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APPLICATION NUMBER:

21-087 / S-016
21-246 / S-010

MEDICAL REVIEW

Medical Officer Review
NDA 21-087, SLR 016 (Labeling Supplement – Prior Approval)
NDA 21-246, SLR 010 (Labeling Supplement – Prior Approval)

Date Submitted:	December 23, 2003
Date Received:	December 29, 2003
Review Completed:	June 21, 2004
Sponsor:	Hoffman-La Roche Inc. 340 Kingsland Street Nutley, NJ 07110-1199
Product:	Tamiflu® (oseltamivir phosphate) 75 mg capsules and for oral suspension 12 mg/mL
Indication:	Treatment and prophylaxis of influenza A and B
Relevant Documents:	———, SN 268 Written Request for Pediatric Studies, issued March 1, 2000 Amended Written Request, issued November 25, 2003 NDA 21-087, N-000 (PM), dated January 14, 2004

Brief Review:

This submission contains proposed labeling in response to findings reported from juvenile toxicology studies previously submitted to the Division (——— SN 268, dated December 19, 2002) and discussed on several occasions with the sponsor. The submission was also accompanied by a Request for Pediatric Exclusivity Determination (dated January 14, 2004). The new labeling submitted in SLR 016 was intended to fulfill the requirement for new pediatric labeling described in the provisions for exclusivity contained in the BPCA of 2002.

No new studies were submitted with SLR 016. New labeling relevant to pediatric patients was based on the results of juvenile animal toxicology studies. These toxicology studies were reviewed by both Clinical and Pharmacology/Toxicology Reviewers and the results were discussed within the Division and with the sponsor via teleconference. The sponsor requested a revision of their Written Request for Pediatric Studies for Tamiflu to delete a study to be completed in infants < 1 year of age. The results of the animal studies and the sponsor's request were discussed internally and with the FDA Pediatric Implementation Team.

In brief, the sponsor attributed increased rat pup mortality to excessive concentrations of Tamiflu and the active metabolite in the immature rat brain. The DAVDP Review Team believed that there was poor correlation between the juvenile rat physiology and human

infant physiology and that there was > 800-fold safety margin in terms of drug levels when the rat data was compared to the known PK in infants > 1 year of age. Although we agreed with the sponsor that neonates should probably not receive Tamiflu, it was considered unlikely that infants older than 3-6 months would be at significant risk. However, it was acknowledged that there was no definitive way to extrapolate the juvenile rat data to infant humans and no way to clearly define the risk. It was also acknowledged that this information would need to be communicated in the Informed Consent Form and the study would likely be difficult to enroll. After learning the results of the juvenile rat study, the previous study site for the infant study had withdrawn from the study. For more detailed descriptions of SN 268, please refer to the Clinical and Pharm/Tox reviews of that submission and the minutes from the subsequent teleconference with Roche dated February 3, 2003.

At the end of the discussions, the Review Team believed that the sponsor had fulfilled all other components of their Written Request and that it was not reasonable to continue to require further study in infants < 1 year of age. The PdIT endorsed this position and approved our recommendation to amend the Written Request to delete the young infant study (meeting dated August 27, 2003). The amended Written Request did require that the results of the juvenile animal studies be incorporated into the label.

The current SLR proposes that a summary of the juvenile animal toxicology studies be included in the label in a new ANIMAL TOXICOLOGY section. Additionally, the proposed label revisions include that Tamiflu should not be used for treatment or prophylaxis of influenza in patients < 1 year of age. Precautionary wording regarding use in infants < 1 year of age is included in the Pediatric Use section, the DOSAGE AND ADMINISTRATION section, and in the patient package insert.

Medical Officer's Assessment:

The proposed label revisions contain a summary of the juvenile animal toxicology studies as requested. Dr. Ita Yuen, the Pharmacology/Toxicology Reviewer, has made minor editing recommendations for this section. The Review Team recommends that the new ANIMAL TOXICOLOGY section be positioned immediately following the Pediatric Use section to emphasize its possible association with infant dosing. However, because of the uncertain clinical significance of these findings for human infants, we have also suggested that the precautionary statements use less definitive wording regarding the use of Tamiflu in infants < 1 year of age. The Review Team raised concerns that if an influenza pandemic strain emerged in the future, the possible benefit of the use of Tamiflu in young infants might outweigh the risks. We recommend that the label state Tamiflu "is not indicated" for the treatment or prophylaxis of influenza in infants < 1 year of age (rather than

Although there were no new virology data reported in this supplement, the Microbiology reviewer suggested some minor revisions to that section of the label. Some of these were

suggestions for format changes (changes in subsection headings) that have been instituted in newer antiviral drug labels. It was recommended that the sponsor include in the text the specific mutations that have been associated with resistance to Tamiflu and other neuraminidase inhibitors. Some rearrangements in the order of the text were also suggested.

Linda L. Lewis, M.D.
Medical Officer
DAVDP/ODE IV/CDER/FDA

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/s/

Linda Lewis
6/24/04 09:45:20 AM
MEDICAL OFFICER
SLR approved. Pediatric exclusivity granted.

Kathrine Laessig
6/24/04 10:32:15 AM
MEDICAL OFFICER

Debra Birnkrant
6/28/04 09:44:13 AM
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