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
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

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
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

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 µg.hr/ml (432 mg/kg/day)
    • Human systemic exposure following an inhaled dose of 10 mg BID in humans (AUC 0.49 µg.hr/ml)
  – Rat NOAEL is 1346 fold higher than typical human plasma exposure

• No treatment related signs indicating a zanamivir effect on behavior
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

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
Clinical Trials: Pediatric Safety

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

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

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
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)

<table>
<thead>
<tr>
<th></th>
<th>Zanamivir N=7697</th>
<th>Placebo N=6493</th>
<th>Zanamivir N=336</th>
<th>Rimantidine N=254</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive Disorders</td>
<td>15 (0.2%)</td>
<td>12 (0.2%)</td>
<td>4 (1.2%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Mood Disorders</td>
<td>9 (0.1%)</td>
<td>6 (&lt;0.1%)</td>
<td>3 (0.9%)</td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>

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

• 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
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

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
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

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
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

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
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%
  - 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

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
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

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
Global Safety Database Review: 2006 – 2007 Influenza Season

Causal Assessment: Rationale for Lack Evidence for Zanamivir

| 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, tipepidine, 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 |

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
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

<table>
<thead>
<tr>
<th>Causal Assessment: Rationale for Lack Evidence for Zanamivir</th>
<th>Registration - 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to onset inconsistent with drug effect (the event occurred prior to administration of zanamivir)</td>
<td>6</td>
</tr>
<tr>
<td>Event resolved with continued zanamivir use</td>
<td>5</td>
</tr>
<tr>
<td>Neuropsychiatric diagnosis not confirmed by or consistent with the events</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia / influenza more likely to have caused the event</td>
<td>31</td>
</tr>
<tr>
<td>Concurrent drug more likely to have caused the event (antihistamines, central acting opioids cough suppressants, beta-adrenergic stimulants, benzodiazepines, tipepide, clarithromycin)</td>
<td>1</td>
</tr>
<tr>
<td>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.)</td>
<td>45</td>
</tr>
<tr>
<td>Insufficiently documented case</td>
<td>30</td>
</tr>
</tbody>
</table>

Total number of reports considered inconclusive for a causal association of events and zanamivir | 119
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

  – No neuropsychiatric events or self harm behaviors observed

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
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

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