CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS SUMMARY

NDA: 21087 (SLR-016); NDA 21246 (SLR-010) **REVIEWER:** Jenny H. Zheng, Ph.D.
DRUG: Tamiflu (Oseltamivir phosphate) **SUBMISSION DATE:** December 24, 2003
(75 mg capsules, 12 mg/mL solution)
SPONSOR: Roche
TYPE: Labeling supplement; request for pediatric exclusivity

BACKGROUND:

Oseltamivir is an ethyl ester prodrug of oseltamivir carboxylate (Ro 64-0802), an inhibitor of the neuraminidase enzyme of influenza virus. Oseltamivir (Tamiflu) is approved for the treatment (age 1 year and older) and prophylaxis (age 13 years and older) of influenza.

The Tamiflu label includes dosing information for children as young as one year of age. The Pediatric Written Request issued on March 1, 2000 asked the sponsor to collect pharmacokinetic and safety data from children as young as less than one month of age. However, subsequent data collected during juvenile animal toxicity studies indicated there is a potential risk of central nervous system toxicity in younger infants. The Division of Antiviral Drug Products (DAVDP) concluded it would be difficult to monitor CNS toxicity in infants less than one year of age, a population that may have an immature blood-brain barrier. Thus, the division removed the request for studies in neonates and infants less than one year of age and issued an amended Written Request on November 25, 2003.

The applicant submitted the current supplement to add the juvenile animal toxicology studies to the label.

In addition, DAVDP addressed the applicant's response to the amended Pediatric Written Request. Pediatric Exclusivity was granted on March 22, 2004.

SUMMARY OF CLINICAL PHARMACOLOGY INFORMATION:

The applicant did not submit any new clinical pharmacology information with this supplement. The following information is excerpted from the Clinical Pharmacology and Biopharmaceutics review of NDA 21-246. The review of NDA 21-246 resulted in pediatric dosing information for Tamiflu.

A total of 1029 patients aged 1-12 years participated in Phase III trials (WV 15758 and WV15759/WV15871), of whom 504 were randomized to receive 2 mg/kg oseltamivir BID for five days. The available PK data are from 5 children (aged 3-11 years) in one of the Phase III trials and 18 healthy children (aged 5-12 years) in a single dose study.

The exposure-response relationship was not studied in children. Also, the PK/PD studies in adult subjects experimentally inoculated with human influenza virus did not identify an exposure-response relationship (see Dr. Rajagopalan's review for NDA 21-087). However, the Phase III studies in adults demonstrated that 75 mg BID and 150 mg BID of oseltamivir have similar safety and efficacy. The 75 mg BID dosing regimen was approved for the treatment of influenza in adults.

Pharmacokinetic data show that Ro 64-0802 exposure after a single oral 2 mg/kg dose of oseltamivir in children is less than exposure in adults given comparable doses, due to more rapid drug clearance of prodrug and active metabolite in children. With advancing age, the difference in exposure between children and adults became less, such that the pharmacokinetic profile in children over 13 years of age was similar to that in adults.

Pharmacokinetic parameters of Ro 64-0802 (oseltamivir carboxylate)

Ro 64-0802 Parameter	Study NP 15758 (2 mg/kg BID)			Study NP 15826 (2 mg/kg single dose)			Study NP 15717 (75 mg BID)		Phase III studies [a,b]
Age (yr)	3	7-8	11	5-9	9-13	13-18	Adults		Adults
							Day 1	Day 5/7 (s.s)	Day 5/7 (s.s)
N	1	2	2	6	6	6	20	20	
C_{max} (ng/ml)									
Mean	178	248	374	183	231	319	225	348	398
SD	-	56	26	36	46	76	49	64	103
$AUC_{0-\infty}$ (ng.hr/ml)									
Mean	1907[b]	2113 [b]	3266 [b]	2746	3208	4534	2227	2719 [b]	3450 [b]
SD	-	514	542	368	394	929	410	538	1018
$t_{½}$ (hr)									
Mean	16.7	5.8	7.5	8.8	7.8	8.1	5.49	5.79	7.94
SD	-	0.5	2.5	2.0	1.8	2.2	1.4	1.3	2.9
CL/F (ml/min/kg)									
Mean	15.9	14.8	9.4	11.1	9.4	5.3	6.0 [c]	6.6 [d]	5.2 [d]
SD	-	3.6	1.6	1.6	1.3	2.0	-	-	-
C_{12} (ng/ml)									
Mean	160	84.7	202.6	87	106	150	75 [c]	138	175
SD	-	74.1	135.8	9	17	30	-	30	57.75

[a] Protocols WV 15670, WV15671, WV15730
[b] AUC_{0-12}
[c] Estimated from the graph sent by the applicant
[d] Estimated based on the reported clearance normalized to standard adult's body weight 70 kg

The applicant proposed an age-based dosing regimen, based on the linear relationship between apparent total clearance and age. The applicant proposed dividing the pediatric population into four age groups; patients within each age groups would receive a specific mg dose (30, 45, 60 or 75 mg). The proposed dosing regimens were based on data collected from pediatric subjects following a 2 mg/kg single dose (aged 5-18 years, n=18) and 2 mg/kg BID (aged 1-12 years, n = 5). Our review of the data indicated that clearance is age or body weight dependant. However, there were some concerns regarding safety of the proposed regimens. First, there were little PK profile data for children under 5-years old (n = 1). Secondly, estimation of AUC was based on ideal body weight (IBW) for age, which allows lower weight children to receive more drug. Thirdly, children of IBW who are less than 9-years old would receive 2.5-3.0 mg/ kg, which is higher than the 2 mg/ kg studied in the Phase III trials.

Oseltamivir 2 mg/kg BID was studied in Phase III trials in children aged 1-12 years, and it is the only oseltamivir dose with sufficient safety and efficacy data in children. However, there were discussions within the clinical division regarding convenience of a fixed mg dose vs. the potential for decreased tolerability at doses >2 mg/kg BID. It is noted that the predicted AUC for children who receive the applicant's proposed regimen would be similar to AUC in adults who received 75 mg BID. Also, using a fixed dose for each age group may decrease medication errors because there is no calculation.

The final decision from the clinical division was to use a fixed dose by weight rather than age, which insures that underweight children will not get a higher mg/kg dose than the proposed dose based on the IBW.

The recommended dosing regimens for children 12 months and older are:

<= 15 kg	or	<= 33 lb	30 mg twice daily
> 15 kg to 23 kg	or	> 33 lb to 50 lb	45 mg twice daily
> 23 kg to 40 kg	or	> 50 lb to 80 lb	60 mg twice daily
> 40 kg	or	> 80 lb	75 mg twice daily

The 75 mg capsule is an alternative dosing regimen only for children over 40 kg or 80 lb. No specific studies were conducted for efficacy and safety in the adolescent population. However,

children aged 13 years or older (IBW = 47-70 kg) were included in trials using the 75 mg capsule in the winter season of 1998-1999.

Even though the recommended dosing regimens allow an oseltamivir dose greater than 2 mg/kg for younger children, the recommended doses are mostly within 2.0 to 2.5 mg/kg, compared to 2.5 to 3.0 mg/kg in the dosing regimen proposed by the applicant. The recommended dosing regimens also reduce the possibility of overdose in underweight children.

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