Pediatric Safety Update for Tamiflu
Pediatric Advisory Committee Meeting
November 18, 2005

Tamiflu capsules and oral suspension (NDA 21-087 and 21-246, respectively) were granted pediatric exclusivity under BPCA on March 22, 2004. Exclusivity was based on clinical trials in children ages 1 through 12 years of age that demonstrated safety and efficacy in the treatment of influenza and on juvenile animal studies that identified a possible safety risk in younger infants. As part of BPCA, a public safety update for Tamiflu is required covering the first year of pediatric drug use after granting exclusivity.

DDRE/ODS conducted a review of the AERS database for all safety reports related to Tamiflu in patients $\leq$ 16 years in the one-year period following granting pediatric exclusivity. The ODS consult focused on review of deaths, serious AEs, and drug usage in pediatric patients reported from March 22, 2004 through April 22, 2005. During this 13 month period, 8 pediatric deaths were reported. An additional 4 deaths were identified in a later search bringing the total to 12. In these reports, deaths were attributed to sudden death (n=4), cardiopulmonary arrest (n=4), and disturbance of consciousness (with fatal fall), pneumonia, asphyxiation, and acute pancreatitis with cardiopulmonary arrest (1 each). All of the deaths were reported in pediatric patients from Japan. The level of detail in these reports was highly variable and determining the contribution of Tamiflu to the deaths was difficult.

A total of 75 unduplicated cases were identified during the safety review (69 from Japan, 5 U.S., and 1 from Canada). The 2 categories of AEs that were reported most often and were most concerning included skin/hypersensitivity reactions and neuropsychiatric events. Twelve cases of skin/hypersensitivity reactions were identified in pediatric patients including events such as Stevens-Johnson syndrome, anaphylactoid reactions, erythema multiforme, toxic epidermal necrolysis, etc. Another 32 cases of neuropsychiatric AEs were reported in the pediatric age group including cases of delirium, abnormal behavior, hallucinations, convulsions, encephalitis, etc. Eleven of 12 skin/hypersensitivity events and 31 of 32 neuropsychiatric events were reported from Japan.

Many of these reports provide insufficient detail to make clear assessments of causality, however, the pattern of the reports from Japan, particularly the neuropsychiatric events, were so unusual that ODS contacted the DAVP Review Team and OCTAP to further evaluate whether they constituted a safety risk for U.S. pediatric patients. Several possible explanations for the increased reporting of neuropsychiatric AEs from Japan were discussed including: differences in pharmacokinetic profile or drug metabolism in Japanese patients, differences in the manifestations of influenza in Japanese patients, differences in dosing or use of Tamiflu in Japan compared to the U.S. (eg. increased number of Tamiflu users in Japan giving a preview of events that have not yet occurred in the U.S.), and increased surveillance or reporting of AEs in Japan.

The DAVP Clinical Pharmacology Reviewer has confirmed that there is no evidence to suggest that Japanese patients metabolize the drug differently or achieve higher drug concentrations compared to patients in the U.S. In the Japanese product label, pediatric dosing recommendations are for 2 mg/kg administered twice daily. This is similar to the dosing in the pediatric clinical trials and was adapted in the U.S. product label into weight-based dose bands that provide a dose of 2-2.5 mg/kg twice daily. We have been assured by the sponsor, Hoffman-La Roche, Inc., that the product marketed in Japan is identical in composition to the product marketed in the U.S.

The DAVP Tamiflu Clinical Reviewer has reevaluated pediatric safety data presented in the original Tamiflu suspension NDA and analyzed data presented in a recent supplemental NDA. The datasets from the original NDA 21-246 review were re-analyzed to evaluate occurrence of neuropsychiatric AEs in more detail. Clinical AEs from body system category "neurological disorder" or "psychiatric disorder" were selected and compared between treatment groups for the primary studies. In Study WV15758 conducted in 695 otherwise healthy, ambulatory children age 1 through 12 years with presumed influenza, 14 (4%) patients in the Tamiflu group and 11 (3%) in the placebo group reported neuropsychiatric AEs. Similar clinical AEs were selected and compared in Studies WV15759/15871, conducted in children with chronic asthma. These were identical studies conducted in the northern and southern hemispheres during concurrent influenza seasons. These studies were similar in design and endpoints to Study WV15758 except that continuation of asthma medications was allowed and their use was recorded. Among 334 children with asthma, neuropsychiatric AEs were reported in 6 (4%) in the Tamiflu group and 15 (9%) in the placebo group. By far the most common neuropsychiatric AE reported in these clinical trials was headache.

In the current supplemental NDA submission, Tamiflu was evaluated as prophylaxis in the setting of potential household transmission in which an index case > 1 year of age was identified and treated with Tamiflu. All households were randomized to receive either Tamiflu prophylaxis (half the usual daily treatment dose given QD for 10 days) or treatment if they developed symptomatic flu-like illness. Consequently, some patients received no Tamiflu while others received Tamiflu QD, BID, or both, and patients receiving prophylaxis were exposed to Tamiflu for a longer course than those receiving treatment. Among the 277 households, there were a total of 534 patients 1 to 18 years of age, 181 as index cases and 353 as contacts. Among the pediatric patients, neuropsychiatric AEs were reported in 18 of 143 (13%) who received no treatment with Tamiflu, 17 of 168 (10%) who received Tamiflu QD prophylaxis, 7 of 212 (3%) who received Tamiflu BID as treatment, and none of 11 who received both some QD prophylaxis and BID treatment.

The selected neuropsychiatric AEs were integrated from all pediatric clinical trials and tabulated below. For this tabulation, all patients who received any dose of Tamiflu were combined and patients who received either placebo or no treatment were combined. The table reflects adverse events reported during both the treatment phase and follow-up periods of the studies.

Table 1: Integrated Neuropsychiatric Adverse Events in Pediatric Age Patients in Treatment and Household Prophylaxis Trials (1-18 years of age)

Clinical AE Preferred Term	Tamiflu (N=903)	Placebo/Not Treated (N=660)
Anxiety	1	0
Balance impaired NOS	0	1
Confusion	0	1
Hallucinations	2	1
Headache	35 (4%)	34 (5%)
Insomnia	2	1
Migraine	0	2
Mood swings	0	1
Nervous breakdown	1	0
Nightmares	1	4
Psychiatric disorder	1	0
Taste disturbance	0	1
Vasovagal attack	1	0
Total Number of Patients with Neuropsych AEs	44 (5%)	44 (7%)

NOS, not otherwise specified.

In the Tamiflu treatment and household prophylaxis trials there were a total of 3 serious adverse events (SAEs) related to neuropsychiatric events, none of which were considered related to Tamiflu. There was one reported neurologic SAE in the combined pediatric treatment trials, a 9 year old male patient with documented influenza B who was reported as having "viral encephalitis." This patient was receiving placebo. In the household prophylaxis study, an 18 year old male contact who received Tamiflu prophylaxis was reported as having a mild "psychological disorder" that was described as being present for 1 month before beginning study drug. Symptoms were not further described but were considered not related to study drug. This patient was not documented to have influenza. Another 17 year old female patient who was an index case with documented influenza treated with Tamiflu was reported as having a nervous breakdown. She was hospitalized for a nervous breakdown (symptoms not otherwise described) but was noted to have a history of depression.

A similar review of dermatologic reactions reported in the pediatric treatment and household prophylaxis trials was undertaken. All skin and soft tissue adverse reactions reported in patients $\leq$ 18 years of age were integrated in the table below. As previously noted, the table reflects adverse events reported during both treatment and follow-up periods of the clinical trials.

Table 2: Integrated Dermatologic and Hypersensitivity Adverse Events in Pediatric Age Patients in Treatment and Household Prophylaxis Trials (1-18 years of age)

Clinical AE Preferred Term	Tamiflu (N=903)	Placebo/Not Treated (N=660)
Dermatitis atopic	0	1
Dermatitis NOS	7	11
Dry skin	1	0
Eczema NOS	3	3
Eczema seborrheic	0	1
Erythema multiforme	1	0
Facial or periorbital edema	3	0
Localized exfoliation	1	0
Petechiae	1	0
Pruritus	1	2
Rash erythematous	0	2
Red face	0	1
Urticaria	5	2
Total Number of Patients with Derm AEs	29 (3%)	22 (3%)

NOS, not otherwise specified.

Review of the pediatric scientific literature was undertaken by the DAVP Clinical Reviewer and the OCTAP Medical Officer. While no literature reports were found of neurologic or neuropsychiatric AEs specifically related to use of Tamiflu, there are numerous reports of encephalitis and encephalopathy related to influenza. The majority of these citations over the last 10 years are from Japanese authors.

Increased reports of unusual neurologic manifestations of influenza in pediatric patients have been documented in Japan beginning in the mid-1990s. These reports were so worrisome to the Ministry of Health, Welfare, and Labor that a nationwide survey was conducted in Japan to evaluate the parameters of the syndrome. Morishima et al, reported the results of one of these surveys in the English-language literature. In their retrospective study of the 1998-99 influenza season, they investigated 217 cases of influenza-associated encephalopathy or encephalitis in pediatric patients and identified 148 that met their definition of encephalopathy with documented influenza. The typical course of these patients included the rapid onset of high fever, seizures, and altered consciousness, with rapid progression to coma within 1-2 days of initial flu-like symptoms. Although both types of influenza were represented, 88% of encephalopathy cases were associated with influenza A. Consequences of encephalopathy in their population were severe with 32% mortality and 28% “disability” in this series. A significant subset of children presenting with influenza-associated encephalopathy were described as having acute necrotizing encephalopathy (ANE), a syndrome characterized

by bilateral symmetric thalamic low density lesions on brain imaging and severe neurologic sequelae. There is no information regarding the use of antivirals in these cases but the survey was completed prior to the approval of Tamiflu.

Other reports from Japanese authors confirm ongoing increased rates of reporting encephalopathy and encephalitis. More recent reports document a decline in mortality from the mid-1990s to the present. Some reports identify specific patterns of "delirious behavior" and hallucinations in children with influenza. To date, there is no consensus as to why these syndromes of neurologic events seem to be recognized more often in Japanese children than in other populations.

Scientific reports originating from the U.S. have appeared as isolated case reports or small case series. The largest of the pediatric series was reported from Houston, Texas, during the early, severe influenza season of 2003-04. In this series, 8 pediatric patients admitted with neurologic symptoms were identified among 478 influenza cases at Texas Children's Hospital. One of these patients was noted to have neurologic sequelae consistent with the ANE syndrome. Only one of the patients in this series received Tamiflu and it was administered after the patient was admitted with neurologic symptoms.

Reviewers from ODS and DAVP have requested additional information related to these events from both Hoffman-La Roche and the Japanese regulatory authorities. We have recently received preliminary responses to our requests and this information is currently under review. As part of their response, Roche has provided copies of 2 additional studies that they commissioned to further evaluate safety in pediatric patients. Both the sponsor and the Japanese regulatory authority confirm that Roche, through its Japanese affiliate Chugai, conducted active surveillance in Japan by soliciting AE reports from 70,000 hospitals, clinics, and physician offices as part of required reporting following the approval of Tamiflu for prophylaxis of influenza. The reports submitted during this active surveillance period are included in the AERS safety database. Both Roche and the Japanese regulatory authority have confirmed that Tamiflu is used extensively among pediatric patients in Japan. Rapid testing for influenza and treatment of illness in pediatric patients are recommended as part of standard health care in Japan and are covered by national health insurance.

As compared to the neuropsychiatric AE reports that may be related, in part, to an increased recognition of influenza-associated neurologic events in Japan, the cases of skin/hypersensitivity reactions do not appear to be related to a manifestation of influenza illness or increased in a specific population. Pediatric and infectious diseases textbooks do not describe significant dermatologic manifestations of influenza. A review of the scientific literature identified rare case reports of rash associated with influenza. At least one older review of respiratory viral infections in Great Britain noted in graphic format approximately 2-8% incidence of rash with influenza but the review did not describe these findings further. With many drugs, however, skin/hypersensitivity reactions are among the most commonly recognized drug-associated adverse reactions and a variety of mechanisms have been described. These reactions have been described in various ways

in drug product labels depending on their frequency, severity, and the strength of the causal association.

Pediatric Safety Update – Expanded Reference List

Sugaya N. Influenza-associated encephalopathy in Japan. Sem in Pediatr Infect Dis 2002; 13(2):79-84.

Morishima T et al. Encephalitis and encephalopathy associated with an influenza epidemic in Japan. Clin Infect Dis 2002; 35:512-7.

Huang Y-C et al. Influenza A-associated central nervous system dysfunction in children presenting as transient visual hallucination. Pediatr Infect Dis J 2003, 22(4):366-368.

Togashi T et al. Influenza-associated acute encephalopathy in Japanese children in 1994-2002. Virus Research 2004; 103:75-8.

Okumura A et al. Delirious behavior in children with influenza: its clinical feature and EEG findings. Brain and Development 2005; 27:271-4.

Maricich S et al. Neurologic complications associated with influenza A in children during the 2003-2004 influenza season in Houston, Texas. Pediatr 2004; 114:e626-33.

Newland JG et al. Encephalitis associated with influenza B virus infection in 2 children and a review of the literature. Clin Infect Dis 2003; 36:e87-95.

Straumanis JP et al. Influenza B infection associated with encephalitis: treatment with oseltamivir. PIDJ 2002; 21(2):173-5.

Severe morbidity and mortality associated with influenza in children and young adults - Michigan, 2003. MMWR 2003; 52(35):837-40.

Update: Influenza-associated deaths reported among children aged < 18 years - United States, 2003-04 influenza season. MMWR 2004; 52(53):1286-8.

CDC-Influenza (flu) weekly report: influenza summary update 20, 2004-05 season. http://www.cdc.gov/flu/weekly/weeklyarchives2004-2005/04-05summary.htm

Silva ME et al. Acute fever and petechial rash associated with influenza A virus infection. Clin Infect Dis 1999; 29:453-4.

Holdiness MR. Adverse cutaneous reactions to influenza vaccinations and chemotherapy. International J of Dermatol 2001; 40:427-30.

Nordstrom BL et al. Skin reactions in patients with influenza treated with oseltamivir: a retrospective cohort study. Antiviral Therapy 2004; 9:187-95. (Roche-sponsored study)

米国 FDA の小児諮問委員会（Pediatric Advisory Committee）の報告

〒220-0012

横浜市西区みなとみらい 3-7-3

神奈川県警友会 けいゆう病院小児科

菅谷憲夫

電話　　045-221-8181

ファックス　045-681-9665

米国 FDA の小児諮問委員会（Pediatric Advisory Committee）は oseltamivir（タミフル）の神経精神系と皮膚過敏反応の安全性について、１１月１８日に検討結果を発表した。ただし、本委員会は日本でのタミフルの副作用報道の騒ぎにより開催されたものではなく、定例の会合であり、他に 7 品目の薬剤についても検討された。

委員会は 2004 年 3 月から 2005 年 4 月までに報告された死亡例と重篤な有害事象について検討した。１２例の死亡例があり、突然死 4 例、心肺停止 4 例、意識障害(墜落死）、肺炎、窒息、心肺停止を伴う急性膵炎が各 1 例であった。１２例は全て日本からの報告であった。報告の内容の詳細がまちまちであり、これだけでタミフルとの因果関係を決定づけることは困難であった。

他に７５例の症例報告があった（６９例が日本、5 例が米国、1 例がカナダから）。皮膚過敏反応（skin/hypersensitivity reactions）の有害事象と神経精神系の有害事象報告が多数を占めた。皮膚の有害事象は１２例あり、Stevens-Johnson syndrome、anaphylactoid reactions、 erythema multiforme、toxic epidermal necrolysis などであった。３２例は、神経精神系有害事象であり、

delirium、異常行動、 hallucinations、痙攣、脳炎などであった。皮膚免疫反応の有害事象の１２例中１１例と、神経精神系有害事象の３２例中３１例が日本からの報告であった。

　これらの報告の詳細が不十分のために因果関係は明らかではないが、特に神経精神系有害事象は通常見られないことであり、日本からの報告が多い理由として、以下の可能性が議論された。1. 日本の患者では 薬剤の metabolism が違う。2. 日本の患者ではインフルエンザの症状が違う。3. 日本ではタミフルの用量が違う。日本での使用量が多いことが見かけ上の有害事象の発生が多くみえる。 4. 日本でのサーベイランス、報告が良くされているなどである。しかし、日本の患者で薬剤の metabolism が異なるとか、血中濃度が高いことを示唆する証拠はないこと、日本での用量も米国とほぼ同じであり、製剤自体米国のものと全く同一であることが示された。

　さらにタミフルの新薬承認時と最近の追加承認までの治験のデータで、神経精神系有害事象をタミフル投与群とプラセボ群で比較した。６９５例の１歳から１２歳の小児外来患者を対象とした治験では、タミフル群で１４例(４％)、プラセボ群で１１例 (３％) の 神経精神系有害事象が報告されていた。また喘

息患児３３４例を対象とした治験では、タミフル群に６例（４％）、プラセボ群に１５例（９％）に 神経精神系有害事象が報告されていた。最も多い神経精神系の有害事象は頭痛であった。

タミフル予防投与の治験での神経精神系有害事象の頻度は、タミフル投与を受けなかった患者群では１４３例中１８例（１３％）、タミフル予防投与群で１６８例中１７例（１０％）、タミフル治療群で２１２例中７例（３％）であった。

小児諮問委員会（Pediatric Advisory Committee）報告ではこれらを表にしてまとめているが、1−１８歳の患者で、タミフル投与群９０３例中４４例(５％)で、プラセボまたは非投与群６６０例中４４例（７％）で神経精神有害事象がみられた。

治験例の中で、３例の重篤の神経精神有害事象が認められたが、タミフルとの関連はないと考えられ、９歳男子のＢ型インフルエンザ患者に脳炎が合併したが、患児はプラセボを服用していた。タミフルの予防投与中の１８歳男子がmild “psychological disorder”と報告されたが、タミフル服用１ヶ月前から発病していた。タミフル治療を受けた１７歳女子は nervous breakdown と診断され入

院したが、患者には depression の病歴があった。

同様の分析を皮膚の症状について実施し、その結果を神経精神系有害事象と同じように表にしている。それによると、タミフル投与群９０３例中２９例（３％）、プラセボまたは非投与群６６０例中２２例（３％）に皮膚過敏反応の有害事象が見られている。

さらに文献調査が実施された。タミフルによる神経精神有害事象の論文はみあたらないが、多数のインフルエンザ脳症、脳炎の論文があり、多くは最近１０年間の日本の著者によるものであった。1990 年代に調査され、報告された日本での脳症の報告の中で引用されている症状、頻度、予後などを説明している。またインフルエンザ患児の“delirious behavior”、 hallucinations の特徴に触れた報告もあることを説明している。これまで日本において神経症状の症例が他国よりも頻回に記載されているように見えるのかの理由についてはコンセンサスは得られなかった。米国からの脳症の報告も引用しているが、２００３－２００４年シーズンのテキサスのヒューストンからの報告では４７８例のインフルエンザの症例中８例の小児に見られたが１例しかタミフルを服用しておらず、また神経症状の後に服用したものであった。

インフルエンザの症状に関連した神経症状が日本で記載される頻度が高まったことに伴い報告されているとも考えられる精神神経有害事象と比べると、皮膚過敏反応はインフルエンザの症状とは関連していないようである。小児科や感染症の教科書でも、インフルエンザの著明な皮膚症状は述べられていない。文献の検索ではインフルエンザに関連し、まれに発疹が報告されている。しかしながら、皮膚過敏反応（skin/hypersensitivity reactions）は、最も普通にみられる薬剤に関連した副作用であり、様々なメカニズムが考えられ、これらは既に様々な医薬品の添付文書にも記載されている。

以上が今回の FDA の安全性調査の報告の抄訳である。