CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Division of Antiviral Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Numbers:	NDA 21-087/SLR-016 NDA 21-246/SLR-010
Name of Drug:	Tamiflu® (oseltamivir phosphate) capsules and dry powder for suspension.
Date submitted:	December 23, 2003
Date received:	December 24, 2003
Date approved:	June 23, 2004
Applicant:	Hoffmann-La Roche Inc. 340 Kinglsand Street Nutley, NJ 07110
Material Reviewed:	Package Insert Patient Package Insert
Submission dates:	January 14, 2004, May 19, 2004, and June 9, 2004.
Receipt dates:	January 15, 2004, May 20, 2004, and June 10, 2004.

Background and Summary:

These supplemental new drug applications provide for revisions to the **Animal Toxicology, Precautions, Dosage and Administration**, and **Microbiology** sections of the package insert. In addition, revisions have been made to the **Who should not take TAMIFLU?** section of the patient package insert.

Review:

Please see attached document comparison for all changes made to the PI and PPI. Inserted text is highlighted and deleted text is shown in the right margin.

In the patient package insert, **What is TAMIFLU?** section, the second sentence incorrectly reads "
The sentence should read "TAMIFLU can also reduce the chance of getting the flu in people age **13** and older..."

The applicant is aware of the error and following a discussion with the DAVDP Project Manager, will submit an amendment to the July 22, 2004 final printed labeling submission that will note the error and contain corrected labeling.

Conclusions

A Supplemental Approval Letter with attached labeling, dated June 23, 2004 was issued to the Sponsor.

Jeff D. O'Neill, ACRN
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Virginia Behr
Chief, Project Management Staff

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Draft Labeling

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/s/

Jeff ONeill
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CSO

Virginia Behr
8/30/04 05:13:33 PM
CSO

BPCA Executive Summary
NDA 21-087/NDA 21-246
Tamiflu® capsules and for oral suspension

I. Description of Data Reviewed for Exclusivity

I. A. NDA 21-246, SN 000, submitted June 15, 2000, review completed December 14, 2000

This NDA submission consisted of 137 volumes of study documents and electronic datasets containing Sections 11 and 12, the Case Report Forms and Case Report Tabulations. The sponsor submitted complete study reports for their pivotal pediatric clinical efficacy trial, WV15758. This study included safety and efficacy data derived from 698 children enrolled in the trial, 342 of whom received at least one dose of Tamiflu suspension. Supportive safety and efficacy data was included from 2 pediatric treatment studies: WV15731, a small pilot study enrolling 10 children, and WV15759/WV15871, a larger combined study enrolling 335 children with known asthma. Pharmacokinetic and safety data were submitted from 3 single dose studies, NP15826, NP15881, and NP15912. Additionally, since adolescents 13-17 years of age were enrolled in some of the adult trials, study reports were submitted for the adult efficacy trial M76001 and the adult prophylaxis study WV15799. These adolescents were included in the sponsor's safety database.

Safety and efficacy data from the CRTs was submitted in electronic format (as SAS transport files) to the CDER Electronic Document Room. Because the electronic files were very large and cumbersome to manipulate, the sponsor was asked to provide some of the primary endpoint data in a more easily manipulated format as a reviewer's aid. This supplemental submission contained no new data or analysis. The review team also requested copies of the CRFs for all children who were diagnosed with OM during the trial and this information was submitted separately.

Table 1: Studies included in the pediatric NDA submission

Study	Description	Dose Groups	Strata	Ages (years)	Number Enrolled (received Tamiflu)
Pediatric Studies: Suspension formulation					
WV15758	Pediatric treatment	Placebo 2 mg/kg BID	Otitis media	1-12	695 (342)
WV15759/ WV15871	Pediatric treatment (with asthma)	Placebo 2 mg/kg BID	Asthma severity	6-12	335 (170)

WV15731	Pediatric dose ranging, PK	1 mg/kg BID 2 mg/kg BID 3 mg/kg BID	Age	1-12	10 (10)
NP15826	Pediatric single dose PK	Placebo 2 mg/kg	None	6-18	18 (18)
NP15881	Pediatric taste test	2 mg/kg	None	6-12	28 (28)
NP15912	Pediatric taste test	2 mg/kg	None	6-12	12 (12)
Adult Studies in which Adolescents were Recruited: Capsule formulation					
M76001	Time to treatment start	Placebo 75 mg BID	None	13-80	140 (94)*
WV15812/ WV15872	Treatment of chronically ill adults	Placebo 75 mg BID	COAD	> 13	8 (4)*
WV15799	Post-exposure prophylaxis	Placebo 75 mg QD	None	> 13	206 (111)*

*Refers to number of adolescents 13-17 years enrolled.

I. B. NDA 21-087, SLR 016 and NDA 21-246, SLR 010, submitted December 23, 2003, review completed June 21, 2004

This submission contains proposed labeling in response to findings reported from juvenile animal toxicology studies previously submitted to the Division [redacted] 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 the SLRs was intended to fulfill the requirement for new pediatric labeling described in the provisions for exclusivity contained in the BPCA, 2002. No new data were submitted with these SLRs. New labeling relevant to pediatric patients was based on the results of juvenile animal toxicology studies.

II. Summary of Study Results and Conclusions

II. A. NDA 21-246, SN 000

This NDA submission contained data from one large, well-controlled study of Tamiflu suspension for treatment of acute influenza-like illness in otherwise healthy children from 1 to 12 years of age and supportive data from a second study in children with known asthma ages 6 to 12 years. Safety data on the use of Tamiflu in adolescents drawn from previously reviewed adult treatment and prophylaxis studies was included for completeness. The submission was generally well organized and clearly presented, although the electronic datasets were somewhat cumbersome to analyze using FDA software.

Review of the pivotal pediatric trial, WV15758, revealed that children with influenza receiving Tamiflu suspension within 48 hours of the onset of flu-like illness experienced a 1.5 day median reduction in the calculated time to freedom from illness compared to children receiving placebo. This modest improvement in the length of illness was similar to that seen in the adult treatment trials of Tamiflu. Children enrolled in the trial who did not have influenza derived no discernable benefit from Tamiflu. Therefore, the median benefit was somewhat less (approximately 1 day) when the analysis included all children in the study population and not only those with proven influenza. While 1.5 days may not seem much of an improvement in a generally self-limited viral infection, for parents of miserable children it may be well worth the extra expense and minimal risk of the medication. The sponsor provided additional analyses of secondary endpoints of duration and severity of symptoms that also suggested a significant drug effect. The review team concurs with these assessments and agrees that Tamiflu provides benefit in terms of the extent of symptoms of influenza.

The treatment benefit of Tamiflu was most notable for subjects with documented influenza A. Unlike the adult trials, in which very few subjects had influenza B, the pediatric trials provided a sufficient number of patients with influenza B to assess antiviral efficacy in this subpopulation. While the treatment effect was not as marked in this group of children, the improvement in the primary endpoint was still significant.

Among the secondary and tertiary efficacy endpoints for this study were assessments of specific secondary infections and use of antibiotics. The sponsor attempted to track bronchitis, OM, pneumonia and sinusitis during the trial and then determined if these events and the need for antibiotics were prevented by the use of Tamiflu. Unfortunately, the diagnostic criteria for these events were left entirely to the individual investigators and confirmatory testing was not done in all patients. This was particularly troublesome in the tracking of OM since the sponsor had made additional efforts to stratify children at study entry according to OM status, collect this data and analyze it separately. The sponsor's analysis supported their claim that Tamiflu prevented the development of OM. However, in applying relatively liberal but uniform criteria for the diagnosis of OM the review team could not confirm a significant difference in either the development of OM or the use of antibiotics between the 2 treatment groups. There were still numerically more cases of probable OM in children receiving placebo but the numbers were small. This reviewer suspects that Tamiflu may provide a beneficial effect in preventing cases of secondary OM but the protocol design and data collection did not adequately support this claim. The sponsor's late assertion that they were attempting to decrease the incidence of viral (influenza) OM in the study population did not provide any resolution to these discrepancies. Neither the protocol nor the analysis plan discussed differentiating viral and acute bacterial OM or provide clearly defined diagnostic criteria for either.

In study WV15759/15871, children with chronic asthma were enrolled in a study of similar design. This study failed to enroll adequate numbers of children to be powered to show a difference in Tamiflu compared to placebo. A small numerical improvement in time to freedom from illness did not reach statistical significance. It is interesting to note that there were accompanying small improvements in some measures of pulmonary function in the children receiving Tamiflu, although no difference in number of asthma exacerbations was identified between treatment groups. Tamiflu did not seem to have any adverse effect on the asthma status of children who received it. Because the study was not fully enrolled, it was not possible to interpret any differences in the secondary endpoints.

The overall safety profile of Tamiflu in children from 1 to 12 years of age was well characterized. Vomiting, the major toxicity identified in the adult trials, was also relatively common in children. In general, children with influenza infection have more vomiting as part of their illness than is observed in adults. Thus, the incidence of vomiting in both the placebo and Tamiflu groups was higher than observed in the adult trials. The difference in rates of vomiting between the 2 groups was similar to that seen in adults. Other adverse events occurred so infrequently that it was not possible to identify patterns specific to Tamiflu use. No significant laboratory abnormalities could be attributed to the use of Tamiflu in children. A small but significant proportion of children in both treatment arms experienced low WBC during the study but this may have been due to the underlying effects of viral illness. A summary of the safety data obtained from adolescents enrolled in the adult treatment and prophylaxis trials revealed no differences in the safety and tolerability of Tamiflu in this age group compared to either younger children or adults.

A major safety concern is in the potential emergence of mutant influenza virus resistant to the neuraminidase inhibitors. As was seen in earlier anti-influenza drug studies, the rate of resistance identified in the pediatric trials (8.6%) was much higher than that observed in the adult trials (1.3%). The mutant viruses were predominately identified in subjects who were infected with influenza A H1N1 and, to date, no mutant influenza B has been isolated. The sponsor asserts that mutant viruses are less pathogenic than wild type influenza, basing this belief primarily on in vitro data. While the number of children with resistant virus was small, the median time to freedom from illness in this subgroup was somewhat longer than that in the larger group of children with documented influenza receiving Tamiflu. It also appeared that the mutant virus may be shed at high titers in some subjects before being cleared. Therefore, this reviewer has not been reassured that these viruses are harmless to the general population. The pediatric studies were not designed to determine if there was secondary spread of the mutant viruses to household or other contacts so there is no data regarding transmission of these viruses in vivo. Since these mutations involve the neuraminidase enzyme and to a lesser (but undefined) extent the hemagglutinin, there are also theoretical concerns that they could be antigenically distinct from wild type influenza. The review team believes that it will be of critical importance for the sponsor to further characterize these mutant viruses, the course of clinical disease

associated with them, their potential for transmission in households and the nature of the antibody response to them compared to wild type influenza.

The sponsor proposed fixed dosing recommendations for Tamiflu suspension based on children's age. Although early PK studies showed a linear decrease in clearance of Tamilfu with age, clinical trials were done with all children receiving a dose of 2 mg/kg. The sponsor's dosing recommendations would have given some children in the younger age group doses of 2.5-3.0 mg/kg depending on body weight. These are doses for which we have no pediatric safety data. Drug exposure was, however, probably in the same range as that measured in the adult trial in which a dose of 150 mg BID was evaluated. The adult study showed no difference in safety profile of 75 mg BID, the currently approved dose, and 150 mg BID. Given the drug's good safety profile, the review team suggested that a fixed dose based on weight would be acceptable as we projected that potentially fewer children might receive doses higher than the 2 mg/kg BID studied in clinical trials.

In summary, the sponsor has presented the results of a large, well-controlled pediatric study that confirms the benefit of Tamiflu oral suspension in the treatment of acute influenza in children older than 1 year of age. Supportive data from a study of children with chronic asthma reveals no evidence of worsening of asthma related to Tamiflu use. Previous adult trials enrolling adolescents revealed no differences in safety or efficacy in this age group. No significant safety concerns would preclude the use of Tamiflu in children, although there is heightened concern about the emergence of influenza virus resistant to the neuraminidase inhibitors.

II. B. NDA 21-087, SLR 016 and NDA 21-246, SLR 010

In IND 53,093, SN 268 the sponsor provided the final study report for a toxicology study conducted in juvenile rats. In the first stage of this study, rat pups were administered a single oral (gavage) dose of 500, 700 or 1000 mg/kg of Tamiflu at either 7, 14, 24, or 42 (adult) days of age. Significant morbidity and mortality were seen in the cohorts of 7-day old pups receiving 700 and 1000 mg/kg. There were no clinical signs of illness or mortality in 7-day old pups receiving 500 mg/kg. Much more limited morbidity and only a single death were observed in the cohorts of 14-day old pups receiving 1000 mg/kg. Other than one drug administration related death, there were no clinical signs of illness or deaths reported in pups older than 14 days. The report states that no treatment-related histopathologic findings were identified in any tissue including brain.

C_{max} and AUC of oseltamivir and its active metabolite, Ro 64-0802, in plasma were highest in 14-day old pups (slightly lower in 7-day olds) and dropped off in the older rats. The pro-drug was higher than the active metabolite over the first 10 hours of sampling in the 7 and 14-day old rats, while the reverse was true in the 24 and 42-day old rats. In brain tissue, drug concentrations decreased dramatically with the age at which the rats were dosed. C_{max} and AUC of oseltamivir in brain tissue were 1500-

fold higher in 7-day old pups compared to the 42-day old (adult) rats. Brain levels of Ro 64-0802 were < 10-fold higher in the younger rats than the older ones.

The sponsor attributed the increased rat pup mortality to excessive concentrations of oseltamivir and its 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 very difficult to enroll. After learning the results of the juvenile rat study, the previous study site for the proposed infant study had withdrawn from the study.

The results of the juvenile toxicology studies 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 (issued March 1, 2000) 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 with the FDA's Pediatric Implementation Team. At the end of these 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 as a condition of the Written Request. 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 (issued November 25, 2003) did require that the results of the juvenile animal studies be incorporated into the label.

III. Summary of Labeling

III. A. NDA 21-246, SN 000

The original NDA 21-246 submission provided pediatric data for inclusion in the product label for Tamiflu. This NDA provided the basis for extending the indication of Tamiflu for the treatment of uncomplicated influenza infection in patients 1 year and older. This labeling included pediatric pharmacokinetic data in the CLINICAL PHARMACOLOGY section, a description of the pivotal pediatric clinical trial and efficacy results in the INDICATIONS AND USAGE section, a summary of the safety data from the pivotal pediatric trial in the ADVERSE REACTIONS section, and dosing recommendations for pediatric patients > 1 year of age in the DOSAGE AND ADMINISTRATION section.

III. B. NDA 21-087, SLR 016 and NDA 21-246, SLR 010

The proposed label revisions in this submission contain a summary of the juvenile animal toxicology studies as requested. The Review Team recommends that this new ANIMAL TOXICOLOGY section be positioned immediately following the Pediatric Use section to emphasize its 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 recommended that the label state Tamiflu "is not indicated" for the treatment or prophylaxis of influenza in infants < 1 year of age rather than "should not be used" and that a statement be included regarding the uncertainty of extrapolating juvenile animal data to human infants.

IV. Summary of Post-Marketing Commitments

IV. A. NDA 21-246, SN 000

The following list of Phase 4 commitments was proposed and agreed to by the sponsor. Most of these requests involved additional evaluation of Tamiflu-resistant influenza isolates.

- Using all available resistant clinical isolates from both adult and pediatric trials, evaluate these isolates for cross-resistance to other neuraminidase inhibitors. Isolates should also be characterized for the emergence of drug-dependent variants.

- In future clinical studies (treatment or prophylaxis) further characterize the clinical aspects of infection with influenza resistant to neuraminadase inhibitors in children including: manifestations and duration of clinical disease, transmission within households or to other contacts, and virological characteristics of the isolates including detailed assessments of the kinetics of growth and clearance of resistant isolates.

- Complete additional studies to evaluate the antibody responses to both wild-type and resistant influenza with respect to their cross-protective potential.

- In additional studies, further evaluate the oseltamivir PK profile (not sparse sampling) of the to-be-marketed dose of Tamiflu suspension in children younger than 5 years of age.

IV. B. NDA 21-087, SLR 016 and NDA 21-246, SLR 010

No Phase 4 commitments were requested after review of this SLR.

V. Recommendations for Exclusivity

The Review Team considered that all requirements contained in the Written Request issued on March 1, 2000, and amended on November 25, 2003, were fulfilled. The studies conducted by the sponsor led to significant pediatric labeling for Tamiflu in all pediatric age groups including PK, dosing, safety, and efficacy data in pediatric patients > 1 year of age. Hoffman-La Roche, Inc. was granted pediatric exclusivity for Tamiflu on the basis of the submission of these studies and the resultant labeling on March 22, 2004. The labeling supplement incorporating the juvenile animal toxicity data and potential implications for human infants was approved on June 24, 2004.

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

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/s/

Debra Birnkrant
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM: IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Mail: ODS (Room 15B-08, PKLN Bldg.)		NDA 21-246	**BPCA PEDS EXCLUSIVITY**	March 23, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
TamiFlu (oseltamivir)			June 22, 2005

NAME OF FIRM:
Roche

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☑ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Per Section 17 of the BPCA, for one year after Peds Exclusivity is granted, FDA is to report on any adverse event related to that drug granted exclusivity.

- **Peds Exclusivity granted: March 22, 2004**
- **BPCA report due date: June 22, 2005 (15 months from date Peds Exclusivity was granted)**

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Debbie Avant	☑ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Debbie Avant
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PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA **03/01/00**, revised: **11/25/03**. Application Written Request was made to:
NDA/IND#: **NDA 21-087 & 21-246 & IND 53,093**
Timeframe Noted in Written Request for Submission of Studies **03/30/04**.
NDA#: **21-087** Supplement #: **S-016**
NDA#: **21-246** Supplement#: **S-010**
Choose one: **SLR**
Sponsor: **Hoffman-La Roche Inc**.
Generic Name **oseltamivir phosphate** Trade Name: **Tamiflu®**
Strength **(21-087) 75mg Capsules & 21-246 (12mg/ml dry powder)** Dosage Form/Route: **Capsules & Dry Powder for Suspension/oral.**
Date of Submission of Reports of Studies **01/15/04**.
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies): **04/14/04**.

Was a formal Written Request made for the pediatric studies submitted?	Y **X**	N ___
Were the studies submitted after the Written Request?	Y **X**	N ___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y **X**	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y **X**	N ___
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y **X**	N ___
Did the studies fairly respond to the Written Request?	Y **X**	N ___

SIGNED _____ **DATE** 3/16/04
(Reviewing Medical Officer)

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity **X Granted** **___ Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
21-087 / 21-246	5763483	Dec 27, 2016
21-087 / 21-246	5866601	Feb 02, 2016
21-087 21-246	595 235	Feb 02, 2016
21-087 21-246	NCE	Oct 27, 2004
~~21-087 21-246~~	~~I 317 NDF~~	~~Nov 17, 2003~~

SIGNED _____ **DATE** 3/22/04

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

PRIOR APPROVAL SUPPLEMENT

Hoffmann-La Roche Inc.
Attention: Lynn DeVenezia-Tobias
Program Manager
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms. DeVenezia-Tobias:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tamiflu® Capsules & Tamiflu® Dry Powder for Suspension

NDA Number: 21-087

Supplement number: S-016

NDA Number: 21-246

Supplement number: S-010

Date of supplements: December 23, 2003

Date of receipt: December 23, 2003

Unless we notify you within 60 days of the receipt date that these applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on February 20, 2004 in accordance with 21 CFR 314.101(a).

All communications concerning these supplements should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, please call Sean J. Belouin, R.Ph, Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

Anthony W. DeCicco, R.Ph
Chief, Project Management Staff
Center for Drug Evaluation and Research
Division of Antiviral Drug Products

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/s/

Tony DeCicco
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