

# DATA SHEET

## RELENZA<sup>®</sup> Rotadisks

*Zanamivir 5mg/blister*

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### Qualitative and quantitative composition

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

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### Pharmaceutical form

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Inhalation powder.

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### Clinical particulars

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#### *Therapeutic Indications*

##### **Treatment of Influenza:**

RELENZA is indicated for treatment of both influenza A and B in adults and children ( $\geq 5$  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 ( $\geq 5$  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.

##### ***Posology and Method of Administration***

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

**Treatment of Influenza:**

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

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 10mg, for 10 days. This may be increased up to 28 days if the period of exposure risk extends beyond 10 days.

**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).

**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.

***Contraindications***

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

***Special Warnings and Special Precautions for Use***

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 zanamivir and seek medical evaluation. Patients with underlying respiratory disease should have a fast acting bronchodilator available when taking zanamivir (see Posology 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.

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 Zanamivir. The events were observed mainly early in the illness and often had an abrupt onset and rapid resolution. The contribution of 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.

### ***Use During Pregnancy and Lactation***

#### **Pregnancy**

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

Reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs. Studies in rats did not show any evidence of teratogenicity, impairment of fertility or clinically significant impairment of peri or post-natal development of offspring following administration of zanamivir. However, there is no information on placental transfer in humans.

RELENZA 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.

#### **Lactation**

In rats zanamivir has been shown to be secreted 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 infant.

### ***Effects on Ability to Drive and Use Machines***

None known.

### ***Interaction with Other Medicinal Products and Other Forms of Interaction***

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

### ***Undesirable 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.

#### **Post-marketing data**

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

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

#### **General:**

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

#### **Respiratory:**

*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

#### **Overdose**

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 64mg/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 1200mg/day for five days showed no adverse effect.

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## **Pharmacological properties**

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### ***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 without any detectable emergence of virus with reduced susceptibility to zanamivir.

## **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 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;  $p = 0.021$ ).

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).

### ***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 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. Following a single 10mg dose the concentrations of zanamivir were measured at the epithelial layer of the airways, the major sites of influenza viral replication. Zanamivir concentrations of approximately 340 and 52 fold above the median viral neuraminidase IC<sub>50</sub> were measured at 12h and 24h respectively. The high concentrations of zanamivir in the respiratory tract will result in the rapid onset of inhibition of the viral neuraminidase. 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 10.9L/h as approximated by urinary clearance. Renal elimination is completed within 24 hours.

**Patients with renal impairment:**

At the therapeutic daily dose of 20mg, bioavailability is low (10-20%), 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 20mg, bioavailability is low (10-20%), 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 paediatric subjects ages 3 months to 12 years using nebulised (10mg) and dry powder (10mg) inhalation formulations. The systemic exposure in children was similar to 10mg of inhaled powder in adults.

**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.

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**Pharmaceutical particulars**

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***List of Excipients***

RELENZA is a white to off-white powder blend of micronised zanamivir and lactose (which contains mild protein).

***Incompatibilities***

None known

***Shelf Life***

84 months

**Special Precautions for Storage**

RELENZA Rotadisks should not be stored above 30°C.

**Nature and Contents of Container**

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

**Instructions for Use/Handling**

The powdered medicine is inhaled through the mouth into the lungs. 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.

**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.

**TO LOAD THE ROTADISK INTO THE DISKHALER**

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.

#### TO PIERCE THE BLISTER IN THE ROTADISK

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.

#### TO INHALE FROM THE DISKHALER

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.

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### **Medicines classification**

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Prescription Only Medicine

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## **Name and address**

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## **Date of preparation**

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15 September 2009

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