CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021246Orig1s045 and 021087Orig1s062

<u>SUMMARY REVIEW</u>

Cross-Discipline Team Leader Review

Date	December 12, 2012
From	Linda L. Lewis, M.D. Medical Team Leader Division of Antiviral Products
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	21087/S-062 21246/S-045
Applicant	Hoffman-LaRoche Inc./Genentech
Date of Submission	June 21, 2012
PDUFA Goal Date	December 21, 2012
Proprietary Name / Established (USAN) names	Tamiflu® (oseltamivir phosphate)
Dosage forms / Strength	Tablets, 75 mg Dry Powder for Oral Suspension, 6 mg/mL
Proposed Indication(s)	1. Treatment of uncomplicated acute influenza in pediatric patients 2 weeks of age and older
Recommended:	*Approval, with modifications in proposed labeling as noted*

1. Introduction

Tamiflu (oseltamivir phosphate or oseltamivir) is an ethyl ester pro-drug of the selective influenza virus neuraminidase inhibitor oseltamivir carboxylate. The compound is active against the neuraminidase of both influenza A and B. After ingestion, oseltamivir pro-drug is rapidly absorbed and converted almost completely to oseltamivir carboxylate, the active metabolite. Tamiflu is currently approved for treatment of influenza in otherwise healthy adults and pediatric patients 1 year of age and older. It is also approved in adult and pediatric patients for prophylaxis of influenza after a known exposure (post-exposure prophylaxis) for 10 days of dosing and for pre-exposure prophylaxis during a community outbreak (seasonal prophylaxis) for up to 6 weeks of dosing. At present, neither Tamiflu nor any other antiviral drug active against influenza is approved for use in pediatric patients less than 1 year of age, a patient population at increased risk of morbidity and mortality.

The current submission provides data to support the use of Tamiflu for the treatment of influenza in pediatric patients less than 1 year of age. The Applicant has submitted final study reports and datasets from two clinical trials to support extension of the treatment indication to infants 2 weeks of age and older:

- CASG114 (WP20749) – A pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir (Tamiflu) in the treatment of children less than 24 months of age with confirmed influenza Infection, and
- WP22849 – An open label, prospective pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir (Tamiflu) in the treatment of infants 0 to < 12 months of age with confirmed influenza infection.

These two trials form the basis for the FDA reviews and conclusions.

2. Background

The regulatory history of Tamiflu's development program in young infants is complex. Previously submitted juvenile rat studies of Tamiflu identified substantially increased mortality in newborn rats compared to older juvenile rats and adult rats. One study also identified markedly increased concentrations of the pro-drug, oseltamivir, in the brain tissue of the newborn animals. Concern about the potential impact of an immature blood-brain barrier in human infants resulting in toxicity led the Applicant to terminate their evaluation of Tamiflu as treatment for influenza in infants less than 1 year of age. The key juvenile rat toxicology study was initially submitted in 2002, and the results were subsequently incorporated into the Tamiflu label. However, a follow-up juvenile rat study conducted by the NIH did not confirm the earlier findings of increased levels of oseltamivir phosphate in brain tissue. The Applicant subsequently retested blood and tissue samples from the original juvenile rat study and identified a miscalculation in the brain oseltamivir levels in the original study. The new findings cast significant doubt on the theory that an immature blood-brain barrier contributed to the juvenile rat toxicity and mortality and the labeling of these findings was revised in February, 2010.

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Pediatric patients less than 2 years of age are known to be at increased risk for hospitalization when they become ill with influenza, with the highest rates in infants less than 6 months of age. Thus, the age group previously excluded from the Tamiflu indication represents a population with potentially greatest need for treatment. For this reason, NIAID/NIH initiated a carefully staged evaluation of Tamiflu for treatment of influenza under their own research IND (IND 71,826) to support potential use in this age group during an influenza pandemic. As noted above, the first step in this evaluation was repeating the juvenile animal study. Additionally, to assess safety of the treatment prior to conducting CASG114, the investigators reviewed medical records of a cohort of 180 infants less than 1 year of age who received influenza treatment "off-label" at the discretion of their health care providers. Only when this review (CASG 113 - "A retrospective chart review to assess the safety of oseltamivir (Tamiflu) compared to alternate antiviral therapy (amantadine or rimantadine) administered to children less than 12 months of age with diagnosed or suspected influenza.") failed to identify any new or worrisome safety signals in patients receiving Tamiflu did the investigators initiate CASG114 to directly assess Tamiflu treatment in young infants. CASG114 began enrolling subjects during the 2006-2007 influenza season.

CASG114 was in progress and enrolling patients at the time the pandemic 2009 H1N1 strain emerged and spread across the US and globally. Based on the available safety information at the onset of the pandemic, the protocol was amended to allow more rapid enrollment of the youngest cohorts. Interim pharmacokinetic (PK) and safety data from CASG114 were reviewed in April 2009 to support the Emergency Use Authorization (EUA) for Tamiflu which included recommendations for dosing infants less than 1 year of age. CASG114 continued to enroll patients after the EUA was issued and was closed at the end of the 2009-2010 influenza season. At the conclusion of the pandemic in June 2010, the EUA and the infant dosing recommendations expired. During this period Roche planned and subsequently initiated WP22849 in the EU to evaluate a slightly different dosing regimen in infants less than 1 year of age. This study enrolled subjects during the 2010-2011 and 2011-2012 influenza seasons.

Thus, these two clinical trials collected PK and safety data on a relatively large number of infants less than 1 year of age (N=135) receiving a range of doses of Tamiflu and using different formulations. The subjects enrolled were infected with a variety of strains of influenza spanning six influenza seasons. Data from the combined trials provided a good safety database and allowed extensive PK analyses. Neither of the trials contained a control arm and neither was designed to prove efficacy. The Applicant proposes that the current data can be used to bridge across the age ranges studied and the PK data can allow extrapolation of the efficacy observed in earlier treatment trials of both adult and pediatric patients.

3. CMC/Device

No new CMC data was presented in the current submission and a formal Chemistry Review was not performed.

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The current Tamiflu packaging includes a 10 mL oral syringe with a push-in adapter. This size oral syringe will not be appropriate for delivering the doses of Tamiflu calculated for some patients less than 1 year of age. (b) (4) To accompany the current sNDA, the Applicant has proposed a communication plan to inform clinicians and pharmacists of the need to provide the appropriate dosing device for each patient.

4. Nonclinical Pharmacology/Toxicology

The Applicant continues to evaluate potential mechanisms for reported Tamiflu toxicity. This submission contains additional rat and marmoset studies to evaluate the distribution of oseltamivir and oseltamivir carboxylate in tissues, particularly the brain.

Doses of 500 mg/kg of oseltamivir resulted in excess mortality in neonatal (7 day old) rats. The accumulated nonclinical data suggest the major factor potentially responsible for the difference in tolerance to oseltamivir between juvenile and adult rats was the higher exposures to oseltamivir in juvenile rat brain. Juvenile rats have lower esterase activity in plasma and lower renal clearance, resulting in much higher exposures to the prodrug. In addition, oseltamivir crossed the blood brain barrier more readily in 7 day old rats which resulted in higher exposures in the brain. However, rat conversion of oseltamivir to oseltamivir carboxylate in juvenile animals may not be representative of human conversion of pro-drug to active metabolite.

Oral and intravenous pharmacokinetics of oseltamivir and oseltamivir carboxylate were studied in adult and newborn marmosets, a species whose pharmacokinetic profile more closely resembles humans than do rats. The results showed that following administration of oseltamivir to neonatal marmosets, significant concentrations of oseltamivir carboxylate are present in plasma. The resulting ratios of oseltamivir to oseltamivir carboxylate are lower in neonatal marmosets than in adult animals.

Using the mean AUC from infants receiving a 3 mg/kg dose and comparing to neonatal rats, the species in which toxicity was observed, the safety margin calculated for oseltamivir toxicity is 120-fold. This margin provides reassurance for use of Tamiflu in pediatric patients 2 weeks of age and older. Safety margins calculated using comparisons of infant exposure to marmoset exposure were greater than 22,000-fold and 3,500-fold for oseltamivir and oseltamivir carboxylate, respectively.

In summary, the new information submitted contains many pharmacokinetic and distribution studies to identify a possible mechanism of action of possible neuropsychiatric toxicity and address the potential safety concern associated with the usage by infants younger than 1 year of age. For a more complete description of the nonclinical data, please see the Pharmacology/Toxicology Review submitted by Dr. Ita Yuen.

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5. Clinical Pharmacology/Biopharmaceutics

The analysis of PK data, assessment of PK/PD relationships, and development of a PK model for infants less than 1 year of age constituted a major aspect of this review. Because of widespread recommendations by the CDC for the use of Tamiflu in pediatric patients, initial concern about feasibility of enrolling a PK-intensive trial in infants, and public health interest in obtaining PK and safety data to guide use during a pandemic, the CASG investigators and the Applicant did not believe a placebo-controlled trial was appropriate or feasible in this age group. The submitted clinical trials were designed with the intent of extrapolating efficacy from adult and pediatric treatment trials by targeting oseltamivir carboxylate exposure previously shown to be safe and effective.

The initial dose selected for CASG114 was 3 mg/kg twice daily for 5 days. This dose was based on data from earlier pediatric PK studies and was expected to provide oseltamivir carboxylate AUC_{12} values between 2,660 ng*hr/mL and 7,700 ng*hr/mL. The upper limit of the target was based on the upper range of exposures observed in adults receiving 150 mg BID (twice the approved dose), a dose evaluated in Phase 3 clinical trials and found to have an acceptable safety profile but no efficacy advantage. The higher exposure was targeted as pediatric patients in this age group were expected to have higher viral replication and longer shedding and the higher exposure was considered critical to maximize antiviral effect and minimize emergence of resistance. Additional cohorts could be added in any age group if the initial cohort failed to meet the target exposure. The doses selected for evaluation in WP22849 ranged from 2 mg/kg to 3 mg/kg with lower doses tested in successively lower age groups. These doses were selected by the Applicant, based on emerging data from CASG114 and early modeling/simulation. A total of 68 subjects less than 1 year of age from CASG114 and 54 subjects from WP22849 provided PK data for these analyses (N=122). The dose range studied, quantity of samples, and age distribution of PK data available allowed development of a robust PK model.

As noted in the Clinical Pharmacology Review, subjects enrolled in CASG114 received Tamiflu for oral suspension commercially available at the time (12 mg/mL) while those enrolled in WP22849 received a pharmacy compounded formulation using Tamiflu 75 mg capsules dispersed in water (to achieve 10 mg/mL). Neither of the trials used the currently marketed 6 mg/mL Tamiflu for oral suspension. Oseltamivir is highly soluble in water and no differences across formulations have been identified.

Both the Applicant and the FDA Clinical Pharmacology team identified 3 mg/kg as an appropriate dose across the age range of 2 weeks to less than 1 year of age. No exposure-response relationship could be identified between the PK parameters AUC, C_{max} or C_{min} and the PD endpoints of time to cessation of viral shedding or time to resolution of fever. The dose recommendation is based on this dose achieving the exposure target noted to be at the upper range of those found to be safe and effective in older patients. After simulating dose regimens of both 2.5 mg/kg and 3 mg/kg, the FDA review confirmed the Applicant's selection of 3 mg/kg. Figure 1 (from Dr. Lee's Clinical Pharmacology Reviewer) displays simulated AUC of oseltamivir carboxylate after a dose of 3 mg/kg, by age cohorts for infants less than one year of age compared to observed AUC in older age groups receiving different doses of

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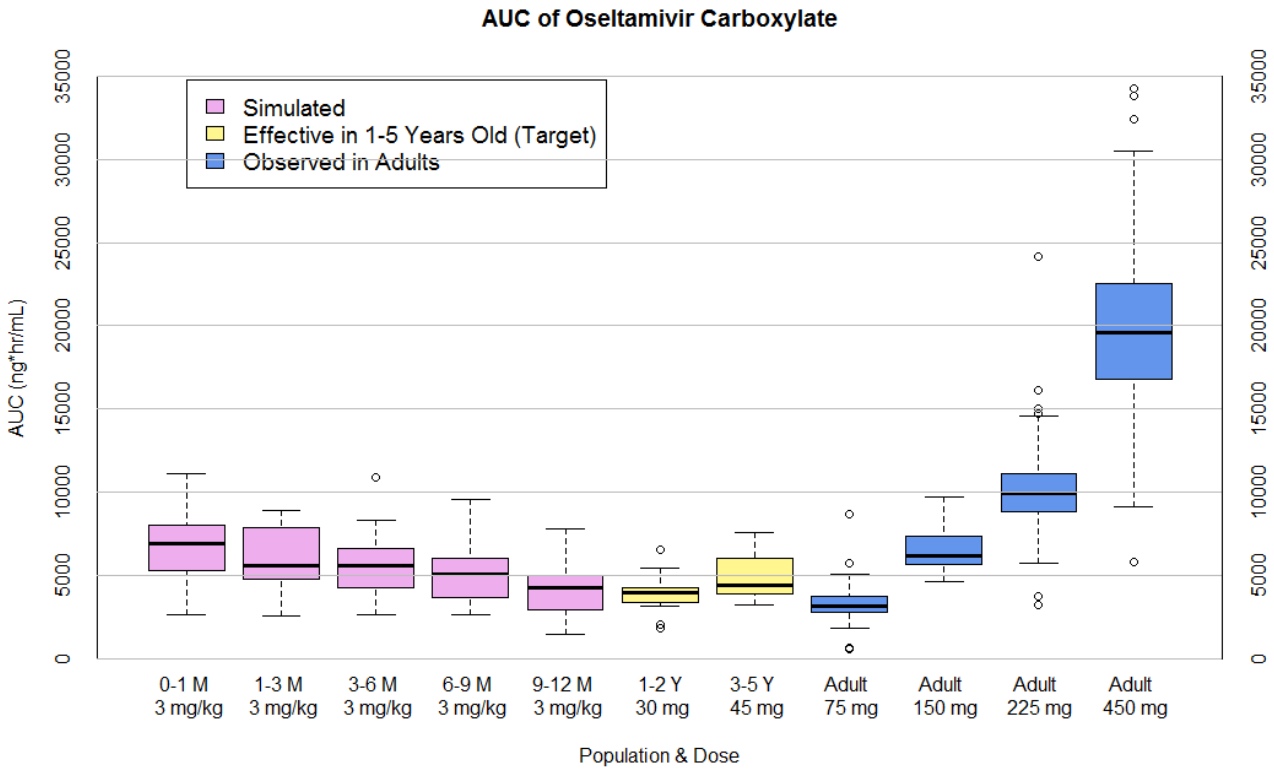
Tamiflu. The simulated AUC following 3.0 mg/kg BID falls between the exposure observed in adults following 75 mg BID and 150 mg BID. Although this dose results in exposures in the youngest cohorts that may exceed those of the 75 mg approved dose in adults, it allows fewer young infants to have subtherapeutic exposure and the safety data support use of this dose.

Figure 1: Simulated AUCs of oseltamivir carboxylate in infants 0-1 year of age following 3 mg/kg BID of Tamiflu in comparison with other populations



In summary, the PK data provided in these two trials and the modeling and simulation performed by the Applicant and confirmed by FDA reviewers support selection of 3 mg/kg BID across the age cohorts less than 1 year of age. PK/PD assessment failed to identify any exposure-response relationships for virologic or clinical resolution. For a more detailed discussion of the PK data and the modeling and simulation supporting the dose recommendation, please refer to the Clinical Pharmacology Review submitted by Drs. Jee Eun Lee and Jenny H. Zheng.

6. Clinical Microbiology

In both CASG114 and WP22849, virologic assessments included viral quantification by RT-PCR (only partial data in WP22849) and culture and analysis of genotypic and phenotypic resistance. In both trials, genotypic resistance analyses included sequencing of hemaglutinin and neuraminidase of culturable isolates and phenotypic analyses included oseltamivir

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susceptibility of first and last culturable isolates using an NAI assay. Nasopharyngeal swabs for virus isolation and testing were collected on slightly different schedules in the two trials but included four planned collections from Day 1 through Day 10 or 11.

In CASG114, 70 subjects across five age cohorts contributed to the virology and resistance analyses. In a pooled analysis by age cohorts, the median time to PCR undetectable ranged from 6 to 11 days and median time to viral culture negative ranged from 5 to 10 days. The median times to clearance of major circulating influenza strains (H1N1, H3N2, and B) ranged from 8 to 10 days by viral culture and 9 to 10 days by RT-PCR. The 0-2 month old cohort required slightly longer to become undetectable for influenza A virus than the 6-8 month old cohort. Otherwise, no statistically significant differences were identified in time to undetectable RT-PCR or culture between cohorts or virus type/subtype. The predominant circulating H1N1 prior to the pandemic was known to be resistant to Tamiflu and 6 of 8 isolates of that strain were documented to have baseline resistance. Resistance rates were about 8% (3/37) for pandemic 2009 H1N1, although techniques (i.e., population sequencing and NAI of cell culture amplified isolates) were used that tend to be biased against detection of resistant isolates. Resistance was not identified in any of the influenza B isolates although they are noted to be less susceptible to Tamiflu than influenza A.

In WP22849, an additional 57 subjects in three age cohorts contributed to the virology and resistance analyses. The median time to viral clearance across the age cohorts ranged from 5 to 6 days for influenza A and 5 to 11 days for influenza B. No differences in clearance rates according to type or subtype could be identified, but the number of subjects represented in some analyses was quite small. No baseline resistance was documented in this study as the predominant circulating strains did not include the seasonal H1N1. Treatment emergent resistance rates of at least 22% (7/32) for H1N1 and at least 10% (1/10) for H3N2 were observed. Potential emergence of a novel NA substitution, A245D, was identified in one influenza B isolate but the phenotypic assessment revealed only low-level shift from baseline susceptibility.

In summary, the virology and resistance assessments performed during these clinical trials are consistent with those observed in other trials submitted for review. Resistance rates were not markedly different in younger infants than in older infants although there was some evidence the youngest cohort in CASG114 required longer to clear virus. The analyses were limited by small numbers in some of the subgroups of interest. For a more complete description of the virology assessments conducted as part of the review of the two pediatric trials in this application, please refer to the Microbiology Review submitted by Dr. Damon Deming.

7. Clinical/Statistical- Efficacy

The two clinical trials submitted in this efficacy supplement were designed to evaluate the PK profile, safety, and tolerability of oral Tamiflu in infants less than 1 year of age (or less than 2 years in CASG114) with confirmed influenza. Investigators leading both trials considered use of a placebo group in this age group to be unethical and, thus, both trials were single-arm, open-label design. In both trials, subjects with symptoms of influenza of less than 96 hours

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duration were eligible, and influenza was confirmed within 96 hours before enrollment. Subjects were stratified into five age cohorts in CASG114 (12 to 23 months, 9 to 11 months, 6 to 8 months, 3 to 5 months, 0 to 2 months) and three age cohorts in WP22849 (91 to < 365 days, 31 to 90 days, 0 to 30 days). Tamiflu was administered twice daily for five days. The distribution of subjects across the age range included in this review and doses administered are shown in Table 1 below.

Although CASG114 enrolled subjects older than 1 year of age (12 to 23 months), the Clinical Review focused on the cohorts less than 1 year. The combined trials enrolled 126 subjects less than 1 year of age; one subject never received study drug and another one never returned for any follow-up. The initial supplement submission contained safety data from 124 subjects, 70 enrolled in CASG114 and 54 enrolled in WP22849 through the 2010-2011 influenza season. The review team became aware that enrollment in WP22849 had continued into the 2011-2012 influenza season and requested all available data from any additional subjects enrolled during that period. Data for 11 subjects enrolled in WP22849 during the 2011-2012 influenza season was subsequently submitted as an amendment and these data were integrated into the FDA Clinical Review (N=135).

Table 1: Number of Subjects Enrolled and Doses Administered by Age Groups

	I	II	III	IV	V
	≤ 1 month (≤ 30 days)	**1-3 months (31-90 days)**	**3-6 months (91-180 days)**	**6-9 months (181-270 days)**	**>9 months (≥ 271 days)**
CASG 114 (dose)	N=8 (3 mg/kg)	N=14 (3 mg/kg)	N=10 (3 mg/kg)	N=22 (3 mg/kg)	N=16 (3 or 3.5 mg/kg)
WP22849 (dose)	N=5 (2 mg/kg)	N=20 (2.5 mg/kg)	N=13 (3 mg/kg)	N=13 (3 mg/kg)	N=14 (3 mg/kg)
Totals by Age group	13	34	23	35	30

Source: Abstracted from NDA 21087/S-062 Clinical Review, T. Vargas-Kasambira

In CASG114, the protocol defined AUC target was the dose which was expected to result in AUC_{12} values for oseltamivir carboxylate between 2,600 ng.hr/mL and 7,700 ng.hr/mL. The exposure target was selected to achieve exposures between those achieved in adults receiving the approved 75 mg dose and those achieved in adults receiving 150 mg, a dose explored in Phase 3 clinical trials. The first nine subjects enrolled in each cohort received 3 mg/kg. Doses were adjusted by predetermined rules to achieve the targeted exposure (AUC_{12}). The 9-11 month and 12-23 month cohorts failed to achieve the specified AUC target and second cohorts of those ages were enrolled and received 3.5 mg/kg BID. Dose levels were not adjusted in WP22849 but subjects with continued symptoms were eligible to receive an additional five days of treatment.

In the pooled trial population 55% of subjects were male, 74% of subjects were non-Hispanic, and 79% were White/Caucasian. The mean age of the subjects at enrollment was 165 days, 76% of subjects had a gestational age over 37 weeks, and 81% had a post-conceptional age greater than or equal to 38 weeks. Thirty-nine percent of subjects were treated as outpatients while 52% were treated as non-ICU inpatients, and 9% were treated in the inpatient ICU.

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As noted in the Clinical Review submitted by Dr. Vargas-Kasambira, both of the clinical trials submitted were intended to evaluate PK and safety and were not designed to directly evaluate efficacy. Consequently, no formal statistical review was performed other than the PK/PD analysis performed by Dr. Lee. The Applicant was unable to identify any exposure-response relationships to directly support efficacy of treatment and relied on extrapolation of efficacy from adult and older pediatric patients based on bridging PK data as allowed in pediatric drug development.

8. Safety

As previously noted, both of the submitted studies were designed to evaluate safety in influenza-infected pediatric subjects less than 1 year of age receiving Tamiflu BID for five days. Subjects were evaluated for clinical adverse events (AEs) at each visit during the study period. Laboratory testing was not required as no Tamiflu-specific laboratory abnormalities have previously been identified in other clinical trials but was done on an as-indicated basis. The Applicant provided an integrated safety analysis of 124 subjects, not including the 11 subjects enrolled in WP22849 during the 2011-2012 influenza season; these 11 subjects were included in an addendum to the Clinical Study Report. The FDA safety review included 135 subjects less than 1 year of age with post-baseline data.

Overall, tolerability of Tamiflu in these studies was acceptable with 88% of subjects receiving 9 or 10 doses, considered a standard course of treatment. Nine percent of subjects received more than 10 doses of treatment, as allowed in WP22849, and 3% received fewer than 9 doses. A total of five subjects, all enrolled in CASG114, discontinued Tamiflu prematurely (i.e., received less than 8 doses); three subjects did not return for follow-up or were non-adherent, one subject's parent withdrew consent, and one subject withdrew because of a serious adverse AE. Subject #25 was a 10 month old male who developed a generalized, erythematous, pruritic rash after the first dose of Tamiflu. The rash worsened after the second dose and was accompanied by cough and difficulty breathing requiring administration of an antihistamine and oral prednisolone. The rash slowly resolved. This serious AE was considered a drug-related hypersensitivity reaction.

No deaths were reported in either of the two clinical trials. Twelve (10%) subjects were reported to have SAEs during treatment or follow-up. Only one of these events, the hypersensitivity reaction described above, was considered drug related. Eight subjects experienced on-treatment SAEs (those during treatment or within 3 days of the last dose of Tamiflu). These SAEs included events such as respiratory syncytial virus (RSV) infection in 2 subjects, orbital cellulitis, diarrhea, pyrexia, oxygen saturation decreased, and "influenza." The other four subjects' SAEs occurred during off-treatment follow-up (study days 10 to 26). Other than the hypersensitivity reaction, the SAEs represent conditions known to occur in young infants with confirmed influenza. Co-infection with other respiratory pathogens such as RSV is not uncommon in this age group. In other clinical trials, GI symptoms such as diarrhea have been reported with Tamiflu use but the reported SAE of diarrhea in WP22849 was considered unrelated to study drug and required no specific intervention.

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On-treatment AEs were relatively common in the study population. Of the 135 subjects with post-baseline data available, FDA review identified 65 (48%) with at least one reported on-treatment AE. Approximately 8% of the reported on-treatment AEs were considered at least possibly related to use of Tamiflu. Only four events were reported to be severe in intensity (hypersensitivity, RSV bronchiolitis, pyrexia, and neutropenia). The AEs reported in 1% or more of subjects are displayed in Table 2 below by MedDRA System Organ Class and AE Preferred Term. The most common AEs include vomiting and diarrhea, observed in 10% and 7%, respectively, of the subjects. These GI events have been noted in previous clinical trials of Tamiflu in other age groups. As might be expected in this younger population, diaper dermatitis was also reported in a significant proportion of subjects (7%) and could possibly be related to study drug in the setting of increased diarrhea. Co-infections with other winter seasonal viruses such as rotavirus and RSV were also reported in this age group but are unlikely to be related to use of Tamiflu. It should be noted that although nausea was also associated with Tamiflu use in the adult clinical trials, this is a subjective symptom that can not be distinguished in young pediatric patients.

Table 2: Adverse Events by System Organ Class and Preferred Term Occurring in 2 (1%) or More of Subjects - Pooled Data, CASG114 and WP22849

Body System **Preferred Term**	**CASG114 and WP22849 subjects with post-baseline safety data** **N=135**
Number of subjects with at least one AE	**65 (48%)**
Blood and Lymphatic System Disorders	**2 (1%)**
Neutropenia	2 (1%)
Eye Disorders	**3 (2%)**
Conjunctivitis	3 (2%)
Gastrointestinal Disorders	**28 (21%)**
Vomiting	14 (10%)
Diarrhea	9 (7%)
Regurgitation	3 (2%)
General Disorders and Administration Site Conditions	**7 (5%)**
Pyrexia	4 (3%)
Irritability	2 (1%)
Infections and Infestations	**16 (12%)**
RSV bronchiolitis	3 (2%)
Otitis media	3 (2%)
Oral candidiasis	2 (1%)
Rotavirus infection	3 (1%)
Metabolism and Nutrition Disorders	**2 (1%)**
Respiratory, Thoracic and Mediastinal Disorders	**3 (2%)**
Skin and Subcutaneous Tissue Disorders	**21 (16%)**
Dermatitis diaper	9 (7%)
Rash	3 (2%)
Rash macular	2 (1%)

Source: Abstracted from NDA 21087/S-062 Clinical Review, T. Vargas-Kasambira.

Since the original approval of Tamiflu in pediatric patients in 2000, postmarketing cases of unusual neuropsychiatric AEs have been reported. These events, including episodes of

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hallucinations and abnormal/dangerous behavior sometimes resulting in injury and death, were not identified in clinical trials and a causal relationship between Tamiflu and the events has not been determined. In this non-verbal, younger age group, neuropsychiatric AEs might be more difficult to identify. Events reported in the current clinical trials that might represent neuropsychiatric AEs include: irritability in two subjects, lethargy in one, and a staring episode in one. One of the events of mild irritability was considered possibly drug-related. These events are non-specific and it is not possible to determine whether they represent age-specific manifestations of the neuropsychiatric events reported in older patients or manifestations of influenza infection.

The Applicant also provided a summary of AEs in pediatric patients less than 1 year of age reported to the Roche postmarketing safety database. The Applicant identified 218 cases reporting a total of 331 AEs. Most of the postmarketing AE reports were from Japan (n=92), UK (n=43), and US (n=32). The most commonly reported AEs included: rash (n=23), vomiting (n=19), no adverse event (n=16), hypothermia (n=14), diarrhea (n=13), convulsion (n=12), and pneumonia (n=8). Nervous system disorders accounted for 16% of the 123 serious AEs reported. Fourteen deaths were reported five of which were related to respiratory events (e.g. ARDS, pneumonia) and two related to multi-organ failure. As the reported events appeared to be similar in character to postmarketing events reported in older pediatric patients, a new FDA review of postmarketing events was not performed. The Office of Surveillance and Epidemiology (OSE) conducted a thorough review of pediatric cases reported to the FDA Adverse Event Reporting System (AERS) database in May 2012 and identified no new safety signals. This review was presented and discussed at the FDA's Pediatric Advisory Committee (see Section 9).

In summary, the pattern of reported adverse events in both CASG114 and WP22849 was consistent with that reported in other treatment trials of Tamiflu and no new safety signals were identified in this younger age group. Only 5/135 subjects failed to complete a full course of Tamiflu and only one subject discontinued prematurely because of an AE (hypersensitivity reaction). In addition, no new safety signals have been identified in recent reviews of postmarketing reports. For additional details of the safety analyses for these studies, please refer to the Clinical Review submitted by Dr. Vargas-Kasambira.

9. Advisory Committee Meeting

The review and approval of this supplement did not warrant convening an Advisory Committee meeting.

As noted, OSE and DAVP presented a review of postmarketing cases from the FDA AERS database to the Pediatric Advisory Committee on May 7, 2012. This review was done as part of the routine post-approval pediatric safety reviews and was triggered by the approval of Tamiflu prophylaxis in immunocompromised patients in February 2010 that included safety data from pediatric patients. OSE staff reviewed AERS serious AE cases including those involving infants less than 1 year of age reported from June 1, 2007 to December 31, 2011 and concluded no new safety signals could be attributed to Tamiflu use in pediatric patients. After

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discussion of the review findings, the Committee agreed with the OSE recommendation to continue routine safety monitoring for Tamiflu. For details of these reviews, please refer to the OSE Review submitted by Neha Gada, Safety Evaluator, dated April 24, 2012 and the Clinical Review Memo submitted by myself dated April 19, 2012. In addition, a link to the Advisory Committee briefing documents and a transcript of the meeting are available on the FDA website at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm283814.htm

10. Pediatrics

The Applicant has had an on-going pediatric development program for Tamiflu for both treatment and prophylaxis of influenza for many years. CASG114 enrolled pediatric patients with confirmed influenza who were less than 2 years of age. WP22849 enrolled pediatric patients less than 1 year of age. Together these trials provide a reasonable safety database for the duration of dosing recommended for treatment of influenza and provide a robust PK database across the age cohorts. An adequate and well-controlled clinical trial in pediatric patients is not required if there is adequate justification for extrapolating efficacy. The use of extrapolation for pediatric studies is codified in 21 CFR 314.55(a): "Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another."

In this case, although the morbidity and mortality of influenza in young infants is greater than in older pediatric patients, the infection and resulting illness is similar in many respects: fever, respiratory symptoms, systemic symptoms, and risk for secondary bacterial infections or other complications in some patients. The previous controlled clinical trials demonstrated very similar treatment benefit across geographic and demographic factors, including age. The 1-1.5 day decrease in time to resolution of symptoms of acute influenza was remarkably similar across adult and pediatric clinical trials.

Therefore, the Review Team believes efficacy of Tamiflu in pediatric patients less than 1 year of age can be extrapolated from efficacy in adults and older pediatric patients in this setting based on the similarity of treatment responses in adult and older pediatric patients with similar oseltamivir carboxylate exposures and achieving a similar or higher exposure in infants less than 1 year of age. The clinical trials submitted provide adequate supporting safety and PK data as required.

The current supplement does not trigger additional pediatric PMRs under the provisions of the Pediatric Research Equity Act (PREA). These studies were not conducted in response to either a PREA PMR or a Written Request under the Best Pharmaceuticals for Children's Act. Roche has previously fulfilled commitments to evaluate Tamiflu in pediatric patients 1 year of

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age and older as outlined in the WR issued for Tamiflu and was granted pediatric exclusivity in March, 2004.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues raised with this application.

12. Labeling

Summaries of the PK and safety results of CASG114 and WP22849 will be incorporated into the package insert (PI). Although the exact wording of these revisions has not been finalized at the time of completing this review, the FDA has proposed the following labeling (new text underlined):

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(b) (4)

For the final agreed upon Package Insert language, refer to the CSO Review submitted by Elizabeth Thompson, Regulatory Project Manager. In addition, revisions to the Patient Package Insert were proposed by DDMAC and DMPP reviewers and forwarded to the Applicant.

13. Recommendations/Risk Benefit Assessment

I concur with the primary review team's recommendation to approve this efficacy supplement with the agreed upon revisions to the PI. Tamiflu should be approved for treatment of uncomplicated acute illness due to influenza infection in patients two weeks of age and older

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who have been symptomatic for no more than two days. Although neither of the two clinical trials was designed to demonstrate efficacy, the data presented in this submission provide a robust PK and safety database allowing extrapolation of efficacy from the comparative clinical trials conducted in adults and older pediatric subjects as allowed under 21 CFR 314.55(a). The target oseltamivir carboxylate exposure in these trials was similar to or slightly higher than that associated with efficacy in other populations.

It must be noted that neither the Applicant nor FDA reviewers were able to demonstrate a PK/PD relationship between oseltamivir (or oseltamivir carboxylate) exposure and cessation of viral shedding or resolution of fever. In previous clinical trials, the timing of initiating treatment was shown to be a critical factor and in the registrational trials demonstrating clinical benefit, the window for enrolling subjects was within 48 hours of onset of symptoms. In order to enroll an adequate number of subjects in CASG114 and WP22849 for the PK and safety database, enrollment was allowed within 96 hours of onset of symptoms. This allowed time for subjects to be identified and influenza infection confirmed prior to beginning treatment in a research setting. Also in order to expedite enrollment in a vulnerable population, the clinical trials allowed enrollment of both outpatients and those who were hospitalized. These enrollment strategies may have decreased the likelihood of demonstrating benefit in an exposure-response analysis. In addition, targeting the upper range of previously studied drug exposure may have decreased the ability to show a difference between the upper and lower exposure quartiles in these trials. The labeled indication is restricted to patients with uncomplicated, acute influenza who have been symptomatic for no more than two days (48 hours), the population for whom clinical benefit has been shown in older patients.

Overall, the data submitted from CASG114 and WP22849 support a favorable risk-benefit assessment for the use of Tamiflu in a treatment regimen in infants less than 1 year of age. The safety profile of drug was consistent with that observed in older pediatric patients and almost all subjects enrolled tolerated a full course of treatment (3% receiving fewer than 9 doses). Only a single subject discontinued Tamiflu prematurely because of an adverse drug reaction (hypersensitivity). Vomiting, diarrhea, and diaper dermatitis were the most commonly reported AEs. GI events have been previously described in other Tamiflu clinical trials and, although these two trials did not have a placebo comparison, the rates of vomiting and diarrhea reported in CASG114 and WP22849 are consistent with those observed in other treatment trials. Thus, Tamiflu is expected to be safe for use in infants less than 1 year of age.

From a regulatory perspective, the use of extrapolation for efficacy in pediatric drug development is grounded in the presumed public health benefit of evaluating drugs in a population that is traditionally difficult to enroll in clinical trials in sufficient numbers to directly demonstrate efficacy. In the case of Tamiflu, the lack of a drug development program in infants less than 1 year of age represented a gap in information that posed a public health inequity. Initial pandemic preparedness plans included instructions for use of antiviral drugs for all age groups except those less than 1 year. Because of initial concern for unexplained animal toxicity, the Applicant was hesitant to launch clinical trials in this age group. Therefore, the NIAID/NIH independently initiated a careful step-wise investigation of the use of Tamiflu in this age group beginning in 2006. This process has led to a safety and PK database larger than usually obtained in this age group and the results provide support for the

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recommended treatment dose of 3 mg/kg twice daily for five days in infants less than 1 year of age.

No additional Postmarketing Requirements or Postmarketing Commitments are recommended and a Risk Evaluation and Mitigation Strategy (REMS) is not required.

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/s/

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12/13/2012