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Zanamivir

A Review of Clinical Safety in Individuals at High Risk of Developing Influenza-Related Complications

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Abstract

Post-marketing experience shows zanamivir to be well tolerated in the general population for the treatment and prophylaxis of influenza type A and B infections. Individuals at high-risk of influenza have potentially more to gain from zanamivir therapy.

We assessed safety and tolerability findings from treatment and prophylaxis studies in over 982 high-risk subjects. Eight treatment studies involving high-risk subjects have been conducted with zanamivir 10mg twice daily for 5 days. The incidence and pattern of adverse events was similar in zanamivir and placebo recipients. Lower respiratory adverse events reported by recipients receiving zanamivir occurred at similar or lower frequencies to those receiving placebo.

In one treatment study involving 525 patients with asthma or chronic obstructive pulmonary disease, zanamivir recipients had a small but significantly increased mean morning peak expiratory flow rate (PEFR) and evening PEFR compared with placebo during the treatment period (days 1 to 5).

Eight prophylaxis studies have been conducted, five in family or community settings and three in nursing homes. Data from these studies demonstrate that zanamivir is well tolerated for prophylaxis. In nursing home studies, where 90% of participants were high risk, the pattern and incidence of adverse events were similar to that reported in otherwise healthy individuals, and similar to both placebo and rimantadine, a comparator in one study.

In treatment and prophylaxis studies the incidence and pattern of adverse events in participants ≥65 years or with chronic underlying respiratory disorders was similar for zanamivir or placebo recipients.

Overall, zanamivir was well tolerated and study drug discontinuations were low. A small number of deaths have been reported in studies of high-risk elderly individuals, but none were considered to be related to zanamivir. Thus clinical studies have demonstrated that zanamivir has a comparable safety profile in high-risk and otherwise healthy recipients.

Approximately 1.72 million treatment courses of zanamivir were prescribed up to the end of January 2001. Many spontaneous adverse event reports received since marketing, a third of these from non-healthcare professionals, reflect the underlying condition being treated. However, a number of events have resulted in changes to the zanamivir prescribing information, including rare reports of bronchospasm, dyspnoea, rash, urticaria and allergic type reactions including facial and oropharyngeal oedema.

The reported safety profile of zanamivir, for treatment and prophylaxis of high risk subjects with influenza type A and B infections supports its continued use in these individuals who are likely to benefit most.

Influenza usually occurs during the winter months, and causes significant morbidity and mortality each year. After an incubation period of 2 to 3 days, there is usually an abrupt onset of fever together with symptoms that may include shivering, myalgia, headache, malaise, sore throat, sneezing, wheezing, anorexia and cough. Children may also complain of ear pain. Patients are often confined to bed for a number of days but symptoms, with the exception of malaise and cough which may persist, usually resolve within a week.[1] However, the elderly, neonates and immunocompromised individuals plus those with underlying conditions such as chronic respiratory disease, cardiovascular disease and diabetes mellitus are particularly at risk of developing influenza-related complications. In this group of 'high-risk' patients, influenza infection can lead to a primary influenza viral pneumonia, exacerbation of underlying conditions or cause lung damage, rendering the lungs susceptible to a secondary bacterial pneumonia.[2,3]

Zanamivir (Relenza®[1]), a novel compound which selectively inhibits the influenza virus neuraminidase enzyme,[4] was first licensed in Australia in March 1999. Since then it has been approved in over 50 countries worldwide for the treatment of influenza and in 15 countries for influenza prophylaxis. In addition, 11 countries have approved its use in children, including the US where zanamivir is licensed for children aged 7 years and older.

A comprehensive programme of clinical studies has provided data from over 6000 individuals. In this volunteer population, zanamivir has been well tolerated, showing a similar incidence and nature of adverse events to that observed in placebo groups.[5] A continuing clinical pharmacology and clinical research programme, together with post-marketing experience, indicate that zanamivir is also well tolerated and effective in the treatment and prophylaxis of influenza in individuals at high-

1 Relenza® is a trademark of the GlaxoSmithKline group of companies. Use of tradenames is for product identification purposes only and does not imply endorsement.

risk of developing complications from this infection. It can, therefore, provide a valuable adjunct to the management of these patients.[6]

This review of the safety of zanamivir focuses on high-risk individuals and provides an update to the previous review of zanamivir published in *Drug Safety* in 1999.[5]

1. Zanamivir in Individuals at High Risk of Influenza-Related Complications

The effect of dry lactose powder, the carrier for inhaled zanamivir, on lung function has been determined in volunteers with asthma.[7] This study used plethysmography to measure specific airways conductance (sGAW) and forced expiratory volume in 1 second (FEV_1). 19 study participants (FEV_1 ≥50%, reversibility >12% in the last 6 months) received treatment [placebo (empty Rotadisk®) or inhalation grade lactose in six doses] with sGAW and FEV_1 measured at various time intervals before and after inhalation.

The primary endpoint, sGAW at 1 and 3 minutes after inhalation, showed no significant change from baseline for any dose of lactose and no trend with dose. FEV_1 showed no significant change from baseline at 20 and 50 minutes for any dose of lactose and no trend with dose. Individual patient graphs suggested no relationship between lactose inhalation and sGAW or FEV_1 at any time after administration.[7]

A study which evaluated the effect of repeat doses of inhaled zanamivir dry powder in 13 patients with asthma, indicated that dry powder zanamivir does not significantly affect pulmonary function [FEV_1, morning and evening peak expiratory flow rate (PEFR)] or bronchial hyperresponsiveness (methacholine challenge tests) in patients with mild/moderate asthma.[8]

1.1 Clinical Studies of Zanamivir Treatment in High-Risk Individuals

The 'high-risk' population was defined as those individuals who, as a result of their age or underlying medical condition, may experience a more prolonged and/or severe course of illness, or may suffer complications as a result of an influenza virus infection. Elderly individuals (≥65 years of age) were included in this definition as were those with chronic respiratory disease (including asthma requiring regular medication and chronic obstructive pulmonary disease), significant cardiovascular disease (excluding hypertension alone), diabetes mellitus and those who were immunocompromised. For the purposes of this review, data have been integrated for individuals ≥12 years of age who took at least one dose of study medication.

Table I. Summary of reasons for inclusion in the high-risk population.[9-16]a Study participants could have more than one high-risk condition; one study recruited individuals with chronic respiratory conditions only[14]

High-risk category	Number of subjects (%)			
	placebo	zanamivir 10mg inhaled twice daily	zanamivir 10mg inhaled 6.4mg intranasal[b]	total
Any high-risk condition	480 (100)	393 (100)	109 (100)	982 (100)
Aged 65 years or over	81 (17)	60 (15)	23 (21)	164 (17)
Chronic respiratory	394 (82)	348 (89)	70 (64)	812 (83)
Cardiovascular	40 (8)	21 (5)	19 (17)	80 (8)
Endocrine/metabolic	20 (4)	7 (2)	10 (9)	37 (4)
Other	1 (<1)	1 (<1)	0	2 (<1)

a High-risk population was defined as those subjects who, as a result of their age or underlying medical condition, may experience a more prolonged and/or severe course of illness, or may experience complications as a result of an influenza virus infection. Subjects with the following conditions were considered 'high risk': chronic respiratory disease (including asthma requiring regular medication, chronic obstructive pulmonary disease), significant cardiovascular disease (excluding subjects with only hypertension), elderly subjects ≥65 years of age (with or without underlying medical conditions), immunocompromised and those with diabetes mellitus.

b Combined twice daily and four times daily data from two studies.

Four principal treatment studies have been conducted involving high-risk individuals with additional data provided from four studies in which some participants were classed as 'high-risk'.[9-16] Of a total of 982 high-risk participants, 480 received placebo and 502 received zanamivir twice daily for 5 days. Table I summarises the reasons for inclusion in the high-risk population.

Adverse events were monitored throughout all clinical studies. The incidence of adverse events reported during treatment was similar in the placebo (202/480; 42%) and zanamivir groups (188/502; 37%). The most commonly reported adverse events, i.e. those occurring with an incidence of at least 1.5%, and present in at least five individuals in any treatment group, are presented in table II. These were typical of the signs and symptoms of influenza and/or the underlying medical condition of the high-risk individual and were reported at a similar frequency in the placebo and zanamivir groups. The incidence of serious adverse events was also similar in the placebo (10/480; 2%) and zanamivir groups (14/502; 3%).

Adverse events affecting the lower respiratory tract are of interest in this high-risk patient population as many have underlying respiratory disease. Lower respiratory adverse events were reported in 89/480 (19%) placebo recipients and in 63/502 (13%) zanamivir recipients. All of the lower respiratory adverse events reported by zanamivir recipients occurred at similar or lower frequencies than in the placebo group. Cough, sputum, and viral respiratory infections were excluded from this analysis in order to focus on the more significant adverse events affecting the lower respiratory tract. Cough, sputum and viral respiratory infections occurred at similar or lower frequencies in the zanamivir group compared with comparator groups in all populations studied (including prophylaxis studies).

A total of seven individuals (four placebo, three zanamivir) reported eight lower respiratory ad-

Table II. Summary of the most commonly reported adverse events during treatment in high-risk individuals with influenza-like illness[9-16]a

Adverse event	Number of subjects (%)			
	placebo (n = 480)	zanamivir 10mg inhaled twice daily (n = 393)	zanamivir 10mg inhaled 6.4mg intranasal[b] (n = 109)	zanamivir all dosage regimens (n = 502)
Any event	202 (42)	154 (39)	34 (31)	188 (37)
Asthma	38 (8)	29 (7)	2 (2)	31 (6)
Bronchitis	38 (8)	16 (4)	2 (2)	18 (4)
Sinusitis	13 (3)	16 (4)	0	16 (3)
Diarrhoea	17 (4)	11 (3)	3 (3)	14 (3)
Nausea	18 (4)	8 (2)	1 (<1)	9 (2)
Headaches	9 (2)	7 (2)	2 (2)	9 (2)
Nasal signs and symptoms	5 (1)	6 (2)	2 (2)	8 (2)
Musculoskeletal pain	3 (<1)	4 (1)	4 (4)	8 (2)
Pneumonia	3 (<1)	7 (2)	0	7 (1)
Dizziness	5 (1)	6 (2)	1 (<1)	7 (1)
Abnormal liver function tests	3 (<1)	6 (2)	0	6 (1)
Cough	13 (3)	5 (1)	0	5 (<1)
Lower respiratory infections	8 (2)	3 (<1)	2 (2)	5 (<1)
Vomiting	11 (2)	4 (1)	0	4 (<1)

a High-risk population was defined as those subjects who, as a result of their age or underlying medical condition, may experience a more prolonged and/or severe course of illness, or may experience complications as a result of an influenza virus infection. Subjects with the following conditions were considered 'high risk': chronic respiratory disease (including asthma requiring regular medication, chronic obstructive pulmonary disease), significant cardiovascular disease (excluding subjects with only hypertension), elderly subjects ≥65 years of age (with or without underlying medical conditions), immunocompromised and those with diabetes mellitus.

b Combined twice daily and four times daily data from two studies.

verse events that were classified as serious. Five (two placebo, three zanamivir) had pneumonia, one (placebo) had an exacerbation of asthma, one (placebo) had a possible worsening of respiratory symptoms and one (zanamivir) had possible respiratory failure. All of these serious adverse events resolved; indeed, one case of pneumonia (zanamivir) resolved with sequelae. With the exception of the exacerbation of asthma (placebo), none of these serious lower respiratory tract adverse events were considered by the investigators to be related to study medication.

The incidence of drug-related adverse events was similar between the placebo group and zanamivir groups with 10% of study participants in both the placebo and zanamivir groups reporting a drug-related adverse event during treatment. The most common adverse event was nausea, reported by 8/480 (2%) placebo recipients and 2/502 (<1%) zanamivir recipients. The frequency of post-treatment drug-related adverse events was low (<1%).

The incidence of withdrawal from study drug because of adverse events was similar in the placebo (10/480; 2%) and zanamivir groups (7/502; 1%).

No deaths were reported in any of the high-risk study participants in these studies.

1.1.1 High-Risk Patients with Underlying Respiratory Disease

Patients with underlying chronic respiratory disease are at particular risk of adverse effects on respiratory function following infection with the influenza virus. The tolerability of zanamivir has been assessed in this important sub-group. A total of 812 patients (394 placebo, 418 zanamivir) with chronic respiratory disease were recruited for these specific studies.[9-16]

The proportion of patients experiencing an adverse event during treatment was similar in the placebo (172/394; 44%) and zanamivir groups (160/418; 38%). The most commonly reported adverse events were typical of the signs and symptoms of influenza and/or the underlying medical condition of the patient. These adverse events occurred with similar frequency in the placebo and zanamivir groups and are detailed in table III. Post-treatment adverse events occurred in similar proportions of patients in the placebo and zanamivir groups (31 and 34%, respectively).

The proportion of patients reporting a serious adverse event was similar in placebo (8/394; 2%) and zanamivir recipients (12/418; 3%).

Adverse events affecting the lower respiratory tract were reported by 79/394 patients (20%) in the placebo group and 57/418 patients (14%) in the zanamivir groups. All types of lower respiratory adverse events were reported at similar or lower frequencies in zanamivir versus placebo recipients. A total of seven patients reported eight lower respiratory adverse events that were classified as serious (see section 1.1).

The incidence of adverse events that, in the opinion of the investigator, were drug-related was similar in the placebo (40/394 patients; 10%) and zanamivir (42/418 patients; 10%) groups. The most commonly reported events were nausea and diarrhoea. During the post-treatment period (up to 28 days, or 56 days in one study) adverse events that were regarded as drug-related occurred at a frequency of <1%; similar proportions of patients in the placebo and zanamivir groups reported drug-related adverse events post-treatment (2 and <1%, respectively).

The incidence of adverse events leading to discontinuation of study drug was similar in the placebo (9/394 patients; 2%) and zanamivir groups (6/418 patients; 1%).

One of the phase III treatment studies recruited exclusively patients with asthma or chronic obstructive pulmonary disease, and investigated the effect of inhaled zanamivir on pulmonary function.[14] A total of 525 individuals were recruited, 60% of whom had laboratory-confirmed influenza. Pulmonary function was monitored at the clinic visits (FEV_1 and PEFR) and twice daily, morning and evening, by the patient (PEFR). The data demonstrated that zanamivir did not adversely affect pulmonary function in this high-risk population. Indeed, those treated with zanamivir were found to have a small but significantly increased mean morn-

Table III. Summary of the most commonly reported adverse events during treatment in high-risk individuals with underlying respiratory disease with influenza-like illness[9-16]a

Adverse event	Number of subjects (%)			
	placebo (n = 394)	zanamivir 10mg inhaled twice daily (n = 348)	zanamivir 10mg inhaled 6.4mg intranasal[b] (n = 70)	zanamivir all dosage regimens (n = 418)
Any event	172 (44)	139 (40)	21 (30)	160 (38)
Asthma	38 (10)	29 (8)	2 (3)	31 (7)
Sinusitis	13 (3)	16 (5)	0	16 (4)
Bronchitis	31 (8)	13 (4)	1 (1)	14 (3)
Diarrhoea	13 (3)	10 (3)	1 (1)	11 (3)
Nausea	17 (4)	7 (2)	1 (1)	8 (2)
Headaches	8 (2)	7 (2)	0	7 (2)
Pneumonia	2 (<1)	7 (2)	0	7 (2)
Abnormal liver function tests	3 (<1)	6 (2)	0	6 (1)
Cough	10 (3)	5 (1)	0	5 (1)
Lower respiratory infections	6 (2)	3 (<1)	1 (1)	4 (<1)
Vomiting	7 (2)	3 (<1)	0	3 (<1)
Pharyngitis	6 (2)	3 (<1)	0	3 (<1)
Ear, nose and throat infections	6 (2)	2 (<1)	0	2 (<1)

a High-risk population was defined as those subjects who, as a result of their age or underlying medical condition, may experience a more prolonged and/or severe course of illness, or may experience complications as a result of an influenza virus infection. Subjects with the following conditions were considered 'high risk': chronic respiratory disease (including asthma requiring regular medication, chronic obstructive pulmonary disease), significant cardiovascular disease (excluding subjects with only hypertension), elderly subjects ≥65 years of age (with or without underlying medical conditions), immunocompromised and those with diabetes mellitus.

b Combined twice daily and four times daily data from two studies.

ing PEFR and mean evening PEFR during the treatment period (days 1 to 5) compared with placebo. There was no evidence of a difference in mean FEV_1 and mean PEFR as recorded in the clinic (days 6 and 28). A similar proportion of individuals in the placebo and zanamivir groups experienced a fall of ≥20% from baseline in FEV_1 (14 and 13%, respectively) and PEFR (4 and 6%, respectively) at any time post-treatment (up to day 28 from start of treatment). A small number of patients in both groups experienced a decrease in FEV_1 of ≥40% from baseline (8/242 placebo recipients; 3% and 6/248 zanamivir recipients; 2%). Two of six zanamivir recipients reported a respiratory adverse event compared with five of eight placebo recipients. Twelve of these 14 individuals had laboratory-confirmed influenza. However, not one had to discontinue the study due to deterioration in respiratory function or due to a respiratory adverse event. Patients in this study were categorised according to the nature and severity of the underlying disease; the majority of patients had mild to moderate asthma. There was no evidence that the safety profile of zanamivir differed from that of placebo in the smaller number of patients with chronic obstructive pulmonary disease (COPD), or with more severe underlying disease.

1.1.2 Studies in the Elderly

All study participants in the high-risk elderly population were ≥65 years of age (mean age 71.6 years; SD ± 5.6); some had underlying medical conditions. Of a total of 164 high-risk elderly individuals, 81 received placebo and 83 received zanamivir for the treatment of influenza infection. The proportion of subjects who reported an adverse event during treatment was similar in the placebo group (35/81; 43%) and the zanamivir group (31/83; 37%).[9-16]

The most commonly reported adverse events (i.e. occurring in ≥1.5% of subjects or in at least five individuals in any treatment group) were typical of the signs and symptoms of influenza and/or the underlying medical conditions of the elderly individuals. Bronchitis was the only adverse event that fulfilled the definition of most commonly reported.

During treatment, 9/81 individuals (11%) in the placebo group and 5/83 (6%) who received zanamivir reported bronchitis.

Post-treatment adverse events were reported in 15/81 (19%) placebo recipients and in 25/81 (30%) zanamivir recipients. No post-treatment adverse events were classified as most commonly reported.

The proportion of patients who reported a serious adverse event was similar in the placebo and (8/394; 2%) zanamivir (12/418; 3%) groups.

The frequency of lower respiratory adverse events was similar or lower in the zanamivir group 12/83 (14%) than in placebo recipients (17/81; 21%). A total of four study participants (three placebo, one zanamivir) reported lower respiratory adverse events that were classified as serious.

The incidence of drug-related adverse events during treatment was similar between the placebo and zanamivir groups (8/8; 10% with placebo and 6/83; 7% with zanamivir). No drug-related adverse events fulfilled the definition of most commonly reported (incidence ≥1.5%). Post-treatment, there were two individuals in the placebo group who reported a drug-related adverse event.

The proportion of individuals who had an adverse event that led to discontinuation of study drug was similar in the placebo (5/81; 6%) and zanamivir (2/83; 2%) groups.

1.2 Zanamivir Prophylaxis in the Community

1.2.1 High-Risk Patients with Underlying Respiratory Disease

A total of five prophylaxis studies have been conducted in a community setting.[17,18] The majority of participants were young and otherwise healthy. On review, 57/1175 (5%) receiving placebo and 60/1470 (4%) receiving zanamivir were considered to be at high risk because of underlying respiratory disease. Within this population, 45 (79%) placebo recipients and 39 (65%) zanamivir recipients reported adverse events during prophylaxis therapy. Similar rates of adverse events were reported in patients who were not high-risk, such high rates arose because in prophylaxis studies, individuals were asymptomatic at the start of therapy and were asked to prospectively record all symptoms that occurred during prophylactic therapy (up to 28 days); all symptoms were recorded as adverse events. Nasal signs and symptoms, headache, throat and tonsil discomfort and pain, and cough were the most commonly reported adverse events. In general, similar or fewer numbers of recipients reported an adverse event with zanamivir compared with placebo. One zanamivir recipient (2%) reported exacerbations of asthma during therapy compared with 6 placebo recipients (11%).

20 (35%) placebo and 15 (25%) zanamivir recipients reported adverse events during the post-prophylaxis period. Exacerbation of asthma was the most common adverse event: reported by eight (14%) placebo and two (3%) zanamivir recipients.

The total number of lower respiratory adverse events during prophylaxis was 8/57 (14%) and 3/60 (5%) in the placebo and zanamivir groups, respectively. These included bronchitis (one placebo recipient, two zanamivir recipients), asthma (six placebo, one zanamivir) and chest sounds (one placebo). None were considered serious but two events (asthma, wheezing) were considered by the investigator to be related to the study drug; both patients had received placebo.

Nine patients (eight placebo, one zanamivir) had adverse events that could have involved bronchoconstriction during prophylaxis. These included asthma, wheezing and shortness of breath. None of the events were serious, six patients required intervention and all events resolved. All individuals had pre-existing asthma and seven were taking concurrent pulmonary medication.

1.3 Prophylaxis in Nursing Homes

In the nursing home studies, the high-risk population consisted of residents who were elderly (≥65 years of age) and/or had certain underlying medical conditions (cardiovascular, respiratory, diabetes mellitus).

Three prophylaxis studies were conducted in nursing homes. [19-21] Two of these studies compared 14 days' treatment with zanamivir (inhaled or inhaled plus intranasal) with standard care

(rimantadine for influenza A, placebo, or no treatment for influenza B) in controlling an outbreak of influenza, whereas the other study was a placebo-controlled study.[19,21] In the 2 studies comparing zanamivir with active treatment (or placebo or no treatment), the population was predominantly elderly with 90% of study participants ≥65 years of age, of whom at least 55% were ≥75 years of age. In the placebo-controlled study, 66% of participants were ≥65 years of age, of whom at least 35% were ≥75 years of age.[20]

As more than one influenza outbreak may have occurred at each nursing home, some participants were entered into the study on more than one occasion. Of the 1114 randomisations, there were 282 recipients of placebo/no treatment, 254 received rimantadine and 578 received zanamivir.

In the active-controlled studies, all placebo/no treatment recipients were considered high-risk, as were 244/254 who received rimantadine and 318/336 who received zanamivir. In the placebo-controlled study, the high-risk population comprised 215/252 placebo and 202/242 zanamivir recipients.

The proportion of participants reporting at least one adverse event during prophylaxis was similar between treatment groups in both the active-controlled studies (53% placebo/no treatment, 54% rimantadine, 52% zanamivir) and placebo-controlled study (37% placebo, 32% zanamivir).

In the active-controlled studies there were no lower respiratory adverse events (not including cough, sputum and viral infections) in the placebo group, 17/254 (7%) in the rimantadine group and 13/336 (4%) in the zanamivir group. In the placebo-controlled study there were 18/252 (7%) lower respiratory adverse events in the placebo group and 12/242 (5%) in the zanamivir group. Two zanamivir recipients experienced serious lower respiratory tract adverse events. One had left lower pneumonia 7 days after the start of treatment and the other, also in the high-risk respiratory population, experienced chronic bronchitis 11 days after the start of treatment. Seven individuals experienced lower respiratory adverse events that were considered by the investigator to be related to study drug. One zanamivir recipient experienced ausculated wheeze 2 days after the start of treatment; the remaining six were in the high-risk respiratory population (section 1.3.1).

Five (17%) placebo/no treatment recipients, 78 (31%) rimantadine recipients and 102 (30%) zanamivir recipients reported drug-related adverse events during prophylaxis in the active-controlled studies. For the placebo-controlled study, 14 (6%) placebo and 16 (7%) zanamivir recipients reported at least one drug-related adverse event during prophylaxis. The most commonly reported drug-related adverse events were cough, nasal signs and symptoms, gastrointestinal signs and symptoms, and headaches.

A similar proportion of subjects in each treatment group reported adverse events that led to study drug discontinuation. For the active-controlled studies, these were 0% in the placebo group, 6% in the rimantadine group and 4% in the zanamivir group. In the placebo-controlled study, <1% of subjects in the placebo group and 2% of subjects in the zanamivir group terminated study drug due to an adverse event.

Changes in laboratory parameters (shifts from baseline and changes over time) observed in subjects who received zanamivir did not differ from those seen in subjects who had received placebo or rimantadine. The changes that were observed occurred at a low frequency and were most likely to be related to influenza infection or other concurrent medical condition. There were no clinically significant laboratory data changes due to zanamivir administration.[19]

In the active-controlled studies, 29/620 subjects (5%) failed to complete study drug due to an adverse event. In the placebo-controlled study, this figure was 8/494 (2%).

None of the five deaths that occurred in the nursing home prophylaxis studies was considered to be related to study drug. In the active-controlled studies, two subjects died. One aged 82 years, who received rimantadine, developed postoperative pneumonia 5 days after discontinuing study drug and died 2 weeks later. The second aged 83 years, who received zanamivir, died of dehydration secondary to pneumonia approximately 30 days after starting the

study. In the placebo-controlled study, two subjects (aged 57 and 63 years) who received placebo died, one of a myocardial infarction 3 days after completing the study and the other 10 weeks after the study following a diagnosis of pleural effusion, acute cholecystitis and probable lung cancer. One subject who received zanamivir (aged 67 years) died 6 months after completing the study following an earlier diagnosis of liver cirrhosis and congestive heart failure.

1.3.1 High-Risk Patients with Respiratory Disease

In the active-controlled studies, 18/30 (60%) placebo/no treatment, 110/254 (43%) rimantadine and 126/336 (38%) zanamivir recipients were identified as having chronic respiratory disease (table IV). Of these individuals, 10 (56%) in the placebo/no treatment group, 65 (59%) in the rimantadine group and 71 (56%) in the zanamivir group reported adverse events during prophylaxis.

In the placebo-controlled study, 80/252 (32%) placebo and 83/242 (34%) zanamivir recipients had chronic respiratory disease (table IV). Of these, 32 (40%) in the placebo group and 30 (36%) in the zanamivir group reported adverse events during prophylaxis.

The incidence of serious adverse events was low in all of the nursing home studies of patients with chronic respiratory disease.[19-21] In the active-controlled studies, 2/126 (2%) zanamivir recipients reported at least one serious adverse event. In the placebo-controlled study, 2/80 (3%) in the placebo group and 2/83 (2%) in the zanamivir group experienced at least one serious adverse event.

Table IV. Summary of the most common adverse events reported during prophylaxis in high-risk individuals with underlying respiratory disease in nursing home studies[a]

Adverse event	Number of subjects (%) in active-controlled studies[19,21][b]			Number of subjects (%) in placebo-controlled study[20][b]	
	placebo/no treatment (n = 18)	rimantadine (n = 110)	zanamivir (n = 126)	placebo (n = 80)	zanamivir (n = 83)
Any event	10 (56)	65 (59)	71 (56)	32 (40)	30 (36)
Cough	1 (6)	19 (17)	20 (16)	10 (13)	8 (10)
Nasal signs/symptoms	1 (6)	19 (17)	20 (16)	10 (13)	8 (10)
Headaches	1 (6)	8 (7)	13 (10)	8 (10)	6 (7)
Musculoskeletal pain	4 (22)	1 (<1)	11 (9)	1 (1)	2 (2)
Constipation	0	5 (5)	9 (7)	1 (1)	2 (2)
Nasal inflammation	0	2 (2)	8 (6)	2 (3)	0
Malaise and fatigue	2 (11)	10 (9)	7 (6)	5 (6)	6 (7)
GI signs/symptoms	1 (6)	5 (5)	6 (5)	1 (1)	0
Throat and tonsil discomfort and pain	2 (11)	8 (7)	5 (4)	2 (3)	1 (1)
Temperature regulation disturbances[c]	0	7 (6)	4 (3)	9 (11)	2 (2)
Breathing disorders	0	7 (6)	4 (3)	4 (5)	2 (2)
Diarrhoea	0	5 (5)	4 (3)	0	2 (2)
Vocal cord disorder	0	7 (6)	3 (2)	1 (1)	2 (2)
COPD	0	2 (2)	0	4 (5)	8 (10)

a High-risk population was defined as those subjects who, as a result of their age or underlying medical condition, may experience a more prolonged and/or severe course of illness, or may experience complications as a result of an influenza virus infection. Subjects with the following conditions were considered 'high risk': chronic respiratory disease (including asthma requiring regular medication, chronic obstructive pulmonary disease), significant cardiovascular disease (excluding subjects with only hypertension), elderly subjects ≥65 years of age (with or without underlying medical conditions), immunocompromised and those with diabetes mellitus.

b All randomisations.

c Adverse events were reported as fever, chills or increased temperature.

COPD = chronic obstructive pulmonary disease; **GI** = gastrointestinal.

A review of the lower respiratory adverse events (with the exception of cough, sputum and viral infections) during prophylaxis revealed that, for the active-controlled studies, there were 0/18 (0%) lower respiratory adverse events in the placebo group, 14/110 (13%) in the rimantadine group and 6/126 (5%) in the zanamivir group. Table V summarises the lower respiratory adverse events reported among the high-risk respiratory nursing home population. One event was classified as serious (bronchitis), but was considered by the investigator to be unrelated to study drug. Seven participants (five rimantadine, two zanamivir) experienced lower respiratory adverse events that were considered by the investigator to be related to study drug; study drug was not terminated in any case.

27 participants (six receiving placebo, 12 receiving rimantadine and nine receiving zanamivir) reported adverse events that might be construed as 'bronchospasm-like'. All individuals experienced asthma, wheezing, exacerbation of COPD or shortness of breath. None of the events was considered serious, six (four rimantadine and two zanamivir recipients) were considered by the investigator to be related to the study drug, treatment was discontinued for three individuals (all receiving rimantadine), 15 required intervention (three placebo, six rimantadine and six zanamivir recipients) and all but one event resolved. Twenty of the 27 participants in this subgroup also had baseline cardiac disease.

Of the patients identified as high risk of influenza-related complications because of respiratory disease in the active-controlled studies, 2/18 (11%) in the placebo/no treatment group, 39/110 (35%) in the rimantadine group and 46/126 (37%) in the zanamivir group reported at least one drug-related adverse event during prophylaxis. In the placebo-controlled study, at least one drug-related adverse event was reported in 3/80 (4%) placebo recipients and in 4/83 (5%) zanamivir recipients.

1.3.2 Elderly Individuals

The incidence, nature and severity of adverse events among individuals aged ≥65 years were similar to that of the general population. In the active-controlled studies, 14/26 (54%) participants in the placebo/no treatment group, 122/231 (53%) in the rimantadine group and 160/292 (55%) in the zanamivir group reported at least one adverse event during prophylaxis.[19-21] In the placebo-controlled study, 63/173 (36%) placebo recipients and 52/153 (34%) patients in the zanamivir group experienced at least one adverse event.[20]

Table V. Lower respiratory adverse events in high-risk individuals with underlying respiratory disease in nursing home studies[19-21]a

Adverse event	Number of subjects (%) in active-controlled studies		Number of subjects (%) in placebo-controlled study	
	rimantadine (n = 110)	zanamivir (n = 126)	placebo (n = 80)	zanamivir (n = 83)
Breathing disorders	7 (6)	4 (3)	4 (5)	2 (2)
Bronchitis	1 (<1)	1 (<1)	3 (4)	0
Chest sounds	3 (3)	1 (<1)	1 (<1)	0
Lower respiratory signs and symptoms	0	1 (<1)	0	0
COPD	2 (2)	0	4 (5)	8 (10)
Asthma	0	0	2 (3)	0
Lung disorders	1(<1)	0	0	0
Pneumonia	0	0	1 (<1)	0

a High-risk population was defined as those subjects who, as a result of their age or underlying medical condition, may experience a more prolonged and/or severe course of illness, or may experience complications as a result of an influenza virus infection. Subjects with the following conditions were considered 'high risk': chronic respiratory disease (including asthma requiring regular medication, chronic obstructive pulmonary disease), significant cardiovascular disease (excluding subjects with only hypertension), elderly subjects ≥65 years of age (with or without underlying medical conditions), immunocompromised and those with diabetes mellitus.

COPD = chronic obstructive pulmonary disease.

In the active-controlled studies, at least one serious adverse event was experienced by 3/231 (1%) rimantadine and 4/292 (1%) zanamivir recipients during prophylaxis. In the placebo-controlled study, 3/173 (2%) placebo, and 2/15 (1%) zanamivir recipients experienced at least one serious adverse event.

At least one drug-related adverse event was reported by 4 of 26 (15%) placebo/no treatment recipients, 69 of 231 (30%) in the rimantadine group and 94 of 292 (32%) in the zanamivir groups for the active-controlled studies. In the placebo-controlled study, 11/173 (6%) placebo and 10/153 (7%) zanamivir recipients experienced at least one drug-related adverse event.

2. Compassionate Use Programme

Up until 31 January 2001, zanamivir has been provided for the treatment or prophylaxis of influenza for approximately 275 adults and children. There have been 15 deaths reported in severely ill and immunocompromised patients for whom zanamivir was requested. For 12 of the deaths, the reporting investigator considered that the fatal events were unrelated to zanamivir. For the remaining three deaths reported following compassionate use, no assessment of causality was provided. A total of 174 residents in two nursing homes received dry powder inhaled zanamivir and the majority of the remaining residents received nebulised solution.

2.1 Compassionate Use in Nursing Homes

Zanamivir was provided to two nursing homes for the treatment and prophylaxis of residents during an outbreak of influenza. The residents of one nursing home were elderly (mean age 70.6 ± 16.4 SD) with multiple co-morbidities. A total of 44 residents received zanamivir as prophylaxis therapy. No serious adverse events were reported, one individual was transferred to acute care for an adverse event unrelated to zanamivir treatment. Another withdrew from the study complaining of sore throat. The only possible adverse event was an influenza-like illness which developed after 9 days of therapy in one study participant.[22] In the second nursing home, 128 elderly residents (median age 85 years) received zanamivir for treatment or prophylaxis. No adverse events were reported which were considered by the investigator to be related to zanamivir prophylaxis therapy.[23]

3. Post-Marketing Surveillance

Zanamivir was first approved for marketing in Australia on 25 March 1999 and launched there on 1 May 1999. It has since been approved for the treatment of influenza A and B in over 50 countries world-wide, including the US (26 July 1999). In addition, 15 countries have approved zanamivir for the prophylaxis of influenza A and B, and nine countries, including the US, have approved its use in children.

Although many of the adverse event reports received reflect the underlying condition being treated, there have been very rare reports of respiratory adverse events, including bronchospasm and/or decline in respiratory function. In some of these cases there was a history of underlying respiratory disease. In the majority of cases the causality of the events was difficult to determine, either because of confounding factors (such as the underlying influenza infection or the presence of other concurrent conditions and/or therapies), or because of insufficient details.[24]

Influenza itself may cause hyper-reactivity of the airways and may exacerbate underlying asthma or COPD.[25,26] Secondary bacterial infections may also contribute. However, despite the difficulties in establishing a causal association with zanamivir, bronchospasm and dyspnoea have been added to the prescribing information for zanamivir as very rare (<1/10000) events. In addition, it is recommended that patients with underlying respiratory disease should have a fast-acting bronchodilator available when taking zanamivir, and any patient who experiences a bronchospasm or decline in respiratory function should stop using the drug and seek medical advice. The US labelling for zanamivir also states that it is not generally recommended for treatment of patients with underlying airways disease

such as asthma or chronic obstructive pulmonary disease.

Other adverse events added as very rare (<1/-10000) to the prescribing information following post-marketing reports are dyspnoea, rash, urticaria, oropharyngeal oedema, facial oedema and allergic-type reaction.

4. Drug Interactions

High-risk patients are likely to be receiving a variety of medications for management of chronic underlying conditions; however, zanamivir is not metabolised and is predominantly excreted renally in the urine as unchanged drug. It, therefore, has a very low potential for drug interactions. Previously reported data from both *in vitro* and *in vivo* studies, has supported the low potential for zanamivir to interact with coadministered therapies in the clinical setting.[5,27] In addition, a study of drug interactions with the influenza vaccine indicated that zanamivir does not impair the immune response to inactivated influenza vaccine.[28]

Thus, there is no theoretical basis for anticipating drug interactions between zanamivir and other coadministered compounds. It is highly unlikely that zanamivir would influence the disposition of other concurrently administered compounds given its low protein binding and limited systemic absorption. Additionally, human pharmacokinetic studies show that zanamivir is eliminated unchanged via the renal route, where drug interactions are unlikely.

In the clinical studies to date (including those in high-risk individuals), together with the post-marketing surveillance, there has been no clinical suggestion of drug interactions involving zanamivir.

5. Discussion

The most recent data from clinical studies involving 982 high-risk individuals clearly demonstrates that zanamivir is well tolerated when administered for both treatment and prophylaxis of influenza type A and B. A more detailed review of specific high-risk groups including patients with chronic respiratory conditions and the elderly (≤65 years of age) indicated that zanamivir has an acceptable tolerability profile. The nature and incidence of adverse events was similar between zanamivir and placebo recipients for both prophylaxis and treatment indications, and were similar to those observed in otherwise healthy individuals.

The incidence of serious adverse events and study drug discontinuations due to adverse events was generally low across all the high-risk populations studied.

As zanamivir is delivered via inhalation to the respiratory tract where the influenza virus replicates, a detailed review of lower respiratory adverse events was undertaken. It was found that lower respiratory adverse events were reported less frequently during treatment with zanamivir than placebo in all high-risk populations. Adverse events reported for the high-risk respiratory population tended to reflect their underlying respiratory condition; however fewer high-risk respiratory individuals receiving zanamivir reported asthma exacerbations during prophylaxis than those receiving placebo.

Similarly, in the elderly and paediatric populations, zanamivir was well tolerated with a safety profile comparable to that seen in the general population.

In addition, no safety concerns with inhaled zanamivir were identified from laboratory data shifts or in laboratory changes over time.

6. Conclusion

This review of tolerability data from treatment and prophylaxis studies of zanamivir demonstrates that the drug is very well tolerated in a wide range of high-risk individuals who are susceptible to severe complications of influenza infection. The data suggests that serious adverse events are unlikely following zanamivir administration to this patient group, and thus treatment or prophylaxis with this agent in an attempt to reduce morbidity and mortality may be appropriate in many cases.

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