myalgia, cough and sore throat. For the paediatric study (NAI30009), this was simplified to fever, with no clinical evidence of a bacterial infection. Where fever was a criterion, the requirement was temperature ≥ 37.8°C except in patients aged 65 years or older (≥ 37.2°C).

In NAIB3001 and NAI30009, patients were recruited and commenced using study medication within 36 hours of the onset of symptoms, while in NAIA3002 and NAIB3002, patients were recruited and commenced treatment within two calendar days.

The primary endpoint was identical for all four Phase III studies, i.e. time to alleviation of clinically significant signs and symptoms of influenza. Alleviation was defined as no fever (temperature <37.8ºC and feverishness score of 'none') and headache, myalgia, cough and sore throat recorded as 'none' or 'mild' and maintained for 24 hours.

Results of primary endpoint analyses for the Intent-to-Treat and Influenza Positive populations are shown below.

Table 3. Median Time (days) to Alleviation of Clinically Significant Influenza Symptoms in Phase III Studies

Study	Placebo (median day)	Zanamivir (median day)	Days Difference	95% Confidence Interval	p-value	Placebo N	Zanamivir N
Intent-to-Treat Population							
NAIB3001	6.5	5.0	1.5	0.5 2.25	0.011	228	227
NAIA3002	6	5.5	0.5	-0.5 1.0	0.228	365	412
NAIB3002	7.5	5.0	2.5	0.75 3.5	<0.001	182	174
NAI30008	7.0	6.0	1.0	0.0 2.0	0.123	263	262
NAI30009	5.0	4.5	0.5	0.0 1.5	0.011	247	224
Influenza Positive Population							
NAIB3001	6	4.5	1.5	0.5 2.5	0.004	160	161
NAIA3002	6	5	1.0	0.0 1.5	0.078	257	312
NAIB3002	7.5	5	2.5	1.0 4.0	<0.001	141	136
NAI30008	7.0	5.5	1.50	0.5 3.25	0.009	153	160
NAI30009	5.25	4.0	1.25	0.5 2.0	<0.001	182	164

The four adult studies included 361 'High Risk' patients treated with zanamivir. Of these, 58 were aged 65 years or older. In a pooled analysis of the Influenza Positive population in the principle 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).

In the paediatric study, median time to symptom improvement was one day shorter in patients receiving zanamivir compared with placebo. Comparable rates of development of complications were observed between the treatment groups.

Study NAI30008 enrolled patients aged 12 years and over, diagnosed with asthma or chronic obstructive pulmonary disease. Baseline status for influenza positive patients is shown in Table 4.

Table 4. Baseline status for influenza positive patients in Study NAI30008

	Placebo (n=153)	**Zanamivir (n=160)**
Asthma and COPD	8 (5%)	8 (5%)
Asthma only	120 (78%)	127 (79%)
COPD only	23 (15%)	25 (16%)
Neither*	2 (1%)	0

*Subjects had asthma/COPD in the opinion of the investigator but did not have a documented history.

The median time to symptom improvement was 1.5 days less in patients receiving zanamivir compared with placebo. Comparable rates of development of complications were observed between the treatment groups (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

There have been no studies of treatment of influenza, where treatment was commenced after 48 hours of onset of symptoms.

Prophylaxis

The efficacy of RELENZA in preventing naturally occurring influenza illness has been demonstrated in two post-exposure prophylaxis studies in households (NAIA30010 and NAI30031) and two seasonal prophylaxis studies during community outbreaks of influenza (NAIA3005 and NAI30034). The primary efficacy endpoint in these studies was the incidence of symptomatic, laboratory-confirmed influenza, defined as the presence of two or more of the following symptoms: oral temperature 37.8C or feverishness, cough, headache, sore throat, and myalgia; and laboratory confirmation of influenza by culture, PCR, or seroconversion (defined as a 4-fold increase in convalescent antibody titer from baseline).

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 (NAIA30010) 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 (NAI30031), index cases were provided with relief medication for supportive care 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 study NAIA3005, patients had to be part of a university community during an influenza outbreak, be aged 18 years or older and enter the study within 72 hours of an outbreak being declared. In this 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 (NAI30034), community-dwelling subjects, 12 years and older, who were at high risk of complications from influenza were enrolled. High risk was defined as subjects >65 years of age, subjects with diabetes mellitus and subjects with chronic disorders of the pulmonary or cardiovascular systems. The study was conducted during a season with low

influenza activity. Despite this, the study demonstrated statistically significant protective benefit in subjects who received RELENZA. 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).

Results of the primary efficacy endpoint analysis are presented for the Intent To Treat population for each of the studies are shown below.

Table 5. Summary of Primary Efficacy Analyses: Primary Studies (ITT Population)

Study	Cases of Influenza		p-value	Approximate Relative Risk (95% CI)	Protective Efficacy (%)
	Placebo n/N (%)	Zanamivir n/N (%)			
NAI30010[1]	32/168 (19)	7/169 (4)	<0.001	0.21 (0.11, 0.43)	79
NAI30031[1]	46/242 (19)	10/245 (4)	<0.001	0.19 (0.10, 0.36)	81
NAIA3005[2]	34/554 (6)	11/553 (2)	<0.001	0.33 (0.17, 0.61)	67
NAI30034	23/1685 (1)	4/1678 (<1)	<0.001	0.17 (0.07, 0.44)	83

1. In at least one contact case in the family/household
2. In all subjects (not just non-vaccinated subjects)

Table 6. Summary of Primary Efficacy Analyses by age in pivotal studies (ITT Population)

Study	Age group (years)	Contact cases/subjects with symptomatic laboratory confirmed influenza	
		Placebo n/N (%)	Zanamivir n/N (%)
Family/Household Studies			
NAI30010	5 - 6	4/33 (12)	1/28 (4)
	7 - 11	7/91 (8)	2/89 (2)
	12- 16	2/64 (3)	2/65 (3)
	17 – 34	4/53 (8)	1/58 (2)
	35 – 49	21/160 (13)	1/151 (<1)
	50 – 64	1/20 (5)	0/23
	65+	1/2 (50)	0/0
NAI30031	5 - 6	4/26 (15)	1/36 (3)
	7 - 11	15/128 (12)	6/122 (5)
	12- 16	9/100 (9)	0/124
	17 – 34	6/100 (6)	3/91 (3)
	35 – 49	20/240 (8)	2/250 (<1)
	50 – 64	1/32 (3)	0/31
	65+	0/4	0/7
Community Studies			
NAIA3005	17 – 34	27/416 (6)	9/416 (2)
	35 – 49	5/116 (4)	2/105 (2)
	50 – 64	2/21 (10)	0/31
	65+	0/1	0/1
NAI30034	12- 16	3/55 (5)	1/51 (2)
	17 – 34	4/114 (4)	1/123 (<1)
	35 – 49	7/246 (3)	1/128 (<1)
	50 – 64	4/320 (1)	0/330
	65+	5/950 (<1)	1/946 (<1)

Two prophylaxis studies conducted in a nursing home setting assessed RELENZA 10 mg once daily for 14 days compared with standard of care in the prevention of influenza infection. In

study NAIA3003 standard of care was rimantadine for influenza A and placebo for influenza B. In study NAIA3004 standard of care was placebo. There was no upper age limit, and once an influenza outbreak was declared in the nursing home, study treatment was initiated. The primary endpoint for both studies was the proportion of subjects who during prophylaxis, developed a new sign or symptom and had laboratory confirmation of influenza. The results of Study NAIA3003 showed a trend toward efficacy against an active comparator, although the results did not reach statistical significance (protective efficacy 56%, p-value 0.085). The results of Study NAIA3004 did not demonstrate significant protective efficacy (protective efficacy 29%, p-value 0.355).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Pharmacokinetic studies in man following inhalation of zanamivir suggest that approximately 4-17% of the dose is absorbed into the systemic circulation. Serum zanamivir concentrations generally peak within 1-2 hours.

Distribution

After oral inhalation, zanamivir is widely deposited in the respiratory tract mucosa, 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 2.6 ng/mL) values for influenza virus neuraminidase for various influenza A (N1 and N2 subtypes) and B viruses. Despite a large proportion of the inhaled dose being swallowed, the absolute oral bioavailability is low (about 2%) and swallowed drug does not contribute significantly to systemic exposure. As an index of systemic absorption, between 3.8% to 17% (median values) of the inhaled dose as dry powder via DISKHALER was excreted unchanged in the urine. There is no evidence of modification in kinetics after repeated dosing with inhaled administration. The plasma protein binding of zanamivir is low, less than 10%, as shown by *in vitro* assay in the presence of 0.5 and 10 micrograms/mL zanamivir.

Metabolism

Animal and human studies show that zanamivir is excreted as unchanged drug. Chromatographic profiling of urine samples from rats, dogs and rabbits show no evidence of biotransformation. These findings indicate that zanamivir does not undergo metabolism.

Excretion

The median serum half-life of zanamivir following intravenous administration ranges from 1.5 to 3.1 hours. The delayed serum half-life following oral inhalation (range 2.5 to 5.1 hours) reflects slow systemic absorption by this route. Zanamivir is excreted unchanged in the urine. Total clearance ranges from 2.5 to 10.9 L/h as approximated by urinary clearance. Elimination is complete within 24 hours.

Pharmacokinetics in Renal Impairment

Dose modification is not required.

Drug clearance is proportional to creatinine clearance; a 50% reduction in renal clearance results in a corresponding 50% reduction in serum clearance of zanamivir. In a single dose

study with intravenous zanamivir (2 mg or 4 mg), in patients with severe renal impairment (creatinine clearance <25 mL/min), systemic exposure to zanamivir was increased approximately 7 fold relative to patients with normal renal function. However, oral inhalation results in very low systemic exposure (approximately 4 to 17% of the dose administered) and in studies much higher systemic exposure (600 mg IV for 5 days) was well tolerated.

Pharmacokinetics in Paediatric Patients

In an open-label single-dose study the pharmacokinetics of zanamivir have been evaluated in twenty-four children aged 3 months to 12 years using nebulised (10 mg) and dry powder (10 mg) inhalation formulations. Six patients had either undetectable zanamivir concentrations or had low drug concentrations after 1.5 hours. Eleven patients, aged 5 to 12 years, administered the dry powder formulation had C_{max} median values of 43 ng/mL (range 15 to 74) and AUC_{∞} median values of 167 ng.hour/mL (range 58 to 279).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Zanamivir was not genotoxic in standard assays for gene mutation (i.e. Ames test, mouse lymphoma cell) or chromosomal damage (human peripheral lymphocyte and mouse micronucleus assay.)

Carcinogenicity

In 2 year rat and mouse oncogenicity studies of aerosolised zanamivir administration, resulting in maximum systemic exposures of 17*x* and 19*x* respectively, of the clinical exposure, there were no neoplastic findings considered related to study drug treatment. In male rats, the incidence of lymphomas was slightly higher for the high dose group (approximately 30-50 mg/kg/day) compared to the control group; there was no dose relationship. Studies in mice and female rats exposed to similar aerosol concentrations of zanamivir showed no increase in lymphoma incidence.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australia Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Each RELENZA ROTADISK consists of a circular foil disk with four regularly distributed blisters each containing 5 mg of zanamivir and 20 mg of lactose monohydrate.

The registered pack sizes are:

20 (5 ROTADISKS x 4 blisters) with DISKHALER
28 (7 ROTADISKS x 4 blisters) with DISKHALER
20 (5 ROTADISKS x 4 blisters) with DISKHALER
4 (1 ROTADISK x 4 blisters) (physician sample)
60 (15 ROTADISKS x 4 blisters) with DISKHALER
4 (1 ROTADISK x 4 blisters) with DISKHALER

Not all pack sizes may be distributed in Australia.

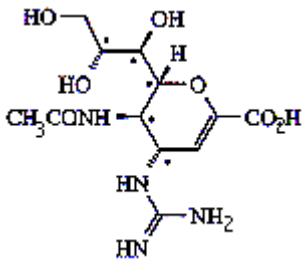
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

Chemically, zanamivir is 5-(acetylamino)-4-[(aminoiminomethyl)amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid, and has the following structural formula:



* chiral centres

The molecular formula of zanamivir is $C_{12}H_{20}N_4O_7$ and the relative molecular mass is 332.3.

CAS number

139110-80-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street

Abbotsford, Victoria 3067
Australia

9 DATE OF FIRST APPROVAL (ARTG ENTRY)

21 April 1999

10 DATE OF REVISION OF THE TEXT

9 April 2019

Summary table of changes

Section changes	Summary of new information
4.4	Clarification of patient population where postmarketing reports of neuropsychiatric events have been observed
4.5	Addition of information regarding interactions
4.8	Deletion of text regarding the tolerance of zanamivir
4.9	Update to information regarding reports of overdose
5.1	Clarification of text
5.2	Update to absorption and distribution information
All	Minor editorial and formatting changes

Version 6.0