

## Administration of *Relenza* via a Nebulizer

This information is provided in response to your request for information about Relenza® (zanamivir) Inhalation Powder, for oral inhalation.

- In a kinetic study comparing a single dose of zanamivir 10 mg administered via a nebulizer to children  $\geq 3$  months to  $< 5$  years to zanamivir 10 mg administration via the *Diskhaler* to children  $\geq 5$  years to  $\leq 12$  years, all pharmacokinetic parameters were similar, including  $AUC_{0-inf}$ ,  $AUC_{0-last}$ ,  $C_{max}$ ,  $T_{1/2}$  and  $T_{max}$ .
- In a clinical study of hospitalized adults with serious influenza disease, zanamivir 16 mg via a nebulizer plus oral rimantadine was compared to oral rimantadine alone. Medications were administered four times daily for 5 days. Although this study was underpowered to assess efficacy, several findings suggest that the patients who received nebulized zanamivir with rimantadine benefited more than the patients who received rimantadine alone.
- A placebo-controlled pilot treatment study of adults was conducted to evaluate the safety and efficacy of zanamivir administered via nebulizer (16 mg dose) and intranasally (6.4 mg dose) twice daily for 7 days. The target recruitment was not achieved and as a result there was not a sufficient power to detect a specific treatment difference. A similar proportion of patients in all groups achieved an alleviation of major influenza symptoms by day 3 (primary outcome).
- In all studies, zanamivir administered via a nebulizer was generally well tolerated, with most adverse events being classified as mild in intensity.

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### CONSIDERATIONS FOR THE PREPARATION OF *RELENZA* FOR ADMINISTRATION VIA A NEBULIZER

*Relenza* is supplied in a circular double-foil pack called a Rotadisk®. (1) Each *Rotadisk* contains four regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose. A 10 mg dose requires the use of two blisters.

Zanamivir is a white to off-white powder with a solubility of approximately 18 mg/mL in water. The solubility of lactose is approximately 190 mg/mL in water.

### CLINICAL STUDIES

#### Pharmacokinetic Study

This open-label, single-dose study evaluated the pharmacokinetics and safety of zanamivir administered to children  $\geq 3$  months to  $< 5$  years of age via a nebulizer compared to children  $\geq 5$  to  $\leq 12$  years of age who were administered zanamivir via the *Diskhaler*®.(2)

Each child  $\geq 3$  months to  $< 5$  years of age who used the nebulizer (N = 7) received 10 mg of zanamivir (from a solution concentration 16 mg/mL) mixed with 2 mL of normal saline via a nebulizer and mask. The solution was nebulized for 10-15 minutes or until "apparent dryness" at an airflow of 5 L/min. The eleven children who received zanamivir 10mg via the *Diskhaler* were separated into two groups: 5-9 years of age (N = 4) and 9-12 years of age (N = 7).

Results from the serum data are summarized in Table 1 .

**Table 1. Median with Minimum and Maximum Values of the Pharmacokinetic Parameters by Age Group<sup>(2)</sup>**

<b>Age</b>	<b>AUC<sub>0-inf</sub> ng*hour/mL</b>	<b>AUC<sub>0-last</sub> ng*hour/mL</b>	<b>C<sub>max</sub> ng/mL</b>	<b>T<sub>1/2</sub> Hour</b>	<b>T<sub>max</sub> Hour</b>
≥3 months - <5 years (N = 7)	184 (54, 282)	161 (36, 265)	47 (16, 85)	1.9 (1.7, 4)	0.8 (0.5, 1.3)
≥5 years - <9 years (N = 4)	192 (58, 272)	167 (43, 252)	47 (15, 74)	2 (1.7, 2.5)	1 (0.4, 1.5)
≥9 years - ≤12 years (N = 7)	167 (123, 279)	142 (103, 248)	40 (34, 54)	2 (1.6, 2.3)	1 (0.4, 1.5)

AUC<sub>0-inf</sub> = Area under the curve of concentration versus time from time 0 to infinity. AUC<sub>0-last</sub> = Area under the curve of concentration versus time from time 0 to last measured concentration. C<sub>max</sub> = Maximum plasma concentration. T<sub>1/2</sub> = Terminal half-life. T<sub>max</sub> = Time to C<sub>max</sub>.

All inhaled doses of zanamivir (via nebulizer and via *Diskhaler*) were well tolerated by all participants, and all adverse events were mild in intensity. There were no serious adverse events, and of the seven adverse events reported, just one (episode of headache) was considered to be possibly drug-related.

### **Study of Hospitalized Patients with Serious Influenza Disease**

#### **Methodology**

Ison et al conducted a randomized, placebo-controlled, double-blinded study of the treatment of influenza infection with nebulized zanamivir and oral rimantadine in hospitalized patients with serious influenza disease.<sup>(3)</sup> Patients (N = 41) enrolled in the study had a median age of 67 years (range 24 - 93 years), were hospitalized with laboratory-confirmed influenza A or B infection with symptoms of 4 days duration or less, and had lower respiratory tract involvement (defined as at least one of the following signs: new infiltrate on chest radiograph; new onset of respiratory distress (dyspnea, severe cough); 15 mmHg or greater decrease in alveolar-arterial oxygen gradient compared to the patient's known or expected baseline gradient; and/or arterial oxygen saturation ≤90% by fingertip oximetry on room air).

This study used an investigational formula of zanamivir (16 mg/mL in normal saline). Zanamivir 16 mg or placebo (normal saline) was administered via nebulizer four times daily for 5 days (a dose exceeding the FDA approved dosing for treatment). Patients with influenza A infections (n = 40) also received rimantadine orally. The disposable nebulizer with mouthpiece was set at an airflow of 6-7 L/min and the dose was completed within 10 minutes.

#### **Results**

This investigational study was terminated prior to full enrollment as the coincidental FDA approval of *Relenza* made the recruitment of additional patients unfeasible. This event resulted in the study to be underpowered to assess efficacy, however, several findings suggest that the group which received nebulized zanamivir with rimantadine benefited more than the patients who received rimantadine alone for the treatment of lower respiratory tract manifestations of influenza.

The median time to no pharyngeal viral shedding (primary study end-point) was 4 days in the placebo plus rimantadine group and 2 days in the zanamivir plus rimantadine group (95% confidence interval (CI):2-5 days). A higher proportion of patients in the zanamivir plus rimantadine group reported no/mild cough on day 3 of treatment (94 vs 55%, P = 0.01). Further assessment on treatment day 3 showed no statistically significant differences in the proportion of patients still hospitalized (95 vs 94%), receiving supplemental oxygen (65 vs 62%) or having resumed full ambulation.

## Safety

Nebulized zanamivir was generally well tolerated, without significant declines in peak expiratory flow rates (PEFRs). There were no significant differences in the number of patients reporting adverse events between placebo plus rimantadine (76%) or zanamivir plus rimantadine (70%) ( $P = 0.66$ ). Seven serious adverse events were observed, but only one episode (retrosternal burning with dyspnea) was felt by study investigators to be caused by the study medication (zanamivir).

## **Pilot Treatment Study**

### ***Methodology***

A double-blind, randomized, comparative, placebo-controlled, multicenter study was conducted to evaluate the efficacy and safety of zanamivir administered by inhalation and by inhalation plus intranasally in the treatment of influenza in adults.<sup>(4)</sup> Patients were 18 to 65 years of age, had laboratory confirmed influenza-like illness (i.e., feverishness, headache and myalgia) for a duration of  $\leq 36$  hours, and were divided into one of 3 groups: Group 1 ( $n = 34$ ) received zanamivir 16 mg via nebulizer plus zanamivir 6.4 mg intranasally; Group 2 ( $n = 37$ ) received zanamivir 16 mg via nebulizer plus placebo intranasally; Group 3 ( $n = 32$ ) received placebos both via nebulizer and intranasally. All doses were administered twice daily for 7 days (a dose and duration exceeding the FDA approved dosing for treatment).

### ***Results***

Due to a low incidence of influenza in the study areas, the targeted recruitment was not achieved, and therefore the study did not have sufficient power to detect a specific treatment difference.

The primary outcome measure was the alleviation of major influenza signs and symptoms, defined as temperatures  $\leq 37.7^{\circ}\text{C}$ , and headache and myalgia recorded as "none" or "mild", all of which were maintained for 24 hours. Table 2 summarizes the alleviation of the major influenza signs and symptoms of the 3 groups.

**Table 2. Patients With Alleviation of Major Symptoms of Influenza by Day 3 (Intent to Treat Population)<sup>(4)</sup>**

Treatment Group*	Alleviation of Major Symptoms
	n/N (%)
Placebo inhaled (nebulized) + Placebo intranasally	16/32 (50%)
Zanamivir inhaled (nebulized) + Placebo intranasally	17/37 (46%)
Zanamivir inhaled (nebulized) + Zanamivir intranasally	19/34 (56%)

\* There were no statistically significant differences between the treatment groups. n/N = Number of patients with alleviation of major symptoms per total number of patients in group.

## Safety

During treatment, four patients (13%) in the placebo group, 12 patients (32%) in the inhaled zanamivir group, and 14 patients (41%) in the inhaled plus intranasal zanamivir group reported drug-related adverse events. At the post-treatment visit (day 8) two patients (6%) in the placebo group, two patients (5%) in the inhaled zanamivir group, and one patient (3%) in the inhaled plus intranasal zanamivir group reported drug-related adverse events. The most frequently reported drug adverse events during treatment are summarized in Table 3:

**Table 3. Most Frequently Reported Drug-Related Adverse Events During Treatment (Intent to Treat Population)<sup>(4)</sup>**

<b>Adverse Event</b>	<b>Placebo + Placebo Group n = 32</b>	<b>Zanamivir Inhaled + Placebo Group n = 37</b>	<b>Zanamivir Inhaled + Intranasally Group n = 34</b>
Dizziness	0	5%	21%
Nausea and vomiting	0	11%	9%
Nasal signs and symptoms	3%	5%	9%
Throat and tonsil signs and symptoms	3%	3%	9%

n = number of patients

One serious adverse event (severe frontal headache and dizziness) deemed possibly related to the study medication occurred during treatment in a patient who received zanamivir via nebulizer plus intranasally after the second dose.

**Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.**

**In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.**

**This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.**

#### **REFERENCE(S)**

1. GlaxoSmithKline Local Label. \*
2. Peng AW, Hussey EK, Rosolowski B, et al. Pharmacokinetics and tolerability of a single inhaled dose of zanamivir in children. *Curr Ther Res Clin Exp* 2000;33-46.\*
3. Ison MG, Gnann JW, Nagy-Agren S, et al. Safety and efficacy of nebulized zanamivir in hospitalized patients with serious influenza. *Antiviral Ther* 2003;183-190.\*
4. Data on File. NAIB2003. 1998.\*