

GLAXOSMITHKLINE

FDA Pediatric Advisory Committee Meeting

**Relenza® (zanamivir) Inhalation Powder
NDA 21-036**

Review of Neuropsychiatric and Behavioral Events

November 27, 2007

Sponsor Backgrounder (Briefing Information)

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SUMMARY

The following Backgrounder provides a summary of the neuropsychiatric and behavioral events reported from multiple sources for review by the Pediatrics Advisory Committee. The overall purpose of this Backgrounder is to provide a review of the possible association of neuropsychiatric adverse events with Relenza (zanamivir). This review was precipitated by reports of increased adverse events in Japan, associated with Tamiflu (oseltamivir) during the past influenza seasons, but also by an increase in spontaneous reports in Japan, of neuropsychiatric adverse events associated with Relenza in the 2007 influenza season.

Relenza[®] (zanamivir) Inhalation Powder is approved in the United States for the treatment and prophylaxis of influenza A and B viral infections in adult and pediatric patients. Relenza is a dry powder that is delivered into the lungs by oral inhalation using an inhaler delivery device (Diskhaler[®]). Relenza is indicated for the treatment of influenza A and B infections in adults and pediatric patients 7 years of age and older. Relenza is indicated for the prophylaxis of influenza A and B infections in adults and pediatric patients 5 years of age and older. The dose is 10mg twice daily for treatment and once daily for prophylaxis in both adults and pediatric patients.

The US Prescribing Information for Relenza provides warnings and precautions specifically for bronchospasm, allergic reactions and for patients who are at high-risk due to underlying medical conditions. The most common adverse events (more common than placebo) with Relenza reported from the treatment and prophylaxis clinical studies are sinusitis, dizziness, fever, chills, arthralgia and articular rheumatism.

Zanamivir is an antiviral drug that is designed to selectively inhibit viral neuraminidase active sites of influenza virus. It affects the release of viral particles and obtunds fulminate disease. After oral inhalation, only 4% to 17% of the inhaled dose is systemically absorbed. Zanamivir has limited plasma protein binding and is renally excreted as unchanged drug, with no metabolites detected in humans.

Influenza is an acute febrile respiratory illness which occurs globally in annual epidemics of variable severity. The severity of annual outbreaks is determined by the antigenic composition of the virus and the extent of pre-existing immunity in the population. The severity of illness associated with influenza ranges from asymptomatic, mild rhinitis or pharyngitis, to primary viral pneumonia, which although uncommon, may be fatal. Typically, in adults with uncomplicated, acute infection, after an incubation period of several days, there is a rapid onset of fever and symptoms that include chills, myalgia, headache, malaise, anorexia, sore throat and cough. Subjects are generally confined to bed while fever is present, and are incapable of routine activity at work, school or in the home. Symptoms of influenza also begin abruptly in children. A rapid onset of fever (usually above 101°), chills, myalgia, malaise, sore throat, cough, vomiting and stomach pain are typical influenza symptoms in children. Children under 2 years old are at high risk of complications, serious illness and hospitalization from influenza.

Relenza has been studied in clinical trials involving over 14,810 subjects, over 1500 of whom were children aged 5 to 12 years. In these studies, over 8000 subjects have

received zanamivir. The original New Drug Application (NDA) for the treatment of influenza A and B with Relenza was approved on July 26, 1999 and a supplemental NDA for treatment of pediatric patients was approved on April 26, 2000. A supplemental NDA for the prophylaxis of influenza A and B with Relenza in adult and pediatric patients was approved on March 29, 2006.

The purpose of this Backgrounder is to provide briefing information on the neuropsychiatric and behavioral events for Relenza (zanamivir) Inhalation Powder, for review by Advisory Committee members prior to the Pediatric Advisory Committee meeting on November 27, 2007. The review and analysis of all the information available in this safety summary of neuropsychiatric events does not implicate or indicate a significant causal role of zanamivir. Therefore, no revisions are warranted for the US Prescribing Information and the FDA-approved Patient Labeling for Relenza.

1. INTRODUCTION

Relenza (zanamivir) is an antiviral drug, inhibiting influenza viral neuraminidase and affecting viral particle release. The following document provides a summary of the neuropsychiatric and behavioral events reported from multiple sources for review by the FDA Pediatrics Advisory Committee.

1.1. Product and Indications

Zanamivir is a potent and highly selective inhibitor of viral neuraminidase. Neuraminidase inhibition occurred in vitro at very low zanamivir concentrations (50% inhibition at 0.64nM-7.9nM) against influenza A and B strains. 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 sub-types 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 occurs in the superficial epithelium of the respiratory tract. The efficacy of topical administration of zanamivir to this site has been confirmed in clinical studies.

Zanamivir is supplied in a circular foil pack (ROTADISK[®]) with four blisters each containing 5mg zanamivir and 20mg lactose. The product is administered by oral inhalation using a DISKHALER[®] device.

Zanamivir is currently approved in 96 markets, including the United States and countries of the European Union. In the United States, zanamivir is indicated for:

- **Treatment of influenza** in patients 7 years of age and older who have been symptomatic for no more than 2 days (dose is 10mg twice daily for 5 days).
- **Prophylaxis of influenza** in patients 5 years of age and older (dose is 10mg once daily for 10 – 28 days).

1.2. Summary of Adverse Events Listed in US Prescribing Information (USPI)

1.2.1. Clinical trials

Overall, two events belonging to the “nervous system disorder” system organ class, (headache and dizziness) and none from the “psychiatric disorder” and “injuries and procedural complications” system organ classes were reported in $\geq 1.5\%$ of subjects in clinical trials with zanamivir, as described in the USPI (Appendix A).

Treatment of influenza: clinical studies in pediatric patients:

A summary of the adverse events that occurred with an incidence of $\geq 1.5\%$ in children 5 to 12 years old receiving Relenza 10 mg inhaled twice daily, and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in Relenza) is displayed in Table 1.

Table 1 Summary of Adverse Events $\geq 1.5\%$ Incidence During Treatment in Pediatric Patients*

Adverse Event	RELENZA 10 mg b.i.d. Inhaled (n = 291)	Placebo (Lactose Vehicle) (n = 318)
Respiratory		
Ear, nose, and throat infections	5%	5%
Ear, nose, and throat hemorrhage	<1%	2%
Asthma	<1%	2%
Cough	<1%	2%
Digestive		
Vomiting	2%	3%
Diarrhea	2%	2%
Nausea	<1%	2%

* Includes a subset of patients receiving Relenza for treatment of influenza in a prophylaxis study.

Prophylaxis of influenza: Family/Household prophylaxis studies including pediatric patients

A summary of the Adverse Events that occurred with an incidence of $\geq 1.5\%$ in the 2 prophylaxis studies in patients ≥ 5 years of age receiving Relenza 10 mg inhaled once daily for 10 days is displayed in Table 2.

Table 2 Summary of Adverse Events $\geq 1.5\%$ Incidence During 10-Day Prophylaxis Studies in Adults, Adolescents, and Children*

Adverse Event	Contact Cases	
	RELENZA (n = 1,068)	Placebo (n = 1,059)
Lower respiratory		
Viral respiratory infections	13%	19%
Cough	7%	9%
Neurologic		
Headaches	13%	14%
Ear, nose, and throat		
Nasal signs and symptoms	12%	12%
Throat and tonsil discomfort and pain	8%	9%
Nasal inflammation	1%	2%
Musculoskeletal		
Muscle pain	3%	3%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	2%	2%
Gastrointestinal		
Nausea and vomiting	1%	2%
Non-site specific		
Malaise and fatigue	5%	5%
Temperature regulation disturbances (fever and/or chills)	5%	4%

- * 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.
- * 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.

1.2.2. Postmarketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during post-marketing use of zanamivir (Relenza). Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to zanamivir (Relenza).

Allergic Reactions: Allergic or allergic-like reaction, including oropharyngeal edema.

Cardiac: Arrhythmias, syncope.

Neurologic: Seizures.

Respiratory: Bronchospasm, dyspnea.

Skin: Facial edema; rash, including serious cutaneous reactions; urticaria.

1.3. Exposure to Drug

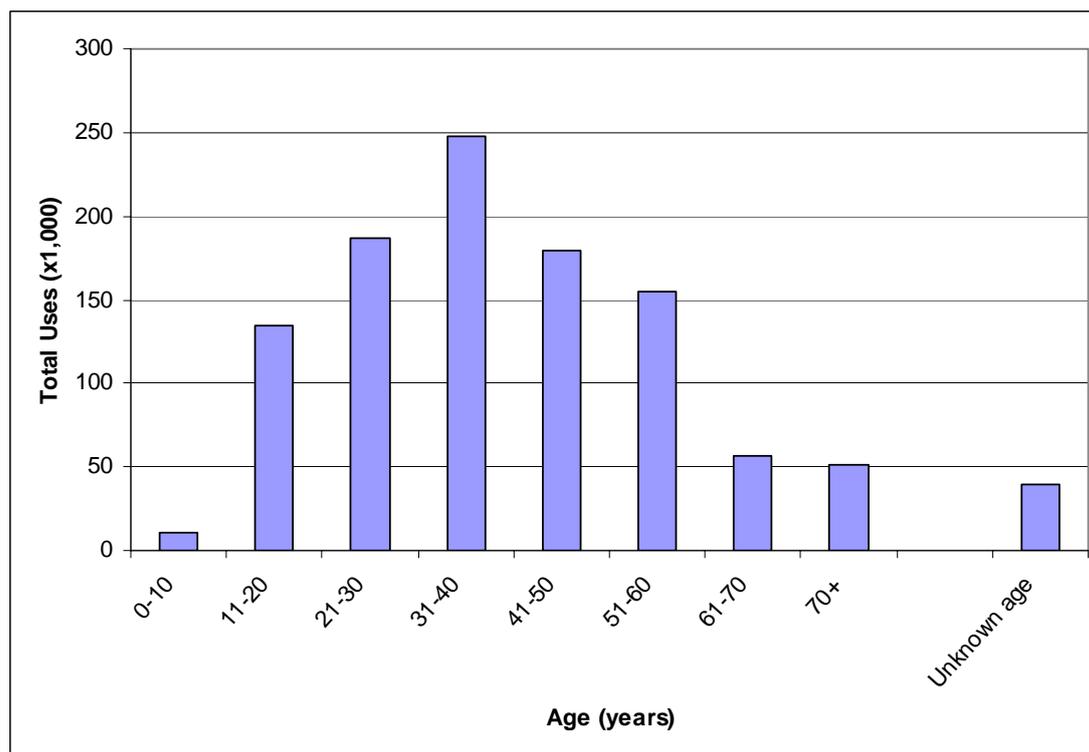
Global Exposure Estimate: Cumulative global post marketing exposure to zanamivir powder for oral inhalation has been estimated at approximately 3.99 million treatment courses since first launch in March 1999 up to the 31 March 2007 (Data source: IMS Health). This was calculated using the last available markets sales volumes (number of units sold). Note that this estimate does not allow for differentiation by target population or indication and potentially includes product purchased for stockpiling by governments in anticipation of an influenza pandemic.

US and Japan Exposure Estimate: For the purpose of this review, an estimate of patient exposure, excluding sales for government stockpiling was calculated for the last two influenza seasons for the US and Japan.

In Japan, the estimate is based on local sales and unused packs returned from pharmacies at the end of the influenza seasons and does not allow break down by age or indication. It is estimated that 100,000 subjects were exposed to zanamivir during the 2005-6 influenza season (from November to April) while 500,000 subjects were exposed during the 2006-7 season.

GSK explored the use of observational databases in Japan and in the USA to gather exposure data. Due to the relatively small global numbers of prescriptions for zanamivir and to the very limited coverage of zanamivir prescriptions in the databases assessed, only partial and fragmented information would be retrieved from such an activity. These limited data would not provide a comprehensive picture of exposure by age group for the countries considered. However, cumulative figures of Relenza use in different age groups have been obtained from Verispan for the USA. These data are based on the Verispan Physician Drug & Diagnosis Audit (PDDA) and covers the time period September 1999 to August 2007 as shown in Figure 1. The PDDA data captures the prescription information from approximately 1% of physicians (from each of 29 specialties), for one typical day of a month, collected each month. The data thus collected is used to estimate the total number of prescriptions for the drug for all of the US.

Figure 1 Cumulative US Relenza Use Estimates by Age from September 1999 to August 2007 (from Verispan PDDA)



PDDA data are a projection of national prescription figures in the US based on a monthly survey that monitors disease states and the associated physician directed drug and non drug therapy. Approximately 3,400 office based physicians representing 29 specialties across the United States report all patient activity during one typical workday per month. The results are projected to reflect the national estimated use of the drug. These data show that total US Relenza use up to August 2007 is estimated to be 1,061,000 treatment courses with adults aged 21-50 years accounting for more zanamivir usage than other age groups. However, there was also a substantial proportion of uses reported (in excess of 140,000 total uses, or 14%) in children and adolescents.

Specific information about retail prescriptions for Relenza in the 2006-2007 influenza season (12 months ending April 2007) was also obtained from Verispan Vector One National (VONA) but no breakdown by age groups was available at this time. VONA provides a comprehensive overview of the national performance of all prescription drugs dispensed by retail pharmacies. Each month, Verispan collects nearly 50% of the retail prescriptions dispensed and projects the activity to provide national estimates. Interrogation of the Verispan VONA database that electronically records prescriptions delivered to patients at the pharmacy point of contact estimates that less than 3,000 subjects were prescribed zanamivir in the USA in the most recent influenza season.

1.4. Spontaneous Reports from 2006-2007 Influenza Season

This review summarizes a cluster of 145 spontaneous reports of neuropsychiatric events of interest, which were all issued from Japan. Ninety-nine percent of them were observed in children/adolescents from 6 to 14 years of age with influenza or influenza-like

illnesses who were exposed to inhaled zanamivir. None were fatal and all were received at GlaxoSmithKline in the spring of 2007. Eighty-six percent (124 out of 145) of these events were reported in March and April 2007. This increased reporting was coincident with the public release of a high level alert by the Japanese Ministry of Health, Labor and Welfare (MHLW) about abnormal / self harm behaviors observed in Japanese adolescents with influenza who were exposed to oseltamivir.

GSK considered this cluster of reports as a new safety signal in need of further exploration. It was apparent that the characteristics of the population and the pattern of adverse events reported in the spring of 2007 differed significantly from the pattern observed in previous years, therefore the data were presented separately for each of these two time periods (Sections 9 and 10).

Of note, various aspects of analysis of a potential causal association between zanamivir and the neuropsychiatric events reported were assessed by the Company. In addition to the spontaneous adverse events reports summary information is provided for:

- Preclinical Toxicology (Section 3)
- Pharmacokinetics (Section 4)
- Data from GSK available GSK Phase II and III centrally sponsored clinical trials and clinical trials conducted in Japanese population (Section 5)
- Ongoing and completed Japanese Drug Utilization Investigations (i.e. Postmarketing Surveillance Studies) (see Section 6)
- Information from epidemiology (Section 8) and review of the published literature (Section 7).

At the same time in the spring of 2007, the FDA was alerted by the receipt of 41 spontaneous adverse event reports with at least one neuropsychiatric symptom in subjects exposed to zanamivir in the AERS database. Further clarification with the FDA revealed that all 41 cases were sent to the FDA by GSK, were issued from the Company's Global Safety Database, were all reported from Japan and therefore were all included in the present safety summary.

The results of our evaluation of this new safety signal follows.

2. SCOPE OF THE EVALUATION

For this summary of neuropsychiatric events and zanamivir, the following sources were reviewed and evaluated:

- Pre-clinical studies.
- Pharmacokinetics studies of zanamivir.
- Integrated clinical trials safety database.
- Reports of the epidemiology of influenza and neuropsychiatric events.

- Published literature for zanamivir.
- Assessment of reports from the GSK Safety Database (all spontaneous reports, post-marketing surveillance reports, and unblinded serious adverse events from clinical trials).

3. INFORMATION FROM PRECLINICAL TOXICOLOGY

A review of toxicology studies performed in rats, mice, rabbits and dogs, including 14-day continuous intravenous infusion studies at the maximum achievable doses in rats and dogs, showed no evidence of any consistent treatment related clinical signs that indicate an effect of zanamivir on behavior. The systemic exposure in the rat at the no observed adverse effect level (NOAEL) of 432 mg/kg/day (approximately 660 µg.hr.ml, mean sexes combined) from the 14 day continuous iv infusion study was 1346 fold higher than the systemic clinical exposure following an inhaled does of 10 mg BID in humans(AUC 0.49 µg.hr/ml).

Some minor behavioral effects were seen in F1 males in the fertility study; however, lack of reproducibility indicated that these observations were equivocal.

4. INFORMATION FROM PHARMACOKINETICS

After inhaled administration, zanamivir is largely deposited in the oropharynx (77.6%) and the lungs (13.2%). Due to poor bioavailability, systemic exposure to zanamivir is low (4-17%). No information on the actual CNS concentrations achieved after inhalational or intravenous administration in humans is available. Whole body autoradiography studies following administration of radiolabeled zanamivir in rats (intratracheal and intravenous) and dog (intravenous) demonstrate the lowest or no exposure in the brain of the animals, which is consistent with the highly polar nature of the drug. Given the low systemic exposure of oral inhaled zanamivir, it is expected that CNS exposure of zanamivir would be low to none. Because of this, it is unlikely zanamivir, administered at the labeled inhalational dose, could result in a direct toxic effect within the CNS.

5. INFORMATION FROM CLINICAL TRIALS

5.1. Clinical Studies in Pediatric Subjects

One thousand five hundred and twenty two children aged five to twelve years were enrolled in four phase III studies.

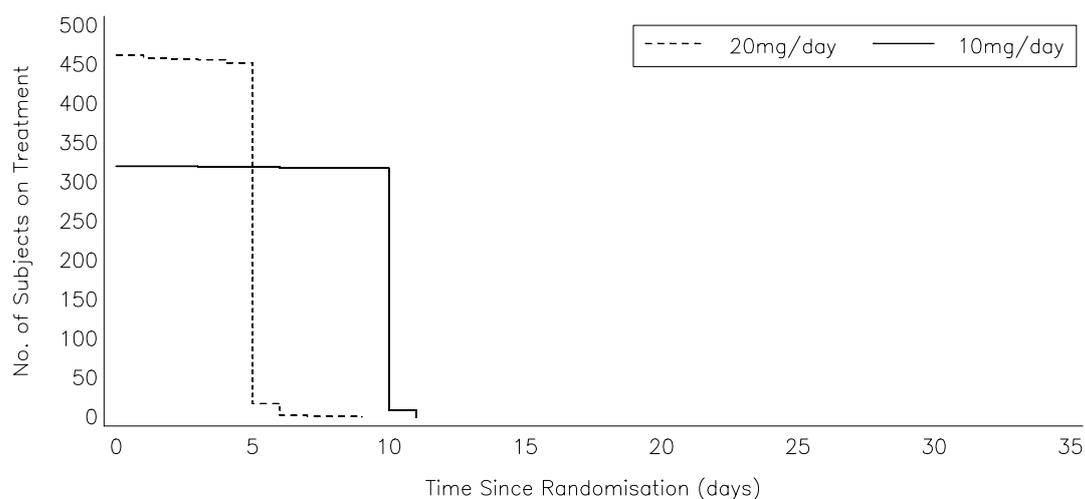
Details from these studies are displayed in Table 3 and the cumulative exposure to zanamivir according to the total inhaled daily dose is shown in Figure 2.

Table 3 Phase III Clinical Studies with Pediatric Subjects

Protocol	Indication / Regimen	Zanamivir (N)	Placebo (N)
NAI30009	Treatment: 10mg BID for 5 days	224	247
NAI30028	Treatment: 10mg BID for 5 days*	176	90
NAI30010	Treatment of index cases in prophylaxis study: 10mg BID for 5 days	67	71
NAI30010	Prophylaxis: 10mg BID QD for 10 days	132	145
NAI30031	Prophylaxis: 10mg BID QD for 10 days	188	182
Total		787	735

* GSK Local Company Study (Germany), data available in the Clinical Trial Registry

Figure 2 Cumulative exposure to zanamivir by total inhaled daily dose among pediatric subjects participating in clinical studies



	Subjects exposed to zanamivir							
20mg/day	462	17	0	0	0	0	0	0
10mg/day	320	319	9	0	0	0	0	0

NOTE: 5 subjects with missing treatment stop dates have been excluded from this plot.

The nature and frequency of adverse events reported in the pediatric studies was similar to that reported in adults and adolescents. Furthermore, many adverse events are consistent with the symptoms of influenza infection or influenza-like illness. There were no notable differences between the placebo and zanamivir groups with regard to the nature or frequency of adverse events or SAEs. There were no deaths reported. Zanamivir did not affect clinical chemistry or hematological parameters.

Further investigations of the tolerability of zanamivir in children are ongoing in Japan, as described in section 6.

5.2. Review of Neuropsychiatric Events in Clinical Studies of Zanamivir

As stated in the US prescribing information for Relenza® (zanamivir) inhalation powder, for oral inhalation (dated September 2007), the most common adverse events reported in > 1.5% of patients treated with Relenza and more commonly than in patients treated with placebo are:

- Treatment studies – sinusitis, dizziness
- Prophylaxis studies – fever and/or chills, arthralgia and articular rheumatism.

A comprehensive review of the clinical trial safety database was performed in November 2005, following reports of suicides in Japanese adolescents exposed to oseltamivir. This included two separate reviews: data from all GSK Phase II and III centrally sponsored studies (plus and one Local Company pediatric study conducted in Germany, NAI30028) and data from all studies conducted in Japan by the Local GSK Company.

The review of centrally sponsored studies included a total of 14,810 subjects, of whom 8033 received zanamivir. All adverse event terms in the neurology and psychiatry body systems were reviewed in order to select events of interest, i.e. events which could be associated with suicide or lead to fatal injuries or harm. Events of interest were contained in the following MIDAS dictionary group terms: bipolar disorders, cognitive function disorders, confusion, depressive disorders, depressive moods, disorientation, hallucinations, mood disorders, panic, paranoia, psychiatric disorders, schizophrenia, social problems, suicide & attempted suicide and thought disorders.

Overall, 76/14,810 (0.5%) of subjects reported a total of 83 events. In both placebo-controlled studies and rimantidine controlled studies, the frequencies and nature of neurological and psychological events were similar between the zanamivir and control groups within each type of controlled setting. In the placebo-controlled studies, the most common neurologic/psychiatric events were contained within the group terms 'depressive disorders' and 'mood disorders', while in the rimantidine-controlled studies, the most common events were contained within the group terms 'confusion' and 'depressive disorders'. This review did not show an increased incidence of neuropsychiatric events in subjects who received zanamivir compared to placebo or a comparator drug. There was no evidence of a causal association between exposure to zanamivir and occurrence of suicide or parasuicide. Since 2005, no further GSK sponsored clinical trials have been conducted with inhaled zanamivir.

In addition, the following specific text strings were searched for in the verbatim and preferred term fields, according to the MIDAS dictionary: ACCIDENT, SUIC, ATTEMPT, BURN, CUT, DROWN, GAS, GUN, HANG, HUNG, IMMOLAT, INJUR, JUMP, MONOXIDE, MUTILAT, OVERDOS, SELF DAMAG, SELF HARM, SELF INFLICT, SELF INJUR, SHOOT, SLASH, POISON, ASPHYXIATION, SUFFOCATION, and FIREARM. None of the verbatim text retrieved by the latter search was indicative of suicidality.

The review of studies in Japan included a total of 1049 subjects, of whom 687 received zanamivir. The database was reviewed for occurrence of any events suggestive of suicidality. There were no AEs of suicide, suicidal ideation or AEs suggestive of these.

Of note, the majority of events in the centrally sponsored clinical trials were coded according to the MIDAS dictionary, and therefore would require re-mapping to MedDRA coding dictionary to allow direct comparison with the list of terms provided for search by the FDA. Since the terms selected for review in 2005 focused mainly on neurology and psychiatric events and did not include all the search terms provided by the FDA Appendix B, an additional review will be conducted to provide supplemental data.

Supplemental data, all clinical Serious Adverse Events in subjects exposed to zanamivir retrieved according to the FDA search criteria:

The GSK Global Safety Database was searched for all serious adverse event case reports from zanamivir clinical trials up to 9th October 2007. The search was limited to patients who had received zanamivir and to the list of adverse event terms of interest specified by FDA. This analysis was limited to serious adverse event reports, since the GSK Global Safety Database does not contain reports of non-serious adverse events from clinical

trials. Twelve cases with injury or neuropsychiatric Serious Adverse Events were identified, all presented in Appendix C.

The subjects were from 19 days to 97 years of age; all but two subjects were adults, 23 years or older. Gender was equally represented with 6 women and 6 men. Outcome was fatal in 3 cases, unknown in one report and resolved in the 8 remaining cases. Of note, in all cases the reporting investigator stated the events were unrelated to treatment with zanamivir.

Three cases reported injuries and nine described neurological or psychiatric events. None of the SAE reports reviewed suggest a causal association with zanamivir. In most cases a clear alternative cause was identified, or the temporal sequence of events is incompatible with a causal role for zanamivir.

6. INFORMATION FROM JAPANESE DRUG UTILIZATION INVESTIGATION (DUI)

Drug utilization investigations (DUI) can be part of Japanese post-authorization commitments for prescription drugs marketed in Japan. They are used to collect information about safety and efficacy of a drug in Japanese subjects in the “real” world of clinical practice.

Zanamivir was/is the object of several DUIs, as follows:

- Treatment of influenza in 4456 subjects infected with influenza, among them 495 children and adolescents, completed in 2002
- Treatment of influenza in children and adolescents (5-15 years of age), currently ongoing
- Investigation of emergence of influenza viruses resistance in children and adolescents (5-15 years old) infected with influenza and treated with zanamivir, currently ongoing

6.1. DUI Treatment of influenza in adults and children infected with influenza

This surveillance program included a total of 4456 subjects with influenza who were prescribed zanamivir for oral inhalation 10 mg twice daily for five days for the treatment of influenza. Four hundred and ninety five subjects were between 12 to 15 years old and 3961 subjects were 16 years of age or older. Suicides or suicidal ideations, jumps or fall from high places were not observed in this Drug Utilization Investigation. The most frequent central nervous system adverse events observed were dygeusia (n=3), hypogeusia (n=2) and sedation (n=1). There were no emerging signals of psychiatric or neuropsychiatric events in this DUI.

6.2. DUI Treatment of influenza in children and adolescents

A DUI to examine the efficacy and safety of inhaled zanamivir in children 5-15 years of age who are diagnosed as influenza positive using a diagnostic kit is currently ongoing in Japan. The observation period is December 2006 to April 2008 (two influenza seasons). The first 250 children were enrolled in this DUI in 2006-7. No neuropsychiatric AEs have been reported to date.

6.3. DUI Emergence of influenza viruses resistance in children and adolescents (5-15 years old) treated with zanamivir

A DUI to detect any emergence of zanamivir-resistant influenza virus in pediatric patients (under 15 years of age) treated with zanamivir is currently ongoing in Japan and will span over three influenza seasons, from December 2006 to April 2009. No adverse events were reported in the first cohort of 100 cases in 2006-7.

7. INFORMATION FROM THE PUBLISHED LITERATURE

A Pubmed search of literature was performed on August 1, 2007, with the search terms “zanamivir” or “Relenza”. No relevant information for the assessment of a potential association of zanamivir and neuropsychiatric adverse events was apparent from the 530 citations or abstracts which were retrieved.

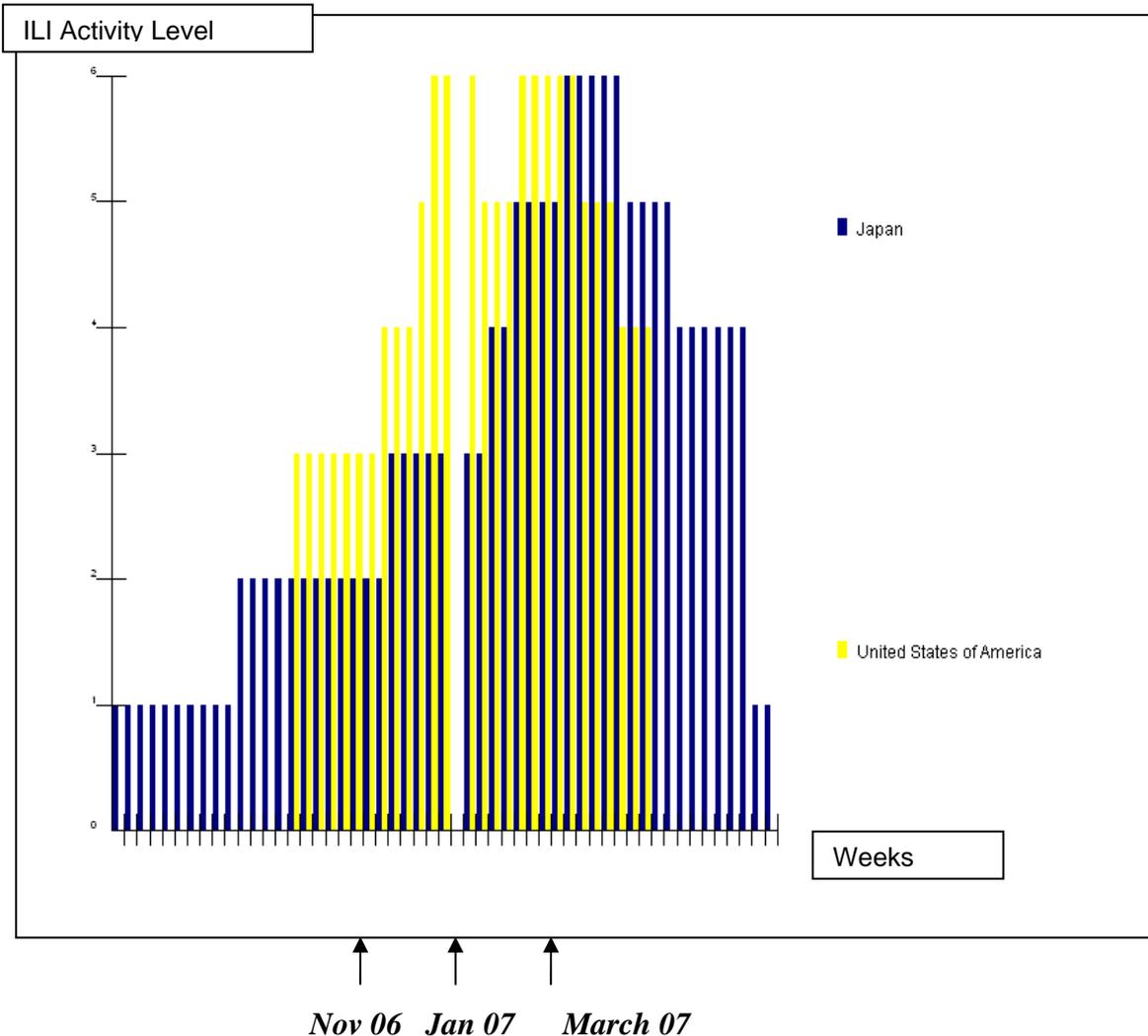
8. INFORMATION FROM EPIDEMIOLOGY

8.1. Yearly occurrence of Influenza-like-illnesses in Japan and in the United States

According to the WHO global atlas of infectious diseases information resource (<http://gamapserver.who.int/GlobalAtlas/home.asp>), the 2006-7 influenza-like illnesses (ILI) seasons in the USA and in Japan in occurred between November and May, as shown in Figure 3.

The period of “widespread outbreak” of ILI in Japan corresponded to the peak of neuropsychiatric AE reporting observed at GSK in March and April 2007, with a total of 124 neuropsychiatric AEs reported. Subsequently, despite persistence of regional and local outbreaks until June 2007, a sharp decrease in the reporting of such AEs was observed in Japan (14 neuropsychiatric AEs received in May and June 2007). In the USA, widespread outbreaks of ILI were described in December 06-January 07, as well as in February and March 2007. No reports of neuropsychiatric adverse events having occurred in the USA were received at GSK during this period of time.

Figure 3 Influenza-like illness (ILI), Activity Level, from week 26/2006 to week 25/2007 (copied from the WHO resource database Flunet)



Activity and severity of seasonal influenza infections in 2005-6 and 2006-7

Influenza activity in the 2005-6 and 2006-7 seasons was described as low, according to the National Institute for Medical Research, World Influenza (Hay A., 2007; www.nimr.mrc.ac.uk)

“Influenza between October 2006 to May 2007:

Influenza activity in the northern hemisphere was in general low. Increasing influenza in North America during December and January was due mainly to AH1N1 viruses, which caused outbreaks in the United States. Influenza AH3N2 viruses have predominated in European countries, in some Asian countries and Canada during 2007. Influenza B viruses circulated at low levels.

Influenza between October 2005 and September 2006:

Influenza activity was in general low compared with past years. Between October 2005 and April 2006, influenza A H3N2 viruses predominated in North America and some Eastern European countries, while in other European countries influenza AH1N1 or influenza B viruses predominated. In Asia influenza A H1N1, AH3N2 and B viruses co-circulated.

Between April and September, influenza AH1N1 viruses predominated in South America, while AH3N2 viruses were responsible for outbreaks in New Zealand and South Africa. Prolonged outbreaks in Hong Kong SAR from March to July were due mainly to A H1N1 viruses.”

It is difficult to find scientific information comparing the influenza epidemics across continents, as individual countries have their own methods of data collection and analysis. However, in Japan, the size of the 2006-7 influenza outbreak was estimated from reports from point medical institutions (information collection centers) and reported by the Japanese government Infectious Disease Surveillance Centre (<http://idsc.tokyo-eiken.go.jp/inf/2006/18.pdf>). By these estimates, the Japanese 2006-7 influenza season was a medium-sized epidemic, the fourth-largest in the past ten years. This represents higher influenza activity than that described for the rest of the northern hemisphere for the same time period. Of note, the Tokyo Metropolitan area recorded cases of influenza from 290 medical institutions in Tokyo (of which 150 are pediatrics departments) and from about 5000 medical institutions in Japan.

Figure 4 shows the number of patients with influenza in Japan during the past five influenza seasons. It is apparent from this figure that a similar number of subjects were diagnosed with influenza in 2005-6 and in 2006-7, and that the peak of activity occurred at different times of the year in these two influenza seasons.

Figure 4 Average Number of influenza patients reported (for each sentinel clinic) in Japan in the last 5 influenza seasons

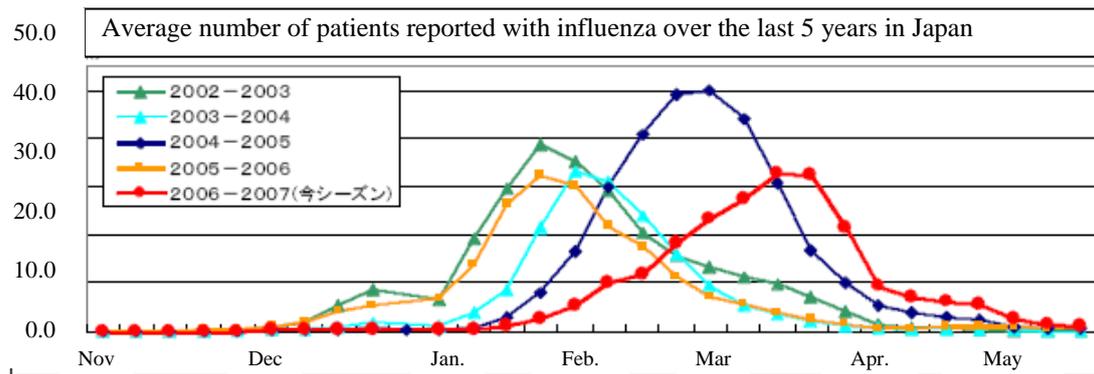
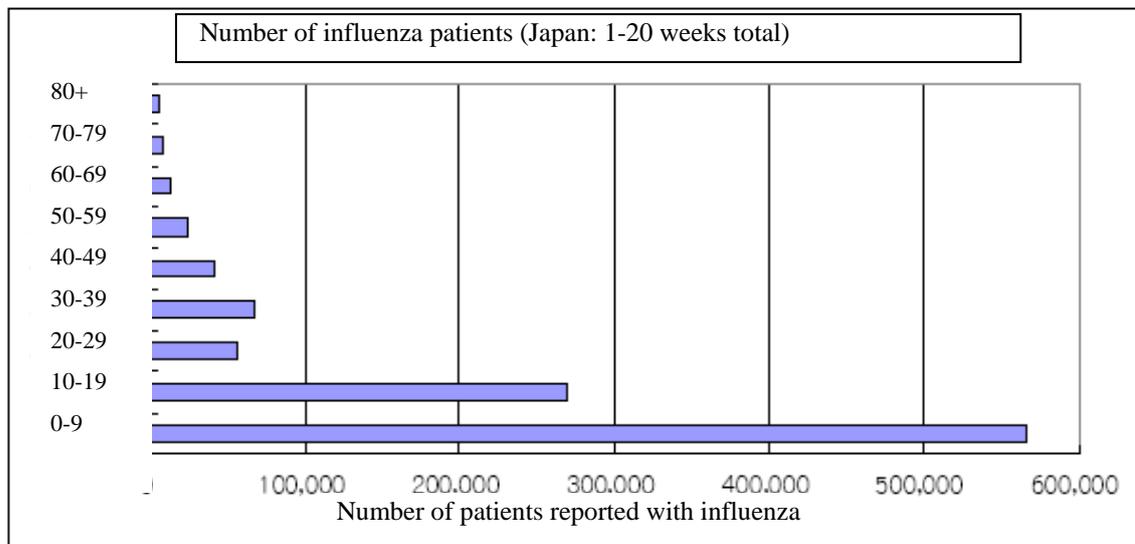


Figure 5 summarizes the distribution of influenza patients by age in the 2006-7 season for the whole of Japan. It is apparent from these figures that the majority of reports of influenza from medical consultations in Japan occurred in a young population in Japan, with approximately half of the subjects below 9 years of age and the majority below 19 years of age.

Figure 5 Age distribution of influenza patients in Japan during the influenza season 2006-7*



*Weeks 1 – 20 represent influenza season months November 06 – April 07

In summary, influenza activity in the northern hemisphere was low in the 2006-7 influenza season, but there are some indicators of slightly higher activity in Japan. The reporting of neuropsychiatric events in Japanese children and adolescents in spring 2007 is unlikely to be explained solely by this increased influenza activity, but may reflect that the majority of subjects who sought medical care were younger than 19 years of age.

8.2. Epidemiology of Influenza and neuropsychiatric events

Although influenza is generally a self-limiting illness, occasionally serious illness can occur with, among other manifestations, neurological involvement. Neurological involvement can be manifested as Reye's syndrome, acute necrotizing encephalopathy, myelitis, Guillain-Barre syndrome, encephalomyelitis and neuritis. Other observed symptoms include confusion, seizures, and psychosis. The mechanisms by which influenza infection results in neurological complications are not known. Although influenza virus replicates in the respiratory tract, there is evidence indicating that the virus may also penetrate into the central nervous system (CNS). Animal models suggest that the virus travels through the free nerve endings in the epithelial cells in the respiratory tract and continues through the olfactory and trigeminal nerve system to the CNS. The different routes of passage, then, may determine the type of neurological manifestation observed in a given patient (Studahl, 2003).

The most frequent neurological manifestations of influenza are encephalitis or encephalopathy. In a retrospective cohort study on influenza-related neurological complications (INC) among 842 children conducted in Pennsylvania, USA, among 842 influenza patients over the years 2000-2004, 72 (8.6%) patients developed INCs and of these 10 (13.9%) developed encephalopathy. Of the 72 patients with INCs, 56 (78%) presented with seizures (Newland et al., 2007). In a similar study in Taiwan, over a period of 29 months, 11 (12%) of 92 admitted influenza patients presented with INCs. Four of these patients presented with seizures and the remaining seven with encephalopathy (Li et al., 2006). The results of these two studies are tabulated below for reference:

Author, Year	Place Study period	Influenza cases N	INC cases N (%)	Encephalopathy N (%)	Seizures N (%)
Newland et al., 2007	Pennsylvania, USA 2000-2004	842	72 (13.9%)	10 (13.9%)	56 (78%)
Li et al., 2006	Taiwan 2001-2003	92	11 (12%)	7 (63.6%)	4 (36.4%)

In Japan, influenza-associated encephalopathy is a frequently recognized serious complication of influenza and the incidence of this complication has been increasing; the reason for this trend remains unexplained in the published literature (Studahl, 2003; Sugaya, 2002). The incidence began increasing after the 1994-1995 epidemic. The cases of influenza-associated encephalopathy occur most frequently in children and the case-fatality rate from this complication is approximately 30% (Sugaya, 2002; Togashi, 2004).

The typical presentation of influenza-associated encephalopathy is rapid onset of high fever, seizure and rapidly progressive coma (Sugaya, 2002). However, occasionally abnormal behavior or delirium has been observed among the affected children in Japan (Okumura, 2005). Huang and colleagues (2003), report five children in Taiwan ranging in age from 3 to 6 years old who experienced visual and auditory hallucinations, in addition to displaying unusual behavior. These were observed to end once the influenza illness resolved and did not reappear after two years of follow-up. These children were characterized as having influenza A-associated CNS dysfunction. The authors conjecture that there is a current bias in reporting severe neurological manifestations of influenza, while mild and transient manifestations maybe more frequent, but under-reported (Huang, 2003). In Japan, Okumura and colleagues (2006) report observing delirious

behavior in nine patients ranging in age between 4 and 10 years. Four of these patients had delirious behavior after the use of oseltamivir, however the authors report no evidence that oseltamivir was the cause of the delirium. The delirious behavior included meaningless speech, disorientation, “fearful response”, and “running around the room” (Okumura, 2006).

Suicides rates in subjects up to 20 years of age are similar in the USA and in Japan. Of note, jumping from height represented a significant proportion of suicidal behaviors in Japan after 1999, after hanging. Ojuma reported in 2004 that among adolescents aged 10-19 years, 16.9% of male suicides and 26.7% of female suicides were committed by jumping from a height.

9. ALL ADVERSE EVENT REPORTS FROM THE GSK GLOBAL SAFETY DATABASE FOR THE 2006-2007 INFLUENZA SEASON IN THE NORTHERN HEMISPHERE (OCT 2006 – JUNE 2007)

9.1. Methods

9.1.1. Identification of Reports

The search strategy included all the adverse event terms provided by FDA (Appendix B).

The GSK Global Safety Database was searched for all clinical (SAEs only), postmarketing and spontaneous adverse event reports with zanamivir received by GSK between October 1, 2006 up to June 30, 2007 and recording at least one event in the MedDRA body system organ classes “*Nervous System Disorders*” “*Psychiatric Disorders*”, “*Injury, Poisoning and Procedural Complications*”.

9.2. Results

All cases identified by this search were spontaneous adverse event reports.

9.2.1. Overall Summary of the Spontaneous Reports

Group of reports from the SOC” Injury, Poisoning and Procedural Complications”

Twelve reports were identified which included events in the SOC “*Injury, Poisoning and Procedural Complications*”. Of these reports, three cases also reported concurrent neuropsychiatric events as presented in Table 4. They are assessed later in this review with the group of reports from the SOC’s psychiatric disorders and nervous system disorders.

The events reported in the remaining cases were not indicative of delusion, delirium, paranoia, suicidal or other behaviors potentially leading to vital accidental injuries, voluntary or involuntary self harm and were therefore excluded from further review.

Table 4 Events from the SOC Injury, Poisoning and Procedural Complications, with events in the SOC's Psychiatric or Nervous Disorders, n=3

Age	Gender	Case Outcome	Adverse Events Reported (MedDRA Preferred Terms)
7 Years	Female	Resolved	Sleep terror, Fall, Convulsion
30 Years	Female	Resolved	Hallucination, Disorientation, Drug exposure during pregnancy
16 Years	Female	Resolved	Sleep walking, Head injury, Fall, Loss of consciousness, Diarrhea

Of note, there were no cases of fall/jumping from buildings or high places in the GSK safety database (either in the time period of this review or in the entire GSK safety database).

Group of reports from the SOC's psychiatric disorders and nervous system disorders

One hundred and forty five reports with at least one event of interest from the SOC's "nervous system disorders" and "psychiatric disorders" were retrieved from the GSK safety database. All 145 reports were from Japan and all were spontaneous reports. None had a fatal outcome.

No reports were received from October 2006 to January 2007. The peak of reporting was observed in March (57%) and April (29%). The time distribution of the reports received at GSK in 2006-7 shows that the peak of reporting coincided with the peak of influenza activity in Japan. Of note, the onset of reporting of neuropsychiatric events associated with zanamivir in February-March 2007, coincided with the severe warning issued by the Japanese MHLW against the use of oseltamivir in adolescents with influenza. Despite uncertain causal association with the drug, the MHLW recommended its use be restricted in this population to subjects at risk of complications of influenza.

Neuropsychiatric events were reported more frequently in males (61%) than females (39%). Ninety nine percent of the patients were children in the 6-14 age range. This is significantly different from that observed prior to the influenza season 2006-2007, in which the events of interest were reported in adults with a median age of 44 years (Section 10.2.1). Zanamivir was prescribed almost exclusively for influenza treatment. Only one report mentioned its use for prophylaxis of influenza. The events most frequently reported were: abnormal behavior, hallucination, agitation, delirium, headache, restlessness, speech disorder, dizziness, crying and fear.

This review assessed the cases in three groups, according to the SOC's of the events reported, as follows:

- Reports with neurological events only (9%)
- Reports with psychiatric events only (61%)
- Reports with neurological and psychiatric events (30%)

9.2.2. Reports with neurological events only (9%)

These reports of nervous system disorders described events which were more likely associated with influenza itself, e.g. parosmia, depressed level of consciousness with pyrexia, feeling abnormal, sleep talking/walking, vasovagal syncope (with altered / loss of consciousness). Where “convulsions” or “epilepsy” were reported, although a likely cause of seizures was not apparent, the information available did not provide evidence for a causal role of zanamivir either.

In conclusion, none of these reports provided convincing evidence for a causal association of neurological events, including seizures and loss of consciousness, and zanamivir.

9.2.3. Reports with psychiatric events only (61%)

In the majority of cases, the events reported were either inconsistent with the diagnosis, or insufficiently documented. In other cases time to onset was not concomitant with zanamivir administration, or alternative diagnoses or concurrent disease/drug were clearly more likely to have caused the events. A significant proportion of cases described events resolved under continuation of zanamivir treatment. Of note, multiple reporters mentioned that their reporting of the events observed in subjects exposed to zanamivir was prompted by their awareness of the recent alert from the Japanese Ministry of Health Labor and Welfare of similar events with the neuraminidase inhibitor oseltamivir.

In a small minority of cases a clear alternative cause was not obvious. These reports described events including screaming at night, loss of sleep, transient hallucinations and delirium. However, some of the events were also compatible with influenza complications and not all were well documented. There was no evidence in these reports to suggest a clear causal association with zanamivir.

9.2.4. Reports with neurological and psychiatric events (30%)

In the majority of cases, the events reported were either inconsistent with the diagnosis, or insufficiently documented. In other cases time to onset was not concomitant with zanamivir administration, or alternative diagnoses or concurrent disease/drug were clearly more likely to have caused the events. A significant proportion of cases described events resolved under continuation of zanamivir treatment. Of note, multiple reporters mentioned that their reporting of the events observed in subjects exposed to zanamivir was prompted by their awareness of the recent publications of similar events with the neuraminidase inhibitor oseltamivir.

A small number of cases described events including “depressive state”, night terrors with seizures, abnormal behavior with possible influenza-associated encephalopathy and hallucinations. While no obvious cause for these events was reported, there was also no clear evidence for a causal association with zanamivir. Some cases were insufficiently documented and others were consistent with possible complications of influenza, or documented a negative rechallenge with zanamivir.

There was one report of “suicidal ideation” as an event. An 11 year old girl with influenza, pyrexia of 38.8 degrees Celsius, and severe headache was reported to have said

“Let me die.”, “My head is spinning and it makes me feel sick”, “Please throw me down through the window”. This event resolved within half an hour, coinciding with the resolution of headache and influenza symptoms, was not accompanied with self harm behavior, and continuation of treatment with zanamivir was not associated with recurrence of the events. Therefore, the events were most plausibly explained by pain from headache and general unwell being from influenza.

In conclusion, none of the cases in this group of reports provided convincing evidence for a causal association of the reported neuropsychiatric events and zanamivir.

9.3. Overall conclusion from the spontaneous reports of neuropsychiatric adverse events received at GSK in the influenza season 2006-2007:

Assessment of spontaneous reports of psychiatric or neuropsychiatric events in children is a complex issue. However, the analysis of the reports in this review did not provide convincing evidence of a causal association of neurological or psychiatric events including seizures, loss of consciousness, suicidal ideation, depression or self harm behaviors with zanamivir.

10. ALL ADVERSE EVENT REPORTS FROM THE GSK GLOBAL SAFETY DATABASE UP TO SEPTEMBER 30TH, 2006 (PRIOR TO THE 2006-2007 INFLUENZA SEASON)

10.1. Methods

10.1.1. Identification of Reports

The reports assessed in this section were identified according to the adverse event terms provided by the FDA (Appendix B). The time period considered in this search of the GSK Global Safety Database was “all adverse event reports up to September 30th, 2006”.

10.2. Results

10.2.1. Overall summary of all the spontaneous adverse event reports of interest received up to September 30th, 2006

Of all the cases retrieved by this search, twelve were serious clinical trial adverse event reports and there were no reports from postmarketing surveillance programs. The clinical trial cases were analyzed in section 5 of this document, therefore only information pertaining to the remaining spontaneous adverse event reports is discussed below.

One hundred and nineteen spontaneous adverse event reports were identified up to the 30 September 2006. These reports were received from multiple countries, mainly from the USA (41%), Japan (15%), Canada (13%) and Germany (11%). Sixty five percent of

patients were female, 33% were male and gender was unknown in 2%. Age ranged from 10 to 97 years of age with a median age of 44 years. Only 12% of cases were reported in subjects younger than 18 years of age. This was significantly different from that observed in the influenza season 2006-2007, where all events of interest were reported in Japan and almost all were in children and adolescents (Section 9.2.1).

The events of interest most frequently reported in this time period were: insomnia, loss of consciousness, syncope, dizziness, anxiety, hallucination, seizure, restlessness, headache, agitation and disorientation.

10.2.2. Spontaneous reports of adverse events linked to accidents, fall or injuries, up to September 30th, 2006 (4%)

Four percent of the cases of interest reported to GSK up to September 30th, 2006 had events coding to the MedDRA SOC “injury, poisoning and procedural complications”. All occurred in adult subjects and none was convincing for a causal association with zanamivir. Additionally, none was indicative of delusion, delirium, paranoia, suicidal or other behaviors potentially leading to vital accidental injuries, voluntary or involuntary self harm behaviors. Four reports described additional neuropsychiatric events and are therefore further included in the review below (Section 10.2.3.).

10.2.3. Spontaneous reports of neuropsychiatric events up to September 30th, 2006 (96%)

Ninety six percent of the reports described at least one neuropsychiatric event coding to the MedDRA SOCs “nervous system disorder” or “psychiatric disorder” corresponding to the adverse event terms provided by the FDA. In these cases, the events reported were either inconsistent with the time to onset, insufficiently documented or alternative diagnosis or concurrent disease were clearly more likely to have caused the events. In some of the cases, events resolved under continuation of zanamivir treatment. There was no apparent evidence that the events reported in these cases were source of self harm behaviors, voluntary or involuntary, linked to “delirium, delusion, paranoia, other potential psychotic disorders, neurotic [affective] disorders”. The events described were more likely caused by pyrexia or influenza itself or other concurrent/underlying diseases, were associated with an implausible time to onset of the events in relation to exposure to zanamivir, or were insufficiently documented to allow sound medical assessment. These results were consistent with the analysis of the CNS events reported in the 2006-2007 influenza season.

In summary, there is no significant evidence of a role of zanamivir in the occurrence of neuropsychiatric events or injuries/accidents. No additional risk minimization measures or changes to the USPI are warranted at present.

11. DISPROPORTIONALITY ANALYSES

The data available in AERS and in GSK Global Safety Database in the areas of interest for this review or in the pediatric population of interest for the November 17th 2007 Advisory Committee Meeting was too limited prior to the 2006-2007 influenza season to allow a robust statistical analysis of the data specifically focused on the pediatric population. Therefore, disproportionality analysis to explore differences between the adult and the pediatric populations were not performed.

In the influenza season 2006-2007, the safety signal identified was based on a cluster of spontaneous reports of CNS events issued exclusively from Japan and almost exclusively in the pediatric population (134 cases \leq 18 years, out of 145). Disproportionality analyses are not presented either for these events/cases, as all the cases were included in the current review.

12. SUMMARY AND CONCLUSION

This safety summary analyzing neuropsychiatric events and Relenza (zanamivir) is the most current evaluation of these events following investigations that began when these events were first reported in Japan. Analyses include an integrated safety summary of Central Nervous System adverse events with zanamivir based on specifications from FDA.

The current analysis was aimed at detecting risks for voluntary and involuntary self harm behaviors with the information provided in the adverse events reports available on the GSK Global Safety Database and at assessing if there was a potential causal association between CNS events and zanamivir.

No indication of a potential neuropsychiatric issue with zanamivir was observed through GSK's routine signal detection process until March 2007, at which time a cluster of such events observed in subjects exposed to zanamivir was reported to GSK from Japan. Almost all cases were in children or adolescents. It was apparent that the characteristics of the populations and the pattern of adverse events reported in the spring of 2007 differed significantly from the pattern observed in previous years, and therefore the data were presented separately for each of these two time periods.

Multiple sources of information were evaluated in this review, and the findings summarized below:

- In studies in animals there were no treatment related clinical signs indicative of effects on behavior. Penetration of zanamivir into the brain was shown to be minimal in radiolabel studies in rats and dogs.
- The pharmacokinetic characteristics of zanamivir make a direct CNS toxicity mechanism for neuropsychiatric events unlikely.
- A review of neuropsychiatric adverse events from all GSK Phase II and III centrally sponsored clinical trials (14,810 subjects enrolled, 8033 of whom received zanamivir) and studies conducted by GSK Japan (1049 subjects, 687 treated with zanamivir) was performed in November 2005. This review did not show an increased incidence of the neuropsychiatric events in subjects who received zanamivir compared with those who received placebo, or a comparator drug. The review was supplemented by an additional analysis of all the clinical trial Serious Adverse Event reports with zanamivir in which the current AE terms specified by FDA were used to search the GSK Worldwide Database. No evidence for a causal association with zanamivir was identified.
- Patterns of neuropsychiatric events or self harm behaviors have not been observed in three recent or ongoing Drug Use Investigations with zanamivir in Japan.
- Published epidemiology data describe that, although influenza is generally a self-limited illness, occasionally serious illness can occur with, among other manifestations, neurological involvement. Neurological involvement can be manifested as Reye's syndrome, acute necrotizing encephalopathy, myelitis, Guillain-Barre syndrome, encephalomyelitis and neuritis. Other observed

symptoms include confusion, seizures, and psychosis. In Japan, influenza-associated encephalopathy is a frequently recognized serious complication of influenza, and the higher reporting of neuropsychiatric adverse events observed from Japan could be partly explained by this observation.

- There is no information available from the published medical and scientific literature linking use of zanamivir and neuropsychiatric events.
- A five fold increase in zanamivir use was observed in the past two years in Japan, which may contribute to the recently observed increase in spontaneous reporting of adverse events from this country.
- The peak of neuropsychiatric events reported in subjects exposed to zanamivir during March and April 2007 corresponded to the peak of a “widespread outbreak” of influenza like illnesses (ILI) in Japan [WHO influenza disease resource information]. In the USA, widespread outbreaks of ILI were described in December 2006 to January 07, as well as in February and March 2007. No reports of neuropsychiatric adverse events have been received from the USA.
- An association was noted between the reporting of neuropsychiatric events from Japan in subjects exposed to zanamivir in the spring of 2007 and the public release of a high level alert by the Japanese Ministry of Health, Labor and Welfare in March 2007 which detailed abnormal / self harm behaviors observed in Japanese adolescents infected with influenza and exposed to oseltamivir. Awareness of this alert was stated in many of these neuropsychiatric adverse events reports sent to GSK by Japanese reporters.
- In the northern hemisphere, influenza activity has been low during the past two influenza seasons. However, data from the Japanese government Infectious Disease Surveillance Center indicate that a slightly higher influenza activity was prevalent in Japan during 2006-7 in comparison with the rest of the northern hemisphere or with the Japanese 2005-6 influenza season. The high reporting of neuropsychiatric events in Japanese children and adolescents in the spring of 2007 may be due partially to a slightly higher influenza activity in Japan in March and April 2007. However, this increased reporting of adverse events in the spring of 2007 could also be due to the fact that this population was more likely than others to seek medical consultation when infected with influenza.
- All reports of neuropsychiatric events received in the spring of 2007 were issued from Japan. Ninety two percent of cases were observed in children and adolescents younger than 18 years of age and 99% in children in the 6-14 age range. The vast majority of these events were transient and a significant proportion of the reports described abnormal behavior in febrile subjects that resolved while zanamivir treatment was continued. No falls or jumps from high places or suicides were reported.
- Neuropsychiatric adverse events reported prior to the 2006-2007 influenza season were significantly different in their origin, clinical presentation pattern and characteristics of the population affected than what was observed in the cluster of reports from Japan in the spring of 2007: the older reports were issued from multiple of countries, did not show a specific medical pattern, and the population affected was significantly older than the population typical of the reports from Japan in the spring of 2007.

- Analysis of the spontaneous cases of interest for the FDA of neuropsychiatric adverse events or injuries available for zanamivir in the company's global safety database provides insufficient evidence to support a causal association between zanamivir and neuropsychiatric events including seizures, loss of consciousness, suicides, depression, self harm behaviors or and association between zanamivir and accidents or injuries.
- The vast majority of the neuropsychiatric events assessed in this review were more plausibly associated with pyrexia and/or influenza encephalitis or with concurrently administered drugs or diseases rather than with zanamivir.

In conclusion

The assessment of spontaneous reports of psychiatric or neuropsychiatric events in children is challenging. Therefore, in addition to the spontaneous adverse events reports from the GSK Global Safety Database additional information from other sources (pre-clinical studies, pharmacokinetic properties, clinical studies, epidemiologic studies and the literature) was also considered in the company's assessment of this issue.

The analysis of all the information available as described in this safety summary of neuropsychiatric events or of accidental injuries did not demonstrate a significant causal role of zanamivir. Therefore, an update of the Relenza USPI or other risk minimization measures is not considered warranted.

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14. APPENDICES

APPENDIX A:

US Prescribing Information for Relenza

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RELENZA safely and effectively. See full prescribing information for RELENZA.

RELENZA® (zanamivir) Inhalation Powder, for oral inhalation

Initial U.S. Approval: 1999

INDICATIONS AND USAGE

RELENZA, an influenza neuraminidase inhibitor, is indicated for:

Treatment of influenza in patients 7 years of age and older who have been symptomatic for no more than 2 days. (1.1)

Prophylaxis of influenza in patients 5 years of age and older. (1.2)

Important Limitations on Use of RELENZA:

Not recommended for treatment or prophylaxis of influenza in:

- Individuals with underlying airways disease. (5.1)

Not proven effective for:

- Treatment in individuals with underlying airways disease. (1.3)
- Prophylaxis in nursing home residents. (1.3)

Not a substitute for annual influenza vaccination. (1.3)

DOSAGE AND ADMINISTRATION

Indication	Dose
Treatment of Influenza (2.2)	10 mg twice daily for 5 days
Prophylaxis: (2.3)	
Household Setting	10 mg once daily for 10 days
Community Outbreaks	10 mg once daily for 28 days

Note: The 10 mg dose is provided by 2 inhalations (one 5 mg blister per inhalation). (2.1)

DOSAGE FORMS AND STRENGTHS

Four 5 mg blisters of powder on a ROTADISK® for oral inhalation via DISKHALER®. Packaged in carton containing 5 ROTADISks (total of 10 doses) and 1 DISKHALER inhalation device. (3)

CONTRAINDICATIONS

Do not use in patients with history of allergic reaction to any ingredient of RELENZA, including lactose (which contains milk proteins). (4)

WARNINGS AND PRECAUTIONS

- **Bronchospasm:** Serious, sometimes fatal, cases have occurred. Not recommended in individuals with underlying airways disease. Discontinue RELENZA if bronchospasm or decline in respiratory function develops. (5.1)
- **Allergic Reactions:** Discontinue Relenza and initiate appropriate treatment if an allergic reaction occurs or is suspected. (5.2)
- **High-risk underlying medical conditions:** Safety and effectiveness have not been demonstrated in these patients. (5.3)

ADVERSE REACTIONS

The most common adverse events reported in >1.5% of patients treated with RELENZA and more commonly than in patients treated with placebo are:

- Treatment Studies – sinusitis, dizziness.
- Prophylaxis studies – fever and/or chills, arthralgia and articular rheumatism. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Live attenuated influenza vaccine, intranasal (7):

- Do not administer until 48 hours following cessation of RELENZA.
- Do not administer RELENZA until 2 weeks following administration of the live attenuated influenza vaccine, unless medically indicated.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: October 2007
RLZ:2PI

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Influenza

RELENZA is indicated for treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients 7 years of age and older who have been symptomatic for no more than 2 days.

1.2 Prophylaxis of Influenza

RELENZA is indicated for prophylaxis of influenza in adults and pediatric patients 5 years of age and older.

1.3 Important Limitations on Use of RELENZA

- RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) due to risk of serious bronchospasm [*see Warnings and Precautions (5.1)*].
- RELENZA has not been proven effective for treatment of influenza in individuals with underlying airways disease.
- RELENZA has not been proven effective for prophylaxis of influenza in the nursing home setting.
- RELENZA is not a substitute for early influenza vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee.
- There is no evidence for efficacy of zanamivir in any illness caused by agents other than influenza virus A and B.
- Patients should be advised that the use of RELENZA for treatment of influenza has not been shown to reduce the risk of transmission of influenza to others.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Considerations

- RELENZA is for administration to the respiratory tract by oral inhalation only, using the DISKHALER device provided.
- The 10 mg dose is provided by 2 inhalations (one 5 mg blister per inhalation).
- Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible. If RELENZA is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional [*see Patient Counseling Information (17.3)*].
- Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should use their bronchodilator before taking RELENZA [*see Patient Counseling Information (17.2)*].

2.2 Treatment of Influenza

- The recommended dose of RELENZA for treatment of influenza in adults and pediatric patients ages 7 years of age and older is 10 mg twice daily (approximately 12 hours apart) for 5 days.
- Two doses should be taken on the first day of treatment whenever possible provided there is at least 2 hours between doses.
- On subsequent days, doses should be about 12 hours apart (e.g., morning and evening) at approximately the same time each day.
- The safety and efficacy of repeated treatment courses have not been studied.

2.3 Prophylaxis of Influenza

Household Setting:

- The recommended dose of RELENZA for prophylaxis of influenza in adults and pediatric patients 5 years of age and older in a household setting is 10 mg once daily for 10 days.
- The dose should be administered at approximately the same time each day.
- There are no data on the effectiveness of prophylaxis with RELENZA in a household setting when initiated more than 1.5 days after the onset of signs or symptoms in the index case.

Community Outbreaks:

- The recommended dose of RELENZA for prophylaxis of influenza in adults and adolescents in a community setting is 10 mg once daily for 28 days.
- The dose should be administered at approximately the same time each day.
- There are no data on the effectiveness of prophylaxis with RELENZA in a community outbreak when initiated more than 5 days after the outbreak was identified in the community.
- The safety and effectiveness of prophylaxis with RELENZA have not been evaluated for longer than 28 days' duration.

3 DOSAGE FORMS AND STRENGTHS

Four 5 mg blisters of powder on a ROTADISK for oral inhalation via DISKHALER. Packaged in carton containing 5 ROTADISKS (total of 10 doses) and 1 DISKHALER inhalation device [*see How Supplied/Storage and Handling (16)*].

4 CONTRAINDICATIONS

Do not use in patients with history of allergic reaction to any ingredient of RELENZA including lactose (which contains milk proteins) [*see Warnings and Precautions (5.2), Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Bronchospasm

RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease).

Serious cases of bronchospasm, including fatalities, have been reported during treatment with RELENZA in patients with and without underlying airways disease. Many of these cases were reported during postmarketing and causality was difficult to assess.

RELENZA should be discontinued in any patient who develops bronchospasm or decline in respiratory function; immediate treatment and hospitalization may be required.

Some patients without prior pulmonary disease may also have respiratory abnormalities from acute respiratory infection that could resemble adverse drug reactions or increase patient vulnerability to adverse drug reactions.

Bronchospasm was documented following administration of zanamivir in 1 of 13 patients with mild or moderate asthma (but without acute influenza-like illness) in a Phase I study. In a Phase III study in patients with acute influenza-like illness superimposed on underlying asthma or chronic obstructive pulmonary disease, 10% (24 of 244) of patients on zanamivir and 9% (22 of 237) on placebo experienced a greater than 20% decline in FEV₁ following treatment for 5 days.

If use of RELENZA is considered for a patient with underlying airways disease, the potential risks and benefits should be carefully weighed. If a decision is made to prescribe RELENZA for such a patient, this should be done only under conditions of careful monitoring of respiratory function, close observation, and appropriate supportive care including availability of fast-acting bronchodilators.

5.2 Allergic Reactions

Allergic-like reactions, including oropharyngeal edema, serious skin rashes, and anaphylaxis have been reported in postmarketing experience with RELENZA. RELENZA should be stopped and appropriate treatment instituted if an allergic reaction occurs or is suspected.

5.3 Limitations of Populations Studied

Safety and efficacy have not been demonstrated in patients with high-risk underlying medical conditions. No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring inpatient management.

5.4 Bacterial Infections

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. RELENZA has not been shown to prevent such complications.

5.5 Importance of Proper Use of DISKHALER

Effective and safe use of RELENZA requires proper use of the DISKHALER to inhale the drug. Prescribers should carefully evaluate the ability of young children to use the delivery system if use of RELENZA is considered [*see Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

See Warnings and Precautions for information about risk of serious adverse events such as bronchospasm (5.1) and allergic-like reactions (5.2), and for safety information in patients with underlying airways disease (5.1).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

Treatment of Influenza: Clinical Trials in Adults and Adolescents: Adverse events that occurred with an incidence $\geq 1.5\%$ in treatment studies are listed in Table 1. This table shows adverse events occurring in patients ≥ 12 years of age receiving RELENZA 10 mg inhaled twice daily, RELENZA in all inhalation regimens, and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in RELENZA).

Table 1. Summary of Adverse Events $\geq 1.5\%$ Incidence During Treatment in Adults and Adolescents

Adverse Event	RELENZA		Placebo (Lactose Vehicle) (n = 1,520)
	10 mg b.i.d. Inhaled (n = 1,132)	All Dosing Regimens* (n = 2,289)	
Body as a whole			
Headaches	2%	2%	3%
Digestive			
Diarrhea	3%	3%	4%
Nausea	3%	3%	3%
Vomiting	1%	1%	2%
Respiratory			
Nasal signs and symptoms	2%	3%	3%
Bronchitis	2%	2%	3%
Cough	2%	2%	3%
Sinusitis	3%	2%	2%
Ear, nose, and throat infections	2%	1%	2%
Nervous system			
Dizziness	2%	1%	<1%

* Includes studies where RELENZA was administered intranasally (6.4 mg 2 to 4 times per day in addition to inhaled preparation) and/or inhaled more frequently (q.i.d.) than the currently recommended dose.

Additional adverse reactions occurring in less than 1.5% of patients receiving RELENZA included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria.

The most frequent laboratory abnormalities in Phase III treatment studies included elevations of liver enzymes and CPK, lymphopenia, and neutropenia. These were reported in similar proportions of zanamivir and lactose vehicle placebo recipients with acute influenza-like illness.

Clinical Trials in Pediatric Patients: Adverse events that occurred with an incidence $\geq 1.5\%$ in children receiving treatment doses of RELENZA in 2 Phase III studies are listed in Table 2. This table shows adverse events occurring in pediatric patients 5 to 12 years old receiving RELENZA 10 mg inhaled twice daily and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in RELENZA).

Table 2. Summary of Adverse Events $\geq 1.5\%$ Incidence During Treatment in Pediatric Patients*

Adverse Event	RELENZA 10 mg b.i.d. Inhaled (n = 291)	Placebo (Lactose Vehicle) (n = 318)
Respiratory		
Ear, nose, and throat infections	5%	5%
Ear, nose, and throat hemorrhage	<1%	2%
Asthma	<1%	2%
Cough	<1%	2%
Digestive		
Vomiting	2%	3%
Diarrhea	2%	2%
Nausea	<1%	2%

* Includes a subset of patients receiving RELENZA for treatment of influenza in a prophylaxis study.

In 1 of the 2 studies described in Table 2, some additional information is available from children (5 to 12 years old) without acute influenza-like illness who received an investigational prophylaxis regimen of RELENZA; 132 children received RELENZA and 145 children received placebo. Among these children, nasal signs and symptoms (zanamivir 20%, placebo 9%), cough (zanamivir 16%, placebo 8%), and throat/tonsil discomfort and pain (zanamivir 11%, placebo 6%) were reported more frequently with RELENZA than placebo. In a subset with chronic pulmonary disease, lower respiratory adverse events (described as asthma, cough, or viral respiratory infections which could include influenza-like symptoms) were reported in 7 of 7 zanamivir recipients and 5 of 12 placebo recipients.

Prophylaxis of Influenza: Family/Household Prophylaxis Studies: Adverse events that occurred with an incidence of $\geq 1.5\%$ in the 2 prophylaxis studies are listed in

Table 3. This table shows adverse events occurring in patients ≥ 5 years of age receiving RELENZA 10 mg inhaled once daily for 10 days.

Table 3. Summary of Adverse Events $\geq 1.5\%$ Incidence During 10-Day Prophylaxis Studies in Adults, Adolescents, and Children*

Adverse Event	Contact Cases	
	RELENZA (n = 1,068)	Placebo (n = 1,059)
Lower respiratory		
Viral respiratory infections	13%	19%
Cough	7%	9%
Neurologic		
Headaches	13%	14%
Ear, nose, and throat		
Nasal signs and symptoms	12%	12%
Throat and tonsil discomfort and pain	8%	9%
Nasal inflammation	1%	2%
Musculoskeletal		
Muscle pain	3%	3%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	2%	2%
Gastrointestinal		
Nausea and vomiting	1%	2%
Non-site specific		
Malaise and fatigue	5%	5%
Temperature regulation disturbances (fever and/or chills)	5%	4%

* 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.

Community Prophylaxis Studies: Adverse events that occurred with an incidence of $\geq 1.5\%$ in 2 prophylaxis studies are listed in Table 4. This table shows adverse events occurring in patients ≥ 5 years of age receiving RELENZA 10 mg inhaled once daily for 28 days.

Table 4. Summary of Adverse Events $\geq 1.5\%$ Incidence During 28-Day Prophylaxis Studies in Adults, Adolescents, and Children*

Adverse Event	RELENZA (n = 2,231)	Placebo (n = 2,239)
Neurologic		
Headaches	24%	26%
Ear, nose, and throat		
Throat and tonsil discomfort and pain	19%	20%
Nasal signs and symptoms	12%	13%
Ear, nose, and throat infections	2%	2%
Lower respiratory		
Cough	17%	18%
Viral respiratory infections	3%	4%
Musculoskeletal		
Muscle pain	8%	8%
Musculoskeletal pain	6%	6%
Arthralgia and articular rheumatism	2%	<1%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	4%	4%
Gastrointestinal		
Nausea and vomiting	2%	3%
Diarrhea	2%	2%
Non-site specific		
Temperature regulation disturbances (fever and/or chills)	9%	10%
Malaise & fatigue	8%	8%

* 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.

6.2 Postmarketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during postmarketing use of zanamivir (RELENZA). Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to zanamivir (RELENZA).

Allergic Reactions: Allergic or allergic-like reaction, including oropharyngeal edema [see *Warnings and Precautions* (5.2)].

Cardiac: Arrhythmias, syncope.

Neurologic: Seizures.

Respiratory: Bronchospasm, dyspnea [see *Warnings and Precautions* (5.1)].

Skin: Facial edema; rash, including serious cutaneous reactions; urticaria [*see Warnings and Precautions (5.2)*].

7 DRUG INTERACTIONS

Zanamivir is not a substrate nor does it affect cytochrome P450 (CYP) isoenzymes (CYP1A1/2, 2A6, 2C9, 2C18, 2D6, 2E1, and 3A4) in human liver microsomes. No clinically significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

The concurrent use of RELENZA with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of potential interference between these products, LAIV should not be administered within 2 weeks before or 48 hours after administration of RELENZA, unless medically indicated. The concern about possible interference arises from the potential for antiviral drugs to inhibit replication of live vaccine virus.

Trivalent inactivated influenza vaccine can be administered at any time relative to use of RELENZA [*see Clinical Pharmacology (12.4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of zanamivir in pregnant women. Zanamivir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Embryo/fetal development studies were conducted in rats (dosed from days 6 to 15 of pregnancy) and rabbits (dosed from days 7 to 19 of pregnancy) using the same IV doses (1, 9, and 90 mg/kg/day). Pre- and post-natal developmental studies were performed in rats (dosed from day 16 of pregnancy until litter day 21 to 23). No malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because of insufficient blood sampling timepoints in rat and rabbit reproductive toxicity studies, AUC values were not available. In a subchronic study in rats at the 90 mg/kg/day IV dose, the AUC values were greater than 300 times the human exposure at the proposed clinical dose.

An additional embryo/fetal study, in a different strain of rat, was conducted using subcutaneous administration of zanamivir, 3 times daily, at doses of 1, 9, or 80 mg/kg during days 7 to 17 of pregnancy. There was an increase in the incidence rates of a variety of minor skeleton alterations and variants in the exposed offspring in this study. Based on AUC measurements, the 80 mg/kg dose produced an exposure greater than 1,000 times the human exposure at the proposed clinical dose. However, in most instances, the individual incidence rate of each skeletal alteration or variant remained within the background rates of the historical occurrence in the strain studied.

Zanamivir has been shown to cross the placenta in rats and rabbits. In these animals, fetal blood concentrations of zanamivir were significantly lower than zanamivir concentrations in the maternal blood.

8.3 Nursing Mothers

Studies in rats have demonstrated that zanamivir is excreted in milk. However, nursing mothers should be instructed that it is not known whether zanamivir is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RELENZA is administered to a nursing mother.

8.4 Pediatric Use

Treatment of Influenza: Safety and effectiveness of RELENZA for treatment of influenza have not been studied in children. Adolescents were included in the three principal Phase III adult treatment studies. In these studies, 67 patients were 12 to 16 years of age. No definite differences in safety and efficacy were observed between these adolescent patients and young adults.

In a Phase I study of 16 children ages 6 to 12 years with signs and symptoms of respiratory disease, 4 did not produce measurable PIFR on only 1 of 2 inhalations. Neither of two 6-year-olds and one of two 7-year-olds produced measurable PIFR. Overall, 8 of the 16 children (including all those under 8 years old) either did not produce measurable inspiratory flow through the DISKHALER or produced peak inspiratory flow rates below the 60 L/min considered optimal for the device under standardized in vitro testing; lack of measurable flow rate was related to low or undetectable serum concentrations [*see Clinical Pharmacology (12.3), Clinical Studies (14.1)*]. Prescribers should carefully evaluate the ability of young children to use the delivery system if prescription of RELENZA is considered.

Prophylaxis of Influenza: The safety and effectiveness of RELENZA for prophylaxis of influenza have been studied in 4 Phase III studies where 273 children 5 to 11 years of age and 239 adolescents 12 to 16 years of age received RELENZA. No differences in safety and effectiveness were observed between pediatric and adult subjects [*see Clinical Studies (14.2)*].

8.5 Geriatric Use

Of the total number of patients in 6 clinical studies of RELENZA for treatment of influenza, 59 patients were 65 years of age and older, while 24 patients were 75 years of age and older. Of the total number of patients in 4 clinical studies of RELENZA for prophylaxis of influenza in households and community settings, 954 patients were 65 years of age and older, while 347 patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients may need assistance with use of the device.

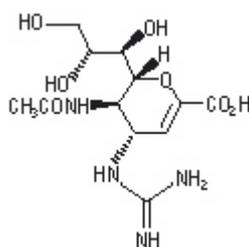
In 2 additional studies of RELENZA for prophylaxis of influenza in the nursing home setting, efficacy was not demonstrated [*see Indications and Usage (1.3)*].

10 OVERDOSAGE

There have been no reports of overdosage from administration of RELENZA.

11 DESCRIPTION

The active component of RELENZA is zanamivir. The chemical name of zanamivir is 5-(acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid. It has a molecular formula of $C_{12}H_{20}N_4O_7$ and a molecular weight of 332.3. It has the following structural formula:



Zanamivir is a white to off-white powder for oral inhalation with a solubility of approximately 18 mg/mL in water at 20°C.

RELENZA is for administration to the respiratory tract by oral inhalation only. Each RELENZA ROTADISK contains 4 regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose (which contains milk proteins). The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the DISKHALER. After a RELENZA ROTADISK is loaded into the DISKHALER, a blister that contains medication is pierced and the zanamivir is dispersed into the air stream created when the patient inhales through the mouthpiece. The amount of drug delivered to the respiratory tract will depend on patient factors such as inspiratory flow. Under standardized in vitro testing, RELENZA ROTADISK delivers 4 mg of zanamivir from the DISKHALER device when tested at a pressure drop of 3 kPa (corresponding to a flow rate of about 62 to 65 L/min) for 3 seconds.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zanamivir is an antiviral drug [see *Clinical Pharmacology* (12.4)].

12.3 Pharmacokinetics

Absorption and Bioavailability: Pharmacokinetic studies of orally inhaled zanamivir indicate that approximately 4% to 17% of the inhaled dose is systemically absorbed. The peak serum concentrations ranged from 17 to 142 ng/mL within 1 to 2 hours following a 10 mg dose. The area under the serum concentration versus time curve (AUC_{∞}) ranged from 111 to 1,364 ng•hr/mL.

Distribution: Zanamivir has limited plasma protein binding (<10%).

Metabolism: Zanamivir is renally excreted as unchanged drug. No metabolites have been detected in humans.

Elimination: The serum half-life of zanamivir following administration by oral inhalation ranges from 2.5 to 5.1 hours. It is excreted unchanged in the urine with excretion of a single dose completed within 24 hours. Total clearance ranges from 2.5 to 10.9 L/hr. Unabsorbed drug is excreted in the feces.

Impaired Hepatic Function: The pharmacokinetics of zanamivir have not been studied in patients with impaired hepatic function.

Impaired Renal Function: After a single intravenous dose of 4 mg or 2 mg of zanamivir in volunteers with mild/moderate or severe renal impairment, respectively, significant decreases in renal clearance (and hence total clearance: normals 5.3 L/hr, mild/moderate 2.7 L/hr, and severe 0.8 L/hr; median values) and significant increases in half-life (normals 3.1 hr, mild/moderate 4.7 hr, and severe 18.5 hr; median values) and systemic exposure were observed. Safety and efficacy have not been documented in the presence of severe renal insufficiency. Due to the low systemic bioavailability of zanamivir following oral inhalation, no dosage adjustments are necessary in patients with renal impairment. However, the potential for drug accumulation should be considered.

Pediatric Patients: The pharmacokinetics of zanamivir were evaluated in pediatric patients with signs and symptoms of respiratory illness. Sixteen patients, 6 to 12 years of age, received a single dose of 10 mg zanamivir dry powder via DISKHALER. Five patients had either undetectable zanamivir serum concentrations or had low drug concentrations (8.32 to 10.38 ng/mL) that were not detectable after 1.5 hours. Eleven patients had C_{max} median values of 43 ng/mL (range 15 to 74) and AUC_{∞} median values of 167 ng•hr/mL (range 58 to 279). Low or undetectable serum concentrations were related to lack of measurable PIFR in individual patients [*see Use in Specific Populations (8.4), Clinical Studies (14.1)*].

Geriatric Patients: The pharmacokinetics of zanamivir have not been studied in patients over 65 years of age [*see Use in Specific Populations (8.5)*].

Gender, Race, and Weight: In a population pharmacokinetic analysis in patient studies, no clinically significant differences in serum concentrations and/or pharmacokinetic parameters (V/F , CL/F , k_a , AUC_{0-3} , C_{max} , T_{max} , CL_r , and % excreted in urine) were observed when demographic variables (gender, age, race, and weight) and indices of infection (laboratory evidence of infection, overall symptoms, symptoms of upper respiratory illness, and viral titers) were considered. There were no significant correlations between measures of systemic exposure and safety parameters.

12.4 Microbiology

Mechanism of Action: Zanamivir is an inhibitor of influenza virus neuraminidase affecting release of viral particles.

Antiviral Activity: The antiviral activity of zanamivir against laboratory and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of zanamivir required for inhibition of influenza virus were highly variable depending on the assay method used and virus isolate tested. The 50% and 90% effective concentrations (EC_{50} and EC_{90}) of zanamivir were in the range of 0.005 to 16.0 μ M and 0.05 to >100 μ M, respectively (1 μ M = 0.33 mcg/mL). The relationship

between the cell culture inhibition of influenza virus by zanamivir and the inhibition of influenza virus replication in humans has not been established.

Resistance: Influenza viruses with reduced susceptibility to zanamivir have been selected in cell culture by multiple passages of the virus in the presence of increasing concentrations of the drug. Genetic analysis of these viruses showed that the reduced susceptibility in cell culture to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both. Resistance mutations selected in cell culture which result in neuraminidase amino acid substitutions include E119G/A/D and R292K. Mutations selected in cell culture in hemagglutinin include: K68R, G75E, E114K, N145S, S165N, S186F, N199S, and K222T.

In an immunocompromised patient infected with influenza B virus, a variant virus emerged after treatment with an investigational nebulized solution of zanamivir for 2 weeks. Analysis of this variant showed a hemagglutinin substitution (T198I) which resulted in a reduced affinity for human cell receptors, and a substitution in the neuraminidase active site (R152K) which reduced the enzyme's activity to zanamivir by 1,000-fold. Insufficient information is available to characterize the risk of emergence of zanamivir resistance in clinical use.

Cross-Resistance: Cross-resistance has been observed between some zanamivir-resistant and some oseltamivir-resistant influenza virus mutants generated in cell culture. However, some of the in cell culture zanamivir-induced resistance mutations, E119G/A/D and R292K, occurred at the same neuraminidase amino acid positions as in the clinical isolates resistant to oseltamivir, E119V and R292K. No studies have been performed to assess risk of emergence of cross-resistance during clinical use.

Influenza Vaccine Interaction Study: An interaction study (n = 138) was conducted to evaluate the effects of zanamivir (10 mg once daily) on the serological response to a single dose of trivalent inactivated influenza vaccine, as measured by hemagglutination inhibition titers. There was no difference in hemagglutination inhibition antibody titers at 2 weeks and 4 weeks after vaccine administration between zanamivir and placebo recipients.

Influenza Challenge Studies: Antiviral activity of zanamivir was supported for infection with influenza A virus, and to a more limited extent for infection with influenza B virus, by Phase I studies in volunteers who received intranasal inoculations of challenge strains of influenza virus, and received an intranasal formulation of zanamivir or placebo starting before or shortly after viral inoculation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In 2-year carcinogenicity studies conducted in rats and mice using a powder formulation administered through inhalation, zanamivir induced no statistically significant increases in tumors over controls. The maximum daily exposures in rats and mice were approximately 23 to 25 and 20 to 22 times, respectively, greater than those in humans at the proposed clinical dose based on AUC comparisons.

Mutagenesis: Zanamivir was not mutagenic in in vitro and in vivo genotoxicity assays which included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in mouse lymphoma, chromosomal aberration assays in human peripheral blood lymphocytes, and the in vivo mouse bone marrow micronucleus assay.

Impairment of Fertility: The effects of zanamivir on fertility and general reproductive performance were investigated in male (dosed for 10 weeks prior to mating, and throughout mating, gestation/lactation, and shortly after weaning) and female rats (dosed for 3 weeks prior to mating through Day 19 of pregnancy, or Day 21 post partum) at IV doses 1, 9, and 90 mg/kg/day. Zanamivir did not impair mating or fertility of male or female rats, and did not affect the sperm of treated male rats. The reproductive performance of the F1 generation born to female rats given zanamivir was not affected. Based on a subchronic study in rats at a 90 mg/kg/day IV dose, AUC values ranged between 142 and 199 mcg•hr/mL (>300 times the human exposure at the proposed clinical dose).

14 CLINICAL STUDIES

14.1 Treatment of Influenza

Adults and Adolescents: The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in the treatment of influenza has been evaluated in placebo-controlled studies conducted in North America, the Southern Hemisphere, and Europe during their respective influenza seasons. The magnitude of treatment effect varied between studies, with possible relationships to population-related factors including amount of symptomatic relief medication used.

Populations Studied: The principal Phase III studies enrolled 1,588 patients ages 12 years and older (median age 34 years, 49% male, 91% Caucasian), with uncomplicated influenza-like illness within 2 days of symptom onset. Influenza was confirmed by culture, hemagglutination inhibition antibodies, or investigational direct tests. Of 1,164 patients with confirmed influenza, 89% had influenza A and 11% had influenza B. These studies served as the principal basis for efficacy evaluation, with more limited Phase II studies providing supporting information where necessary. Following randomization to either zanamivir or placebo (inhaled lactose vehicle), all patients received instruction and supervision by a healthcare professional for the initial dose.

Principal Results: The definition of time to improvement in major symptoms of influenza included no fever and self-assessment of “none” or “mild” for headache, myalgia, cough, and sore throat. A Phase II and a Phase III study conducted in North America (total of over 600 influenza-positive patients) suggested up to 1 day of shortening of median time to this defined improvement in symptoms in patients receiving zanamivir compared with placebo, although statistical significance was not reached in either of these studies. In a study conducted in the Southern Hemisphere (321 influenza-positive patients), a 1.5-day difference in median time to symptom improvement was observed. Additional evidence of efficacy was provided by the European study.

Other Findings: There was no consistent difference in treatment effect in patients with influenza A compared with influenza B; however, these trials enrolled

smaller numbers of patients with influenza B and thus provided less evidence in support of efficacy in influenza B.

In general, patients with lower temperature (e.g., 38.2°C or less) or investigator-rated as having less severe symptoms at entry derived less benefit from therapy.

No consistent treatment effect was demonstrated in patients with underlying chronic medical conditions, including respiratory or cardiovascular disease [*see Warnings and Precautions (5.3)*].

No consistent differences in rate of development of complications were observed between treatment groups.

Some fluctuation of symptoms was observed after the primary study endpoint in both treatment groups.

Pediatric Patients: The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in the treatment of influenza in pediatric patients has been evaluated in a placebo-controlled study conducted in North America and Europe, enrolling 471 patients, ages 5 to 12 years (55% male, 90% Caucasian), within 36 hours of symptom onset. Of 346 patients with confirmed influenza, 65% had influenza A and 35% had influenza B. The definition of time to improvement included no fever and parental assessment of no or mild cough and absent/minimal muscle and joint aches or pains, sore throat, chills/feverishness, and headache. Median time to symptom improvement was 1 day shorter in patients receiving zanamivir compared with placebo. No consistent differences in rate of development of complications were observed between treatment groups. Some fluctuation of symptoms was observed after the primary study endpoint in both treatment groups.

Although this study was designed to enroll children ages 5 to 12 years, the product is indicated only for children 7 years of age and older. This evaluation is based on the combination of lower estimates of treatment effect in 5- and 6-year-olds compared with the overall study population, and evidence of inadequate inhalation through the DISKHALER in a pharmacokinetic study [*see Use in Specific Populations (8.4), Clinical Pharmacology (12.3)*].

14.2 Prophylaxis of Influenza

The efficacy of RELENZA in preventing naturally occurring influenza illness has been demonstrated in 2 post-exposure prophylaxis studies in households and 2 seasonal prophylaxis studies during community outbreaks of influenza. The primary efficacy endpoint in these studies was the incidence of symptomatic, laboratory-confirmed influenza, defined as the presence of 2 or more of the following symptoms: oral temperature $\geq 100^{\circ}\text{F}/37.8^{\circ}\text{C}$ or feverishness, cough, headache, sore throat, and myalgia; and laboratory confirmation of influenza A or B by culture, PCR, or seroconversion (defined as a 4-fold increase in convalescent antibody titer from baseline).

Household Prophylaxis Studies: Two studies assessed post-exposure prophylaxis in household contacts of an index case. 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 RELENZA 10 mg inhaled twice daily for 5 days or inhaled placebo twice daily for 5 days. In this study, the proportion of households with at least 1 new case of symptomatic laboratory-confirmed influenza was reduced from 19.0% (32 of 168 households) for the placebo group to 4.1% (7 of 169 households) for the group receiving RELENZA.

In the second study, index cases were not treated. The incidence of symptomatic laboratory-confirmed influenza was reduced from 19.0% (46 of 242 households) for the placebo group to 4.1% (10 of 245 households) for the group receiving RELENZA.

Seasonal Prophylaxis Studies: Two seasonal prophylaxis studies assessed RELENZA 10 mg inhaled once daily versus placebo inhaled once daily for 28 days during community outbreaks. The first study enrolled subjects 18 years of age or greater (mean age 29 years) from 2 university communities. The majority of subjects were unvaccinated (86%). In this study, the incidence of symptomatic laboratory-confirmed influenza was reduced from 6.1% (34 of 554) for the placebo group to 2.0% (11 of 553) for the group receiving RELENZA.

The second seasonal prophylaxis study enrolled subjects 12 to 94 years of age (mean age 60 years) with 56% of them older than 65 years of age. Sixty-seven percent of the subjects were vaccinated. In this study, the incidence of symptomatic laboratory-confirmed influenza was reduced from 1.4% (23 of 1,685) for the placebo group to 0.2% (4 of 1,678) for the group receiving RELENZA.

16 HOW SUPPLIED/STORAGE AND HANDLING

RELENZA is supplied in a circular double-foil pack (a ROTADISK) containing 4 blisters of the drug. Five ROTADISKS are packaged in a white polypropylene tube. The tube is packaged in a carton with 1 blue and gray DISKHALER inhalation device (NDC 0173-0681-01).

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature). Keep out of reach of children. Do not puncture any RELENZA ROTADISK blister until taking a dose using the DISKHALER.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.5).

17.1 Bronchospasm

Patients should be advised of the risk of bronchospasm, especially in the setting of underlying airways disease, and should stop RELENZA and contact their physician if they experience increased respiratory symptoms during treatment such as worsening wheezing, shortness of breath, or other signs or symptoms of bronchospasm [see Warnings and Precautions (5.1)]. If a decision is made to prescribe RELENZA for a patient with asthma or chronic obstructive pulmonary disease, the patient should be made aware of the risks and should have a fast-acting bronchodilator available.

17.2 Concomitant Bronchodilator Use

Patients scheduled to take inhaled bronchodilators at the same time as RELENZA should be advised to use their bronchodilators before taking RELENZA.

17.3 Instructions for Use

Patients should be instructed in use of the delivery system. Instructions should include a demonstration whenever possible. For the proper use of RELENZA, the patient should read and follow carefully the accompanying Patient Instructions for Use.

If RELENZA is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional [see *Dosage and Administration (2.1)*].

17.4 Risk of Influenza Transmission to Others

Patients should be advised that the use of RELENZA for treatment of influenza has not been shown to reduce the risk of transmission of influenza to others.

17.5 FDA-Approved Patient Labeling and Instructions for Use

See separate leaflet.

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APPENDIX B: Search Terms

Appendix

List of MedDRA High Level Terms

Soc	High level terms
07-psych	Anxiety disorders nec (incl obsessive compulsive disorder)
07-psych	Anxiety symptoms
07-psych	Fear symptoms
07-psych	Panic symptoms
07-psych	Increased physical activity levels
07-psych	Attention deficit and disruptive behavior disorders
07-psych	Specific cognitive ability disturbances
07-psych	Communications disorders
07-psych	Speech and language usage disorders
07-psych	Confusion and disorientation
07-psych	Deliria
07-psych	Delusional symptoms
07-psych	Impulse control disorders
07-psych	Affect alterations nec
07-psych	Emotional and mood disturbances nec
07-psych	Mood disorders nec
07-psych	Behavior and socialization disturbances
07-psych	Personality disorders nec
07-psych	Abnormal behavior nec
07-psych	Psychiatric symptoms nec
07-psych	Disturbances in initiating and maintaining sleep
07-psych	Dyssomnias
07-psych	Parasomnias
07-psych	Sleep disorders nec
07-psych	Suicidal and self-injurious behavior
08-nerv	Encephalitis nec
08-nerv	Traumatic central nervous system hemorrhages
08-nerv	Encephalopathies nec
08-nerv	Memory loss (excl dementia)
08-nerv	Mental impairment (excl memory loss and dementia)
08-nerv	Disturbances in consciousness nec
08-nerv	Speech and language abnormalities
08-nerv	Generalized tonic-clonic seizures
08-nerv	Seizures and seizure disorders nec
08-nerv	Abnormal sleep related events
24-inj&p	Non-site specific injuries nec Including: accident, accident at home, Fall, injury; road traffic accident; self mutilation

NEUROPSYCHIATRIC SEARCH CRITERIA

This search used a combination of the following 51 MedDRA HLT selected from the Psychiatric Disorders (SOC), Nervous System Disorders (SOC), and Injury, Poisoning and Procedural Complications (SOC).

- **SOC** *Psychiatric Disorders*
 - **HLGT** **Anxiety disorders and symptoms**
 - 1. **HLT** **Anxiety disorders NEC (incl obsessive compulsive disorder)**
 - 2. **HLT** **Anxiety symptoms**
 - 3. **HLT** **Fear symptoms**
 - 4. **HLT** **Panic symptoms**
 - **HLGT** **Changes in physical activity**
 - 5. **HLT** **Increased physical activity levels**
 - **HLGT** **Cognitive and attention disorders and disturbances**
 - 6. **HLT** **Attention deficit and disruptive behaviour disorders**
 - 7. **HLT** **Specific cognitive ability disturbances**
 - **HLGT** **Communication disorders and disturbances**
 - 8. **HLT** **Communications disorders**
 - 9. **HLT** **Speech and language usage disturbances**
 - **HLGT** **Deliria (incl confusion)**
 - 10. **HLT** **Confusion and disorientation**
 - 11. **HLT** **Deliria**
 - **HLGT** **Depressed mood disorders and disturbances**
 - 12. **HLT** **Mood alterations with depressive symptoms**
 - **HLGT** **Disturbances in thinking and perception**
 - 13. **HLT** **Delusional symptoms**
 - 14. **HLT** **Perception disturbances**
 - 15. **HLT** **Thinking disturbances**
 - **HLGT** **Impulse control disorders NEC**
 - 16. **HLT** **Impulse control disorders**
 - **HLGT** **Mood disorders and disturbances NEC**
 - 17. **HLT** **Affect alterations NEC**
 - 18. **HLT** **Emotional and mood disturbances NEC**
 - 19. **HLT** **Mood disorders NEC**
 - **HLGT** **Personality disorders and disturbances in behaviour**
 - 20. **HLT** **Behaviour and socialisation disturbances**
 - 21. **HLT** **Personality disorders NEC**
 - **HLGT** **Psychiatric and behavioural symptoms NEC**
 - 22. **HLT** **Abnormal behaviour NEC**
 - 23. **HLT** **Psychiatric symptoms NEC**
 - **HLGT** **Sleep disorders and disturbances**
 - 24. **HLT** **Disturbances in initiating and maintaining sleep**
 - 25. **HLT** **Dyssomnias**
 - 26. **HLT** **Parasomnias**
 - 27. **HLT** **Sleep disorders NEC**

- 28. HLT Sleep disorders due to general medical condition
- HLGT Suicidal and self-injurious behaviours NEC
- 29. HLT Suicidal and self-injurious behaviour
- SOC *Nervous system disorders*
 - HLGT Central nervous system infections and inflammations
 - 30. HLT Encephalitis NEC
 - 31. HLT Encephalitis of viral origin
 - a. HLGT Central nervous system vascular disorders
 - 32. HLT Traumatic central nervous system haemorrhages
 - 33. HLT Central nervous system vascular disorders
 - HLGT Encephalopathies
 - 34. HLT Encephalopathies NEC
 - 35. HLT Encephalopathies toxic and metabolic
 - HLGT Mental impairment disorders
 - 36. HLT Memory loss (excl dementia)
 - 37. HLT Mental impairment (excl dementia and memory loss)
 - HLGT Movement disorders (incl Parkinsonism)
 - 48. HLT Paralysis and paresis (excl cranial nerve)
 - HLGT Neurological disorders NEC
 - 39. HLT Disturbances in consciousness NEC
 - 40. HLT Speech and language abnormalities
 - 41. HLT Coma states
 - 42. HLT Cortical dysfunction NEC
 - HLGT Neurological disorders of the eye
 - 43. HLT *Neurologic visual problems NEC*
 - HLGT Seizures (incl subtypes)
 - 44. HLT Generalised tonic-clonic seizures
 - 45. HLT Seizures and seizure disorders NEC
 - 46. HLT Absence seizures
 - 47. HLT Partial complex seizures
 - HLGT Sleep disturbances (incl subtypes)
 - 48. HLT Abnormal sleep-related events
 - HLGT Structural brain disorders
 - 49. HLT Structural brain disorders NEC
- SOC *Injury, poisoning and procedural complications*
 - HLGT Injuries NEC
 - 50. HLT Non-site specific injuries NEC (including only the following 6 PT)
 - PT Accident
 - PT Accident at home
 - PT Fall
 - PT Injury
 - PT Road traffic accident
 - PT Self mutilation
 - HLGT Bone and joint injuries
 - 51. HLT Fractures and dislocations NEC

APPENDIX C: Serious Adverse Events from clinical trials corresponding to the search criteria provided by the FDA

	Case Outcome	Age	Gender	Country Of Reporter	Suspect Drugs	Events (Preferred Terms)	System Organ Classes for the Primary event reported in the case
1	Unresolved	32 Years	Male	United States	Zanamivir	Road traffic accident, Spinal fracture, Quadriplegia	Injury, poisoning and procedural complications
2	Resolved	97 Years	Female	United States	Zanamivir	Fall, Abdominal pain, Cholelithiasis, Hypokalaemia, Lymphopenia, Mean cell volume increased, Red blood cells urine positive, Hiatus hernia, Urinary tract infection, Oral intake reduced, Dehydration, Excoriation	Injury, poisoning and procedural complications
3	Fatal	23 Years	Female	United Kingdom	Zanamivir	Brain herniation, Mechanical ventilation	Injury, poisoning and procedural complications
4	Resolved	68 Years	Female	United States	Zanamivir	Paralysis, Headache, Balance disorder, Malaise, Diplopia	Nervous system disorders
5	Resolved	75 Years	Female	United States	Zanamivir	Transient ischaemic attack, Hypoaesthesia, Hypoaesthesia facial, Carotid artery stenosis	Nervous system disorders
6	Resolved	36 Years	Female	Canada	Zanamivir	Bipolar disorder, Suicide attempt, Overdose, Somnolence, Confusional state	Psychiatric disorders
7	Resolved	85 Years	Male	United States	Zanamivir	Dehydration, Mental status changes, Headache, Depressed level of consciousness	Metabolism and nutrition disorders
8	Resolved	62 Years	Male	United States	Zanamivir	Cardiac failure congestive, Dyspnoea, Cough, Oedema peripheral, Orthopnoea, Cyanosis, Anxiety, Hyperhidrosis, Weight increased, Joint swelling	Cardiac disorders

9	Fatal	83 Years	Male	United States	Zanamivir	Influenza, Lobar pneumonia, Dehydration, Productive cough, Oxygen saturation decreased, Oral intake reduced, Confusional state, Skin discolouration, Respiratory disorder	Infections and infestations
10	Resolved	7 Years	Male	United States	Zanamivir	Influenza like illness, Gastroenteritis, Cough, Abnormal behaviour, Anorexia, Vomiting, Fatigue, Micturition frequency decreased, Body temperature increased, Otitis media, Beta haemolytic streptococcal infection, Pneumonitis, Pneumonia, Malaise	General disorders and administration site conditions
11	Fatal	19 Days	Female	United Kingdom	Zanamivir	Pneumonia influenzal, Bradycardia, Oxygen saturation decreased, Staphylococcal infection, Immunodeficiency, Condition aggravated, Lung disorder, Atrial septal defect, Portal shunt, Cerebral atrophy, Head deformity	Infections and infestations
12	Resolved	80 Years	Male	Japan	Zanamivir	Temporal arteritis, Headache, Myalgia, Pyrexia	Vascular disorders