

Pediatric Advisory Committee Meeting: Zanamivir for Inhalation

**GlaxoSmithKline
27 November 2007**

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Summary of Neuropsychiatric Safety Analysis

- **Clinical Development Program (1993 start) through Post-Registration: No signal for zanamivir and neuropsychiatric adverse events**
 - Routine pharmacovigilance and monitoring of clinical trials and post-marketing reports
- **2004 – 2005: Reports of neuropsychiatric events associated with oseltamivir from Japan triggered more thorough review**
 - Completed November 2005
 - Included: Clinical Trials Data (Registrational and Japanese studies) and post-marketing reports
 - Conclusion: No association between zanamivir and neuropsychiatric events
 - Action: Continued surveillance for neuropsychiatric events

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Summary of Neuropsychiatric Safety Analysis

- **Spring 2007: Spike in neuropsychiatric event reports in Japan prompted further analysis including more recent data**
 - FDA DAVP also requested a safety summary
 - Completed October 2007
 - Included: Adverse event data from the 2006 - 2007 influenza season
 - Conclusion: No association between zanamivir and neuropsychiatric events
 - Action: Continued surveillance for neuropsychiatric events

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Conclusion of Safety Analysis

- **Thorough review and analysis of all information available on zanamivir and neuropsychiatric events was performed**
- **Zanamivir does not demonstrate evidence for a causal role in neuropsychiatric events during the treatment or prophylaxis of influenza infection**
- **No revision or update is warranted for the Relenza US Prescribing Information**

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Safety Analysis: Components

- Pre-clinical studies
- Pharmacokinetics studies of zanamivir
- Integrated clinical trials safety database
- Surveillance in Drug Utilization Investigations
- Epidemiology of influenza associated neuropsychiatric manifestations
- Published literature for zanamivir
- Assessment of reports from the GSK Safety Database
 - Spontaneous reports, post-marketing surveillance reports, and unblinded SAEs from clinical trials

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Pre-Clinical Studies

- Multiple animal toxicology studies performed
 - Rats, mice, rabbits and dogs
 - Inhalation, oral and intravenous administration
- Intravenous: Rat
 - 14-day continuous intravenous infusion studies at the maximum achievable doses
 - Rat systemic no observed adverse effect level (NOAEL) = 660 $\mu\text{g}\cdot\text{hr}/\text{ml}$ (432 mg/kg/day)
 - Human systemic exposure following an inhaled dose of 10 mg BID in humans (AUC 0.49 $\mu\text{g}\cdot\text{hr}/\text{ml}$)
 - Rat NOAEL is 1346 fold higher than typical human plasma exposure
- No treatment related signs indicating a zanamivir effect on behavior

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Pharmacokinetics

- **Human: zanamivir deposition after inhalation**
 - Oropharynx (77.6%)
 - Lungs (13.2%)
 - Systemic exposure (4-17%)
 - Poor oral bioavailability
 - CNS exposure
 - No data available for inhaled or intravenous routes of administration
- **Whole body autoradiography**
 - Rats (intravenous administration of 10mg)
 - Lowest or no exposure in the brain
- **Compound Attributes**
 - Highly polar
 - Substantial penetration of blood brain barrier not expected

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Pharmacokinetics

- **Estimated human CNS exposure to zanamivir is low to none due to:**
 - Poor oral bioavailability
 - Preclinical evidence of minimal CNS exposure after IV administration
 - Unlikely BBB penetration
- **Inhaled zanamivir unlikely to result in a direct toxic effect within the CNS**

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Clinical Trials: Pediatric Safety

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
	Prophylaxis: 10mg BID QD for 10 days	132	145
NAI30031	Prophylaxis: 10mg BID QD for 10 days	188	182
Total		787	735

Conducted 1998 - 2001

- **Four Phase III studies with children (5 – 12 years old)**
 - Pediatric AEs similar to Adult AEs
 - Frequency of AEs and SAEs similar to placebo
 - No effect on clinical chemistry or hematology
 - No deaths reported

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Clinical Trials: Review for Neuropsychiatric Adverse Events

- **Clinical trials outside Japan (Conducted 1993-2001):**
 - All GSK Phase II and III centrally sponsored studies
 - One pediatric study conducted in Germany by the Local GSK Company
 - Total Subjects = 14,810 subjects
 - 8033 received zanamivir
- **Clinical trials in Japan (Conducted 1993-2001):**
 - Conducted by the Local Japanese GSK Company
 - Total Subjects = 1049 subjects
 - 687 received zanamivir
- **All relevant adverse event terms in the neurology and psychiatry body systems**

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Clinical Trials: Review for Neuropsychiatric Adverse Events

- **Clinical trials outside Japan**
 - 76/14,810 (0.5%) of subjects reported a total of 83 events
 - Neurological and psychological events were similar between zanamivir and control groups (placebo or rimantidine)

	Zanamivir N=7697	Placebo N=6493
Depressive Disorders	15 (0.2%)	12 (0.2%)
Mood Disorders	9 (0.1%)	6 (<0.1%)

	Zanamivir N=336	Rimantidine N=254
Confusion	4 (1.2%)	1 (0.4%)
Depressive Disorders	3 (0.9%)	1 (0.4%)

- No increased incidence of neuropsychiatric events in zanamivir vs. control groups
- No evidence of a causal association between zanamivir and suicide or parasuicide

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Clinical Trials: Review for Neuropsychiatric Adverse Events

- **Clinical trials outside Japan**
 - Initial neuropsychiatric evaluation completed 2005
 - FDA provided specific MedDRA AE terms of interest for consideration
 - Additional analysis of AE data using updated terms
 - No evidence of a causal association between zanamivir and identified neuropsychiatric events
- **Japanese clinical trials**
 - Neurological and psychological events were similar between zanamivir and placebo groups
 - No AEs of suicide, suicidal ideation or AEs suggestive of suicidality reported

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Clinical Trials: Review of SAEs in the GSK Global Safety Database

- **Review encompassed:**
 - All SAE case reports from zanamivir clinical trials (1993 to present)
 - Subjects who had received zanamivir in GSK clinical trials
 - FDA specified list of AE terms of interest from MedDRA
- **Result: 12 cases with injury or neuropsychiatric SAEs**
 - Age: 19 days to 97 years of age
 - All but two subjects were adults, . 23 years old
 - Male : Female = 6 : 6
 - 3 injuries and 9 neuropsychiatric events
 - All were considered “unrelated to treatment” by the investigator
- **None of the SAE reports suggests a causal association with zanamivir**
 - In most cases a clear alternative cause was identified, or the temporal sequence of events was incompatible with a causal role for zanamivir

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Drug Utilization Investigations from Japan

- **Japanese post-authorization commitment for Relenza includes 3 Drug Utilization Investigations (DUIs):**
 - Treatment of influenza infection
 - Completed 2002
 - Treatment of influenza infection in children and adolescents (5-15 years old)
 - Currently ongoing
 - Investigation of emergence of drug resistant influenza viruses in children and adolescents (5-15 years old) treated with zanamivir
 - Currently ongoing
- **All DUIs reviewed for any neuropsychiatric events**

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DUI Review: Results

- **Treatment of influenza infection (completed 2002)**
 - **4456 subjects infected with influenza**
 - Including 495 children and adolescents
 - **No suicides or suicidal ideations, jumps or falls from high places were observed**
 - **Most frequent central nervous system AEs:**
 - Dysgeusia (n=3), hypogeusia (n=2) and sedation (n=1)
 - **No emerging signals for neuropsychiatric events**

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DUI Review: Results

- **Treatment of influenza infections in children and adolescents (5-15 years old)**
 - **Observation period of 2 influenza seasons**
 - December 2006 to April 2008
 - **First 250 children enrolled in the 2006-7 season**
 - **No neuropsychiatric AEs reported to date**
- **Investigation of emergence of zanamivir resistant influenza viruses in treated children and adolescents (5-15 years old)**
 - **Observations period of 3 influenza seasons**
 - December 2006 to April 2009
 - **No AEs reported in the first cohort of 100 cases to date**

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Review of the Published Literature

- **PubMed search of literature**
 - Search terms “zanamivir” or “Relenza”
- **530 citations or abstracts retrieved**
- **No relevant information to assess for association between zanamivir and neuropsychiatric AEs**

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Epidemiology of Influenza and Neuropsychiatric Events

- **Most common neurologic manifestations of influenza are encephalitis and encephalopathy**
 - Can be accompanied by seizure
- **Others include:**
 - Reye's syndrome
 - Myelitis
 - Guillain-Barre syndrome
 - Encephalomyelitis and neuritis
- **Neuropsychiatric events observed during zanamivir treatment of influenza infection may be attributable to the infection itself**

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Epidemiology of Influenza Associated Encephalopathy: Japan

- **Frequently recognized serious complication**
- **Increasing in incidence since the 1994-5 season**
 - Etiology unknown
- **Most frequently seen in Children**
 - **Case fatality rate ~ 30%**
 - Sugaya N. (2002). Influenza-associated encephalopathy in Japan. *Seminars in Pediatric Infectious Diseases* 13(2): 79-84.
 - Togashi T, Matsuzono Y, Narita M et al. (2004) Influenza-associated acute encephalopathy in Japanese children in 1994-2002. *Virus Research* 103: 75-78.
 - **Typical presentation: rapid onset of high fever, seizure, and rapidly progressive coma**
 - Delirium and hallucinations have been observed
- **Heightened clinical awareness of neuropsychiatric complications in Japan**

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Global Safety Database Review: 2006 – 2007 Influenza Season

- **GSK Global Safety Database includes:**
 - Spontaneous reports, post-marketing surveillance reports, and unblinded SAEs from clinical trials
- **Comprehensive review includes:**
 - Reports received from October 1, 2006 to June 30, 2007
 - Reports containing ≥ 1 event in the MedDRA body system organ classes (SOCs)
 - Nervous System Disorders
 - Psychiatric Disorders
 - Injury, Poisoning and Procedural Complications

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Global Safety Database Review: 2006 – 2007 Influenza Season

- **145 reports with ≥ 1 event within the “nervous system disorders” or “psychiatric disorders” retrieved**
- **All occurred after January 2007**
 - Peak March – April 2007 (88%)
 - Coincided with a Japanese MHLW alert
- **All reported from Japan**
- **All spontaneous reports**

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Global Safety Database Review: 2006 – 2007 Influenza Season

- **Of 145 spontaneous reports of neuropsychiatric events associated with zanamivir**
 - Zanamivir was prescribed for Treatment
 - Male : Female ~ 2 : 1
 - 99% children (ages 6 – 14 years old)
 - Note: in previous years, most reported events occurred in adults [median age = 44 years]
 - Most frequently reported events included:
 - Abnormal behavior, hallucination, agitation, delirium, headache, restlessness, speech disorder, dizziness, crying, and fear
- **Causality assessment without convincing evidence of association with zanamivir**

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Global Safety Database Review: 2006 – 2007 Influenza Season

Causal Assessment: Rationale for Lack Evidence for Zanamivir	2006 - 2007 Influenza Season N = 145
Time to onset inconsistent with drug effect (the event occurred prior to administration of zanamivir)	3
Event resolved with continued zanamivir use	38
Neuropsychiatric diagnosis not confirmed by or consistent with the events	2
Pyrexia / influenza more likely to have caused the event	55
Concurrent drug more likely to have caused the event (antihistamines, central acting opioids cough suppressants, beta-adrenergic stimulants, benzodiazepines, tiopidine, clarithromycin)	15
Another disease or event more likely to have caused the event (bronchospasm, mycoplasma superimposed infection, septic shock, progressive respiratory illness, cardiovascular or metabolic diseases, etc.)	3
Available information with no evidence of causal role but likely alternative cause of the events not identified	10
Insufficiently documented case	19
Total number of reports considered inconclusive for a causal association of events and zanamivir	145

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Global Safety Database Review: Registration - 2006

- **GSK Global Safety Database includes:**
 - Spontaneous reports, post-marketing surveillance reports, and unblinded SAEs from clinical trials
- **Review includes:**
 - All AE reports received by GSK through September 30, 2006
 - Reports identified through FDA specified list of AE terms of interest from MedDRA
- **119 reports with ≥ 1 event within the MedDRA terms of interest retrieved**

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Global Safety Database Review: Registration - 2006

- Of 119 spontaneous neuropsychiatric AE reports
 - Most from the USA (41%)
 - Japan (15%), Canada (13%) and Germany (11%)
 - Male : Female ~ 2 : 1
 - Age: 10 to 97 years of age
 - Median age = 44 years
 - 12% of reports were in subjects < 18 years old
 - Note: Significantly different from the 2006-2007 AE reports
 - All from Japan
 - 99% were in children and adolescents
 - Most frequently reported events included:
 - Insomnia, loss of consciousness, syncope, dizziness, anxiety, hallucination, seizure, restlessness, headache, agitation and disorientation
- Causality assessment without convincing evidence of association with zanamivir

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Global Safety Database Review: Registration - 2006

Causal Assessment: Rationale for Lack Evidence for Zanamivir	Registration - 2006 N = 119
Time to onset inconsistent with drug effect (the event occurred prior to administration of zanamivir)	6
Event resolved with continued zanamivir use	5
Neuropsychiatric diagnosis not confirmed by or consistent with the events	1
Pyrexia / influenza more likely to have caused the event	31
Concurrent drug more likely to have caused the event (antihistamines, central acting opioids cough suppressants, beta-adrenergic stimulants, benzodiazepines, tipepidine, clarithromycin)	1
Another disease or event more likely to have caused the event (bronchospasm, mycoplasma superimposed infection, septic shock, progressive respiratory illness, cardiovascular or metabolic diseases, etc.)	45
Insufficiently documented case	30
Total number of reports considered inconclusive for a causal association of events and zanamivir	119

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Summary

- **Preclinical animal studies:**
 - No treatment related clinical neuropsychiatric signs
 - Minimal penetration of zanamivir into the brain in radiolabel studies
- **Pharmacokinetic characteristics:**
 - Direct CNS toxicity mechanism unlikely
- **Clinical trials (1993 – 2001):**
 - No increased incidence of the neuropsychiatric events with zanamivir
 - No evidence of causal association with zanamivir from analysis of SAEs
- **Drug Utilization Investigations in Japan (2002/2006 – present):**
 - No neuropsychiatric events or self harm behaviors observed

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Summary

- **Neurological manifestations of influenza infection**
 - Encephalitis, encephalopathy, confusion, seizures, and psychosis
 - Influenza-associated encephalopathy more readily recognized in Japan
 - May contribute to the higher reporting of neuropsychiatric adverse events observed from Japan
- **Spring 2007: cluster of neuropsychiatric AE reports issued from Japan**
 - Coincided with Japanese MHLW alert
 - 99% of the cases were in children in the 6-14 age range
 - Most events transient
 - Many events resolved during zanamivir treatment
 - No suicides or falls/jumps reported

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Summary

- **Prior to the 2006-2007 influenza season neuropsychiatric AE reports differed:**
 - Multiple countries of origin
 - Nonspecific clinical presentation pattern
 - Adult population
- **GSK Global Safety Database Analysis**
 - Clinical development plan (start 1993) through 2006-7 influenza season
 - All clinical post-marketing SAEs and spontaneous events reported to GSK
 - No convincing evidence for a causal association between zanamivir and neuropsychiatric events
 - Seizures, loss of consciousness, suicides, depression, self harm behaviors and accidents or injuries

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Conclusion

- **The analysis of all the information available did not demonstrate evidence of a causal association between zanamivir and adverse neuropsychiatric events**
- **Relenza USPI accurately reflects the safety profile of zanamivir**
 - No revisions to the USPI or other risk minimization measures are warranted at this time

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