CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-246

ADMINISTRATIVE DOCUMENTS

EXHIBIT A

PATENT INFORMATION FOR NDA NO. 21-246

1)	Active Ingredient(s)	oseltamivir phosphate
2)	Strength(s)	1.2% powder, 12 mg/mL when reconstituted
3)	Trade Name	TAMIFLU™
4)	Dosage Form and Route of Administration	Powder for Oral suspension
5)	Applicant (Firm) Name	Hoffmann-La Roche Inc.
6)	NDA Number	21-246
7)	First Approval Date of original NDA	Not yet approved*
8)	Exclusivity: Date first ANDA could be approved	ANDA can not be approved for at least three (3) years from the date pending NDA is approved
9)	Patent Information	See Attachment

CONFIDENTIAL INFORMATION

*Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.

Rev. 12/97

98912

ATTACHMENT TO EXHIBIT A

First US Patent Number: 5,763,483

Expiration Date: December 27, 2016 subject to patent term extension.

Type of Patent-Indicate all that apply (check applicable boxes):

1.	Drug Substance (Active Ingredient)	[X]	Y	[ ]	N
2.	Drug Product (Composition/Formulation)	[X]	Y	[ ]	N
3.	Method of Use	[X]	Y	[ ]	N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent:
Treatment of Influenza.

Name of Patent Owner: Gilead Sciences, Inc.

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number **5,763,483** covers the composition, formulation and/or method of use of oseltamivir phosphate. This product is:

[X] currently approved under the Federal Food, Drug, and Cosmetic Act.

OR

[ ] the subject of this application for which approval is being sought.

By: Briana C. Buchholz

Name: Briana C. Buchholz
Date: May 25, 2000
Title: Senior Counsel
Telephone Number: (973) 235-6208

Second US Patent Number: 5,866,601

Expiration Date: February 2, 2016 subject to patent term extension.

Type of Patent-Indicate all that apply:

1.	Drug Substance (Active Ingredient)	[X] Y [ ] N
2.	Drug Product (Composition/Formulation)	[X] Y [ ] N
3.	Method of Use	[ ] Y [ ] N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent:

Name of Patent Owner: Gilead Sciences, Inc.

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number **5,866,601** covers the composition, formulation and/or method of use of oseltamivir phosphate This product is:

[X] currently approved under the Federal Food, Drug, and Cosmetic Act.

OR

[ ] the subject of this application for which approval is being sought.

By: Briana C. Buchholz

Name: Briana C. Buchholz
Date. May. 25. 2000
Title: Senior Counsel
Telephone Number: (973) 235-6208

Third US Patent Number: 5,952,375

Expiration Date: February 2, 2016 subject to patent term extension.

Type of Patent-Indicate all that apply (check applicable boxes):

1.	Drug Substance (Active Ingredient)	[X]	Y	[ ]	N
2.	Drug Product (Composition/Formulation)	[X]	Y	[ ]	N
3.	Method of Use	[ ]	Y	[ ]	N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent:

Name of Patent Owner: Gilead Sciences, Inc.

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number **5,952,375** covers the composition, formulation and/or method of use of oseltamivir phosphate. This product is:

[X] currently approved under the Federal Food, Drug, and Cosmetic Act.

OR

[ ] the subject of this application for which approval is being sought.

By: Briana C. Buchholz

Name: Briana C. Buchholz
Date: May 25, 2000
Title: Senior Counsel
Telephone Number: (973) 235-6208

A copy of the above information should be submitted with the NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit that information within 30 days of the date of issuance of the patent.

To expedite publication in ***The Orange Book,**** a deskcopy should be submitted to:

Mailing address: (US Mail)

US Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Drug Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

OR

Location address: (for Federal Express deliveries)

US Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Drug Information Services Team
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Building A
Kensington, MD 20895
Phone (301) 827-5470
OR faxed to: (301) 594-6463

* - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in ***The Orange Book***.

Rev. 12/97

98898

EXCLUSIVITY SUMMARY for NDA # 21-246 SUPPL # __

Trade Name Tamiflu Generic Name oseltamivir phosphate

Applicant Name Hoffmann-La Roche, Inc. HFD- 530
Approval Date December 13, 2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ X / NO / /

   b) Is it an effectiveness supplement? YES / / NO /_X_/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /X/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

   Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

   YES /X/ NO /___/

   If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

   NDA # 21-087 Tamiflu 75mg Capsules

   NDA # _____ _____

   NDA # _____ _____

2. Combination product.

   If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

   YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # WV 15758

Investigation #2, Study # WV 15759/WV 15871

Investigation #3, Study #_____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /X/
Investigation #3	YES /___/	NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # WV 157858

Investigation #2, Study # WV 15759/WV 15871

Investigation #3, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # 53093 YES /X/ ! NO /___/ Explain: ____

! _____

! _____

Investigation #2 !

IND # ____ YES /___/ ! NO /___/ Explain: ____

! _____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

!

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

LST

Signature of Preparer Date
Title: Regulatory Project Manager

LST

Signature of Acting Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

FDA Links Tracking Links Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number:	021246	**Trade Name:**	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML
Supplement Number:	000	**Generic Name:**	OSELTAMINVIR PHOSPHATE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	AP	**COMIS Indication:**	TREATMENT OF INFLUENZA
Action Date:	12/14/00		

Indication # 1 treatment of uncomplicated acute illness due to influenza in patients older than one year of age
Label Adequacy Adequate for SOME pediatric age groups
Forumulation Needed: NO NEW FORMULATION is needed
Comments (if any):

Lower Range	Upper Range	Status	Date
0 months	11 months	Deferred	6/30/03

Comments Neonates and infants less than one year of age are deferred until the completion of the studies assessing the PK profile and safety of oseltamivir

This page was last edited on 12/21/00

Signature _____ Date _____

DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Group Leader's Memorandum

NDA 21-246
Tamiflu (oseltamivir) oral suspension
Hoffmann La-Roche

Proposed Indication: Treatment of influenza in children greater than 1 year of age.

Background
Roche submitted this NDA to support the approval of Tamiflu oral suspension for the treatment of influenza in pediatric patients age 1 year and older. Tamiflu was previously approved for the treatment and prophylaxis of influenza in adults in November 1999 and 2000, respectively.

Please refer to the review prepared by Linda Lewis M.D., primary clinical reviewer, for a detailed review of this application.

Studies Submitted
Roche submitted the results from two phase 3 studies to support the safety and efficacy of Tamiflu oral suspension for the treatment of influenza in pediatric patients. The pivotal study, WV15758, was a multicenter, double-blind, placebo-controlled study in otherwise healthy children between the ages of 1-12 years who presented with symptoms of influenza. In addition, another study was designed to evaluate Tamiflu for the treatment of influenza in children with asthma. Although asthmatic children were recruited during flu seasons in the northern and southern hemispheres, targeted enrollment was not achieved. This study was therefore submitted as a supportive study.

For both studies the dose of Tamiflu was 2 mg/kg bid up to a maximum dose of 100 mg bid. The primary study endpoint for both studies was time to freedom from illness, which consisted of four components: 1) return to normal activity 2) alleviation of cough, 3) alleviation of coryza, 4) return to afebrile state.

Efficacy

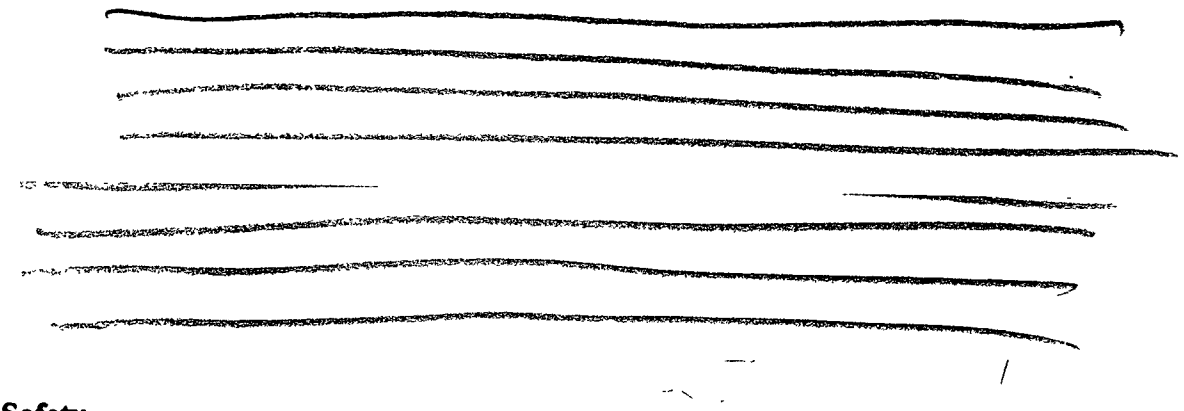
Overall
A total of 698 patients were enrolled in study WV15758, approximately two-thirds were confirmed to have infection with influenza. Among patients with confirmed infection, the median time to freedom from illness was reduced by approximately 1.5 days for patients receiving Tamiflu compared to those receiving placebo. These results were statistically significant and are similar to the results of treatment studies in adults. In addition, for all four of the components of this composite endpoint, there was a reduction in the time to alleviation of symptoms.

In the study of asthmatic children, 335 subjects were enrolled, 56% of whom had document influenza infection. The median difference in the time to freedom from illness between the Tamiflu and placebo groups for this study was approximately 10 hours and was not statistically significant. For some of the individual components of the primary endpoint, specifically time to alleviation of cough and coryza, the differences between treatment groups were closer to 1 day. The applicant postulated several explanations for why the treatment effect appeared to be less in this study than in the pivotal study. These included, inadequate sample size, baseline imbalances between treatment groups with respect to asthma class, and overlap between the symptoms of asthma and influenza that may have obscured some of the influenza treatment effect. These explanations are plausible. Tamiflu did not appear to worsen asthma related signs or symptoms.

Influenza Virus Infection with Type A vs. B

In contrast to treatment studies in adults, a larger proportion (approximately one-third) of infected patients had type B influenza. The median difference in time to freedom from illness for those infected with type B in the pivotal study was approximately ½ of a day favoring the Tamiflu group. This treatment effect for the subset of patients with influenza B was smaller than the size of the overall treatment effect in this study. In the time to event analysis, it appears that most patients in both the Tamiflu and placebo groups recovered quickly. A separation between treatment groups with respect to the time to freedom from illness was apparent at the tail end of the time to event plots. Although not as robust as the data for influenza A, this subset analysis offers supportive evidence that Tamiflu exerts activity against both influenza A and B.

Secondary Complications



Safety

In this safety data base of approximately 500 children who received Tamiflu for the treatment of influenza, vomiting appeared to be the only noteworthy adverse event that occurred with greater frequency among patients receiving Tamiflu compared to placebo. The safety/tolerability profile was similar to that of adults in which nausea, vomiting and headache were the most common events.

Resistance

Neuraminadase phenotype was evaluated in paired isolates (pre and post treatment onset) from 105 children. Nine isolates (8.6%) showed a decrease in neuraminadase

susceptibility to Tamiflu. This proportion is higher than that observed in adult studies (1.3%). The 9 children harboring these isolates cleared virus by study day #10, but there were too few patients to conclude whether there were any clinical consequences related to the emergence of resistance. In addition, since contacts of patients were not studied, it is not known whether virus with reduced neuraminadase susceptibility can be transmitted. The applicant will be asked to continue further investigations, as phase four commitments, to determine the potential clinical consequences and transmissability of resistant virus.

Adolescents
Although adolescents were not included in the primary pediatric studies, a small proportion was enrolled in adult studies. Pharmacokinetic studies show similar clearance for adolescents (age > 13) and adults. In addition the treatment effect in adults and children were quite similar. The division concurs that no additional studies targeting adolescents need to be pursued.

Dose
Although the dose administered in pediatric studies was 2 mg/kg, the applicant proposed

Given the favorable therapeutic index of this drug in adults (both 75 mg bid and 150 mg bid appeared equally safe and efficacious), the division concurs that a simplified dosing scheme is reasonable. However, the division preferred a fixed dosing scheme based on weight category. Compared to the scheme this would provide for somewhat lower concentrations for children who may be less than ideal body weight for their age. Overall, the dosing scheme should provide for plasma AUC exposures that are mostly between that observed for adults receiving 75 mg bid and 150 mg bid, respectively.

Conclusions
The applicant has demonstrated that Tamiflu is safe and efficacious in the treatment of influenza. At this time data supporting efficacy against type B revealed a smaller treatment effect than that observed for type A. Given the probability that type A will usually predominate and that clinicians will not have knowledge of influenza type prior to treatment, discriminating treatment response between the two subtypes is not particularly crucial.

The applicant has devised a safe, effective, and relatively convenient dosing scheme for children age 1 year an older.

I concur with the review prepared by Linda Lewis M.D., the primary clinical reviewer for this application. I also concur with her conclusions that Tamiflu oral suspension administered twice daily at a fixed dose according to weight category should be approved for the indication proposed.

Jeffrey S. Murray

Concurrence:
Birnkrant/Acting Div. Dir.

2 pages redacted from this section of the approval package consisted of draft labeling

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 9/11/2000	DUE DATE: 12/01/2000	OPDRA CONSULT #: 00-0248

TO: Heidi M. Jolson, M.D.
Director, Division of Anti-Viral Drug Products
(HFD-530)

THROUGH: Grace Carmouze
Project Manager
(HFD-530)

PRODUCT NAME:
Tamiflu
(oseltamivir phosphate for oral suspension)
12 mg/mL

MANUFACTURER: F. Hoffmann-La Roche Ltd.

NDA #: 21-246

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Anti-Viral Drug Products (HFD-530), OPDRA conducted a review of the proposed proprietary name, Tamiflu for Oral Suspension. Tamiflu is currently available as 75 mg capsules.

OPDRA RECOMMENDATION: OPDRA has no objections to the use of the proprietary name, Tamiflu for Oral Suspension, at this time. We have also made recommendations for labeling revisions to minimize potential errors with the use of this product. See review for details.

FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the Name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☒ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B-03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 15, 2000

NDA NUMBER: 21-246

NAME OF DRUG: **Tamiflu** (oseltamivir phosphate for oral suspension)

NDA HOLDER: **F. Hoffmann-La Roche Ltd.**

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Viral Drug Products to review the proprietary name, Tamiflu for Oral Suspension. In addition, the container label, the carton labeling, and the package insert were reviewed for possible interventions in minimizing medication errors.

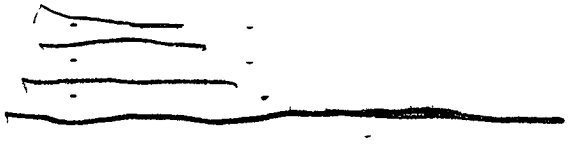
BACKGROUND INFORMATION

The proprietary name, Tamiflu, was first introduced for the capsule formulation under NDA 21-087. The agency approved Tamiflu on October 27, 1999, and it is available as 75 mg capsules. The sponsor has submitted another application, NDA 21-246, for the same active ingredient, but the proposed product will be supplied as an oral suspension.

PRODUCT INFORMATION

Tamiflu (oseltamivir phosphate) is an antiviral agent active against influenza viruses. The active form, oseltamivir carboxylate, inhibits influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release. Tamiflu is indicated for the treatment of uncomplicated acute illness due to influenza infection in adults and adolescents 13 years and older who have been symptomatic for no more than two days. Tamiflu is also indicated for the treatment of acute illness due to influenza in pediatric patients one-year and older who have been symptomatic for no more than two days.

Tamiflu for oral suspension is supplied as a white powder blend for reconstitution to a white tutti-frutti flavored suspension in a 100 mL glass bottle with a bottle adapter and an oral dispenser with 30 mg, 45 mg, and 60 mg graduations. Tamiflu for oral suspension is available in a final concentration of 12 mg/mL. The treatment with Tamiflu should begin within two days of onset of symptoms of influenza. The recommended oral dose of Tamiflu for Oral Suspension for pediatric patients 1 year and older or adult patients who cannot swallow a capsule is as follows:



30 mg
45 mg
60 mg
75 mg

II. RISK ASSESSMENT

A. AERS/DQRS DATABASE SEARCHES

Tamiflu capsules are currently marketed. In order to find any post-marketing safety reports of medication errors associated with Tamiflu, the searches in *the FDA Adverse Event Reporting System (AERS)* were performed. The Meddra Preferred Term (PT), "Drug Maladministration," and the drug names, "Tamiflu%" and "oseltamivir%" were used to perform the searches. The *Drug Quality Reporting System (DQRS)* database was also searched for medication error reports with the search terms, "Tamiflu%" and "oseltamivir%."

The search resulted in five (5) reports, but only one was a potential medication error report involving Tamiflu. The only potential medication error report, *Individual Safety Report (ISR)* # 3456487-4, resulted from the AERS search. On January 5, 2000, a physician called a drug information center to inquire about a new flu drug called *Theraflu*. After discussing with the physician, the drug information specialist identified the new flu drug as Tamiflu, not *Theraflu*. *Theraflu* is an over-the-counter agent that has a combination of acetaminophen, pseudoephedrine, chlorpheniramine, and/or dextromethorphan. The drug information specialist was concerned about the potential medication errors that can result between Tamiflu and *Theraflu*, because the names sound and look alike. The drug information specialist also noted that Tamiflu and *Theraflu* are available in similar oral dosage forms; Tamiflu is available as capsules, and *Theraflu* is available as caplets. This report was a drug information request and did not result in an adverse event. Other reports from the AERS and DQRS searches were either possible drug interactions or adverse drug reactions, and did not involve medication errors.

B. SAFETY EVALUATOR RISK ASSESSMENT

The review of the post-marketing medication error reports revealed a single incidence of name confusion involving Tamiflu and *Theraflu*. The potential medication error report was an inquiry made to a drug information center; a physician mistakenly inquired about *Theraflu*, instead of Tamiflu. The potential error was due to the name similarity; Tamiflu is phonetically very similar and look similar to *Theraflu*.

In addition to similar sound-alike and look-alike names, Tamiflu and *Theraflu* also have overlapping indications and oral dosage forms. Tamiflu is indicated for the treatment of uncomplicated acute illness due to influenza infection, and *Theraflu* is indicated for the temporary relief of symptoms associated with flu, common cold, and upper respiratory infections. Tamiflu is currently available as capsules, and if the proposed application is approved, it will also be supplied as powder for oral suspension. *Theraflu* is supplied as powder in foil packets; each packet needs to be dissolved in 6 ounce of hot water. *Theraflu* is also supplied as caplets.

Despite similar sound-alike and look-alike names, indication, and dosage forms, only one potential medication error was reported to the agency so far. One reason may have contributed to the low incidence of medication error reports; Tamiflu is a new drug, and was first available during the last year's flu season. However, it is difficult to ascertain the magnitude of name confusion relating to Tamiflu with only one medication error report. Futhermore, this potential medication error report did not result in an

adverse event, and therefore, is insufficient evidence to warrant a name change at this time. OPDRA will continue to monitor post-marketing medication errors in association with the proprietary name, Tamiflu.

In regard to the proposed name, Tamiflu for Oral Suspension, OPDRA encourages the use of the same proprietary name, "Tamiflu," since different formulations containing the same active ingredient do not require the use of a new proprietary name. However, in order to differentiate the capsules and the oral suspension, we recommend including the dosage form, "for Oral Suspension," in the established name.

Given the above findings, OPDRA has no objection to the continued use of the proprietary name, Tamiflu, at this time, since the proposed formulation contains the same active ingredient as the capsule.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the container label, the carton labeling, and the package insert for Tamiflu for Oral Suspension, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

A. CONTAINER LABEL

B. CARTON LABELING

C. PACKAGE INSERT LABEL

1. Dosage and Administration

   a. The statement reads, [redacted] This statement is

misleading. For example, if a 5-year-old child can swallow capsules, he or she can take 75 mg capsules. However, this dose is inconsistent with the recommended dose, [redacted] for oral suspension. We recommend clarifying the dosing instruction.

b. The recommended dose of Tamiflu oral suspension is only stated in milligrams. We also recommend stating the doses [redacted] since the final proposed product is an oral suspension. In a clinical setting, prescribers frequently order liquid medications in [redacted]

c. The sample of the oral dispenser was not provided, but according to the insert, an oral dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension. When the oral dispenser is available, we recommend calibrating the oral dispenser in units of volume corresponding to the strengths. In a clinical setting, a pharmacist frequently generates pharmacy labels instructing patients to take liquid medications in volume, such as mL or CC.

d. We note that " [redacted] " is not included on the oral dispenser. We recommend including " [redacted] along with the corresponding volume on the oral dispenser, since [redacted] is one of the recommended doses.

e. It is unclear if "twice daily for 5 days," applies to Tamiflu oral suspension as well as the capsules. We recommend clarifying dosing interval for Tamiflu for Oral Suspension.

2. How Supplied

In this section, we recommend deleting "in 100 mL glass bottle." Placing oseltamivir powder in a 100 mL bottle implies that the total content of oseltamivir phosphate is 1200 mg, not 750 mg.

3. Preparation of Oral Suspension

The *Preparation of Oral Suspension* section is located [redacted] section. We recommend relocating the *Preparation of Oral Suspension* section after the *Special Dosage Instruction* section.

IV. RECOMMENDATIONS

A. OPDRA has no objections to the continued use of the proprietary name, Tamiflu.

B. OPDRA recommends implementation of the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Hye-Joo Kim, Pharm.D. at 301-827-3243.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

/s/

Hye-Joo Kim
1/4/01 02:26:33 PM
UNKNOWN

Jerry Phillips
1/5/01 10:45:25 AM
DIRECTOR

This consult has been previously signed off manually

Martin Himmel
1/9/01 01:23:36 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 12, 2000

To: Barbara S. Taylor	**From:** Grace Carmouze
Company: Hoffmann - La Roche, Inc.	Division of Antiviral Drug Products
Fax number: 973/562-3700	**Fax number:** 301/827-2471
Phone number: 973/562-3664	**Phone number:** 301/827-2335
Subject: NDA 21-246 Postmarketing Commitments	
Total no. of pages including cover : 3	

Comments:

Document to be mailed: ☐ **YES** ✓ **NO**

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 12, 2000

To: Barbara S. Taylor, Ph.D.,
Program Director, Drug Regulatory Affairs

Address: Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

From: Grace N. Carmouze, Regulatory Project Manager, HFD-530

Through: Jeffery Murray, M.D., M.P.H, Medical Team Leader, HFD-530
Linda Lewis, M.D., Medical Officer Reviewer, HFD-530
Narayana Battula, Ph.D., Microbiology Reviewer, HFD-530

NDA: 21-246

Subject: Postmarketing Commitment Recommendations

Below are the division's recommended postmarketing commitments with estimated dates for completion for your review.

1. Using the resistant clinical isolates that you have from both adult and pediatric trials, evaluate the potential for cross-resistance to other neuraminidase inhibitors [redacted] (to be completed by Jan., 2002).

2. In future clinical studies (treatment or prophylaxis), further characterize the clinical aspects of infection with influenza resistant to neuraminidase 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 (to be completed by Jan., 2003).

3. Complete additional studies to evaluate the antibody responses to both wild-type and resistant influenza with respect to their cross-protective potential (to be completed by Jan., 2003).

4. In additional studies, further evaluate the [redacted] of the to-be-marketed dose of Tamiflu™ for oral suspension [redacted] in children younger than 5 years of age (to be completed by Jan., 2003).

In your response, please include estimated timelines for the following:

- Protocol submission
- Study start
- Final report submission

DAVDP/HFD-530 • 5600 Fishers Lane • Rockville, MD 20857 • (301) 827-2335 • Fax: (301) 827-2523

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Grace N. Carmouze
Regulatory Project Manager
Division of Antiviral Drug Products

/s/

Grace Carmouze
12/12/00 10:50:52 AM
CSO
NDA 21-246 Postmarketing Commitment Recommendations

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 1, 2000

To: Barbara S. Taylor	**From:** Grace Carmouze
Company: Hoffmann - La Roche, Inc.	Division of Antiviral Drug Products
Fax number: 973/562-3700	**Fax number:** 301/827-2471
Phone number: 973/562-3664	**Phone number:** 301/827-2335
Subject: NDA 21-246 Labeling Comments	
Total no. of pages including cover: 2	
Comments:	

Document to be mailed: ☐ YES ✓ NO

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 1, 2000

To: Barbara S. Taylor, Ph.D., Program Director, Drug Regulatory Affairs

Address: Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

From: Grace N. Carmouze, Regulatory Project Manager, HFD-530

Through: Jeffery Murray, M.D., M.P.H, Medical Team Leader, HFD-530
Linda Lewis, M.D., Medical Officer Reviewer, HFD-530
Kellie Reynolds, Pharm.D., Biopharmaceutics Team Leader, HFD-530
Jenny Zheng, Ph.D., Biopharmaceutics Reviewer, HFD-530
Walla Dempsey, Ph.D., Associate Director, HFD-530
Rebecca Sheets, Ph.D., Acting Microbiology Reviewer, HFD-530
Narayana Battula, Ph.D., Microbiology Reviewer, HFD-530
Stephen Miller,Ph.D., Chemistry Team Leader, HFD-530
Daniel Boring, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-246

Subject: Labeling comments

These comments related to the suspension label (and pediatric indication) should be viewed in the context of the draft label submitted by the sponsor dated 11/28/00.

1. We believe that the pediatric clinical trials provide adequate numbers of patients infected with influenza B to be assured that Tamiflu is active in natural infection with influenza B. It is now appropriate to delete the following sections of the label

2. After additional consideration, the review team still disagrees with the assertions suggesting that Although there are only 9 children in study WV15758 who were identified with mutant virus, these children appeared to have a somewhat longer course of illness compared to children receiving Tamiflu in whom resistant virus was not identified. Therefore, please delete the last 2 sentences contained in lines 49-51.

3. In the **CLINICAL PHARMACOLOGY:** ***Pharmacokinetics*** section [redacted] please add "and oseltamivir carboxylate" after "oseltamivir".

4. In the **CLINICAL PHARMACOLOGY:** ***Pharmacokinetics*** section, [redacted] please add appropriate "n" following 5 to 16 years and 3 to 12 years.

5. In the **CLINICAL PHARMACOLOGY:** ***Pharmacokinetics*** section, [redacted] please delete: " [redacted] , and add "For oseltamivir carboxylate, apparent total clearance decreases linearly with increasing age (up to 12 years)."

6. Thank you for making the requested changes in the ***Description of Clinical Studies: Studies in Naturally Occurring Influenza: Pediatric Patients*** section. It is, however, not necessary to be so precise in the reduction of duration of illness. Please change [redacted] ' to "1.5 hours".

7. As we discussed in our conference call of 11/27/00, the division anticipates that the sentence regarding [redacted] will be deleted in the ***Description of Clinical Studies: Studies in Naturally Occurring Influenza: Pediatric Patients*** (lines 168-169). We agree to discuss further evaluation of your database and use of this data at some time in the future.

8. In ***Description of Clinical Studies: Studies in Naturally Occurring Influenza: Pediatric Patients*** lines 169-170, please delete the sentence regarding the symptom ' [redacted] ". This symptom was included as one of the components of the primary endpoint that is reported in an earlier paragraph. It is not the Division's practice to report individual symptoms when so many are analyzed as part of the secondary endpoints. It is also counterintuitive and potentially misleading that a child may " [redacted] " sooner than he is free of illness. Additionally, we have not been able to confirm your analysis on this point.

9. In the ***Carcinogenesis, Mutagenesis, and Impairment of Fertility*** section please delete [redacted]

10. In the **ADVERSE REACTIONS:** ***Treatment*** **Studies on Pediatric Patients** section, [redacted] the proposed revision does nothing to clarify the time frame during which the adverse events were reported. The reviewer's intention was to identify in some way that the reported events occurred within 7 days of beginning treatment (the 5 day dosing period and the following 2 days) and does not represent any long term toxicity reporting. In retrospect, this may be of little significance and the original wording was clearer than the revised version.

11. In the **ADVERSE REACTIONS:** ***Treatment*** **Studies on Pediatric Patients** section, [redacted] , please change the word " [redacted] to "resolved".

12. In the **OVERDOSAGE** section, please delete the last sentence. It is of little clinical relevance since patients who receive Tamiflu for prophylaxis may receive more than a single pack of 10 capsules. An alternative would be to include the

13. Please make some provisions in the label for how Tamiflu suspension should be dosed (i.e., volume required) in the event that a family accidentally loses or damages the dosing dispenser.

14. In **DOSAGE AND ADMINISTRATION:** ***Standard Dosage –Treatment of Influenza*** section, , please add "in adults and adolescents 13 years and older".

15. In **DOSAGE AND ADMINISTRATION** section, please add headers for treatments in ' and "pediatric patients".

16. In the table under **DOSAGE AND ADMINISTRATION** section, please change lbs" to "33 lbs" for consistency with kg, and add "twice daily" after each recommended dose. This was an error in the table we sent you previously. Please add "twice daily" after each recommended dose and

17. In **DOSAGE AND ADMINISTRATION:** ***Standard Dosage –Treatment of Influenza*** section, please add "A 75 mg dose can be measured using a combination of 30 mg and 45 mg."

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Grace N. Carmouze
Regulatory Project Manager
Division of Antiviral Drug Products

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 30, 2000

To: Duane Voss, CMC Drug Regulatory Affairs

Address: Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

From: Grace N. Carmouze, Regulatory Project Manager, HFD-530

Through: Stephen Miller, Ph.D., Chemistry Team Leader, HFD-530
Daniel Boring, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-246

Subject: CMC Postmarketing Commitment

Please respond to the DAVDP recommended postmarketing commitment below.

The applicant commits to reassess the acceptance criteria for degradants in the drug product specification when the 36-month timepoint of the stability studies on the first three commercial scale lots of oseltamivir for oral suspension has been completed. During this reassessment, release and stability data from both commercial and representative NDA lots will be considered. The applicant will submit this data, with the proposed acceptance criteria, through a prior approval supplement to NDA 21-246.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Grace N. Carmouze
Regulatory Project Manager
Division of Antiviral Drug Products

/s/

Grace Carmouze
12/6/00 10:17:58 AM
CSO
NDA 21-246 CMC Postmarketing Commitment Recommendations

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 22, 2000

To: ~~Barbara Taylor, Ph.D.~~ Duane Voss

From: Grace Carmouze

Company: Hoffmann - La Roche, Inc.

Division of Antiviral Drug Products

Fax number: 973/562-3700

Fax number: 301/827-2471

Phone number: 973/562-3664

Phone number: 301/827-2335

Subject: NDA 21-246 Labeling Comments

Total no. of pages including cover: 4

Comments:

Document to be mailed: **YES** **NO**

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 22, 2000

To: Duane Voss, CMC Drug Regulatory Affairs

Address: Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

From: Grace N. Carmouze, Regulatory Project Manager, HFD-530

Through: Stephen Miller, Ph.D., Chemistry Team Leader HFD-530
Daniel Boring, Ph.D., Chemistry Reviewer, HFD-530

NDA: 21-246

Subject: Comments for Labeling

The following comments refer to your submission dated November 14, 2000.

1. [redacted]

2. [redacted]

3. Please provide some data on the level of [redacted] that is contained in the powder for suspension. If [redacted] is present in the reconstituted solution at levels below 0.5 %, it need not be included as a constituent on the package insert. However if [redacted] is present, please suggest an appropriate qualifying statement [e.g., [redacted] (typically less than x% after reconstitution)"]. Since there are no toxicity concerns for [redacted] its presence may be omitted.

4. Please include instructions for how to obtain the 75 mg dose.

5. [redacted]

DAVDP/HFD-530 5600 Fishers Lane Rockville, MD 20857 (301) 827-2335 Fax: (301) 827-2523

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Grace N. Carmouze
Regulatory Project Manager
Division of Antiviral Drug Products

/s/

Grace Carmouze
11/22/00 11:17:31 AM
CSO
NDA 21-246 CMC labeling

Stephen Paul Miller
11/22/00 12:54:08 PM
CHEMIST
I concur

MESSAGE CONFIRMATION

11/22/00 13:00
ID=DAVDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
11/22	00'47"	973 562 3700	CALLING	04	OK	0000

11/22/00 12:59 DAVDP → 919735623700 NO.736 P01

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 22, 2000

To: ~~Barbara Taylor, Ph.D.~~ Duane Voss

From: Grace Carmouze

Company: Hoffmann - La Roche, Inc.

Division of Antiviral Drug Products

Fax number: 973/562-3700

Fax number: 301/827-2471

Phone number: 973/562-3664

Phone number: 301/827-2335

Subject: NDA 21-246 Labeling Comments

Total no. of pages including cover: 4

Comments:

3 Page(s) Withheld

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 21, 2000

To: Barbara Taylor, Ph.D.	**From:** Grace Carmouze
Company: Hoffmann - La Roche, Inc.	Division of Antiviral Drug Products
Fax number: 973/562-3700	**Fax number:** 301/827-2471
Phone number: 973/562-3664	**Phone number:** 301/827-2335
Subject: NDA 21-246 Labeling Comments	
Total no. of pages including cover: 4	

Comments:

Document to be mailed: ☐ YES ✓ NO

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 21, 2000

To: Barbara Taylor, Ph.D., Program Director,
Drug Regulatory Affairs

Address: Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

From: Grace N. Carmouze, Regulatory Project Manager, HFD-530

Through: Jeffrey Murray, M.D., M.P.H., Medical Team Leader HFD-530
Linda Lewis, M.D., Medical Officer, HFD-530

NDA: 21-246

Subject: Labeling Comments

The following DAVDP comments related to the suspension label (and pediatric indication) should be viewed in the context of the final label agreed upon during the adult prophylaxis indication (November 17, 2000). Please note that the line numbers itemized below refer to the e-mail transmission received on November 20, 2000.

1. The Microbiology Reviewer has suggested the following revisions to the proposed suspension label Microbiology Section incorporating data from the pediatric clinical trials.

   1.1 Beginning in [redacted], restore the previous resistance rate of 1.3% (4/301) as DAVDP agreed upon in the adult treatment indication.

   1.2 In the description of the pediatric patients, substitute a resistance rate of 8.6% (9/105). This represents the resistance rate calculation using the method that was agreed upon at the pre-NDA meeting (February 18, 2000) and that you outlined in your original analysis plan.

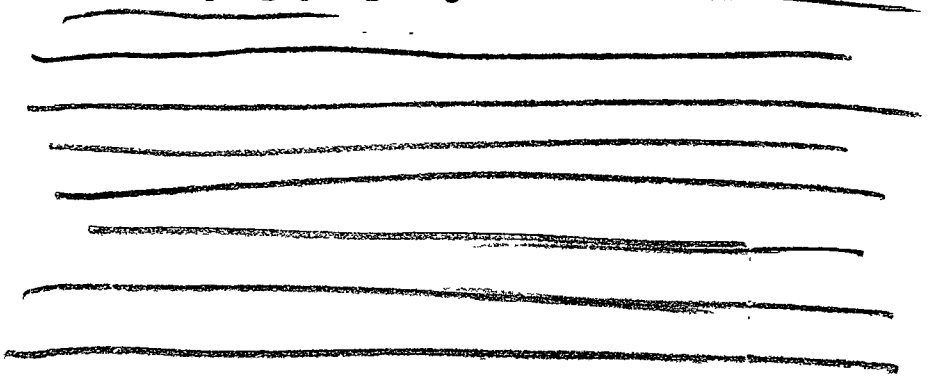
   1.3 Delete the [redacted] which claims the [redacted] DAVDP believes that currently available data fail to support this claim.

   1.4 Delete [redacted] stating [redacted] Given the relatively small number of isolates of influenza B studied DAVDP believes there are insufficient data to say [redacted]

2. In the section on INDICATIONS AND USAGE, please incorporate the indication for pediatrics into the current statement regarding adults and adolescents. For example, "TAMIFLU is indicated for the treatment of uncomplicated acute illness due to influenza infection in patients older than 1 year of age who have been symptomatic for no more than 2 days."

3. In the *Description of Clinical Studies - Treatment of Influenza: Pediatric Patients*, please follow the format used in the description of the adult treatment studies. For example, please include the total number of patients enrolled and number of patients with proven influenza infection. Please include the dose of Tamiflu suspension given in the clinical trial. Please express the difference in median time to freedom from illness in days

4. Please delete the paragraph regarding



5. In the section ADVERSE REACTIONS: *Treatment Studies in Pediatric Patients*, please include a comment identifying the timeframe covered in the reported adverse reactions. For example, "Adverse events occurring within the on-treatment period in > 1% of pediatric patients....."

Additional suggestions regarding the pediatric adverse event reporting and the pediatric pharmacokinetics and dosing may be forwarded to you in the near future after additional consideration by the review team.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Grace N. Carmouze
Regulatory Project Manager
Division of Antiviral Drug Products

/s/

Grace Carmouze
11/21/00 10:58:28 AM
CSO
NDA 21-246 Labeling Comments

Jeffrey Murray
11/21/00 12:28:42 PM
MEDICAL OFFICER

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Barbara Taylor, Ph.D., Program Director, Drug Regulatory Affairs

Fax Number: (973) 562-3700

Date: October 27, 2000

Company: Hoffmann-La Roche Inc.

No. of pages (excluding cover): 2

Message: Dosing proposal based on weight-Tamiflu Suspension

From: Sean J. Belouin, R.Ph., Project Manager

Telephone: (301) 827- 2335

Fax Number: (301) 827-2471

Mail:
Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:
Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 27, 2000

To: Barbara Taylor, Ph.D., Program Director, Drug Regulatory Affairs

Address: Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

From: Grace N. Carmouze, Regulatory Project Manager, HFD-530

Through: Jeffrey Murray, M.D., M.P.H., Medical Team Leader, HFD-530

NDA: 21-246

Subject: Clinical comment and pediatric dosing attachment

This comment is being conveyed on behalf of Dr. Jeff Murray:

Please see Attachment. This is the Division's flat dosing proposal based on weight using Tamiflu suspension.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

GN

Grace N. Carmouze
Regulatory Project Manager
Division of Antiviral Drug Products

Concurrence
HFD-530/MOTL/Murray
HFD-530/RPM/Carmouze

cc:
Original NDA 21-246
Division File
HFD-530/MO/Lewis
HFD-530/RPM/Carmouze

Facsimile

Location: V:\DAVDP\CSO\CARMOUZE\NDA\21246\FAXES\001027fx.doc

11/6/02

HFD-530
Carmouze

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Duane Voss, CMC Drug Regulatory Affairs

Fax Number: (973) 562-3700

Date: October 12, 2000

Company: Hoffmann-La Roche Inc.

No. of pages (excluding cover): 3

Message: CMC comments

From: Grace N. Carmouze, Project Manager

Telephone: (301) 827- 2335

Fax Number: (301) 827-2471

Mail:
Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:
Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 12, 2000

To: Duane Voss, Program Director, CMC Drug Regulatory Affairs

Address: Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

From: Grace N. Carmouze, Regulatory Project Manager, HFD-530

Through: Stephen Miller, Ph.D., Chemistry Team Leader, HFD-530 /S/
Daniel Boring, Ph.D., Chemistry Reviewer, HFD-530 /S/

NDA: 21-246

Subject: CMC Comments

These comments are being conveyed on behalf of Dr. Dan Boring, Chemistry Reviewer, and are directed towards your submission dated June 15, 2000.

DAVDP acknowledges that late in development, homogeneity, during the course of a manufacturing run, was a demonstrated issue and measures were taken to correct this problem.

Because of the variability in the pharmacokinetic data of study WP16225 (using formulation V20), concerns were raised about whether older formulations (V06 and V20) had also demonstrated similar problems with homogeneity.

DAVDP would like to know if you have any batch data from any source (e.g., clinical, PK, archive, stability, etc.), using the older formulations (V06 and V20), that would indicate that no manufacturing problems with homogeneity existed.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Grace N. Carmouze
Regulatory Project Manager
Division of Antiviral Drug Products

Concurrence
HFD-530/ChemTL/Miller
HFD-530/Chem/Boring
HFD-530/RPM/Carmouze-12-Oct-00

cc:
Original NDA 21-246
Division File
HFD-530/MO/Lewis
HFD-530/ChemTL/Miller
HFD-530/Chem/Boring
HFD-530/RPM/Carmouze
HFD-530/BiopharmTL/Reynolds
HFD-530/Biopharm/Zheng

Facsimile

Location: V:\DAVDP\CSO\CARMOUZE\NDA\21246\FAXES\001012fx.doc

DS 10/12/00

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Duane Voss, Program Director, CMC Drug Regulatory Affairs

Fax Number: (973) 562-3700

Date: September 21, 2000

Company: Hoffmann-La Roche Inc.

No. of pages (excluding cover): 2

Message: CMC Comments for NDA 21-246

From: Grace N. Carmouze, Project Manager

Telephone: (301) 827- 2335

Fax Number: (301) 827-2471

Mail:
Division of Antiviral Drug Products
5600 Fishers Lane (HFD-530)
Rockville, Maryland 20857

Courier:
Division of Antiviral Drug Products
HFD-530
Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

1770.530
Carmouze

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 21, 2000

To: Duane Voss, Program Director, CMC Drug Regulatory Affairs

Address: Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

From: Grace N. Carmouze, Regulatory Project Manager, HFD-530

Through: Stephen Miller, Ph.D., Chemistry Team Leader, HFD-530 LSM
Daniel Boring, Ph.D., Chemistry Reviewer, HFD-530 LSM

NDA: 21-246

Subject: CMC Comments

These comments are being conveyed on behalf of Dr. Dan Boring, Chemistry Reviewer, and are directed towards the amendment dated September 1, 2000.

1. DAVDP strongly recommends that you be prepared to launch TAMIFLU (oseltamivir phosphate) for Oral Suspension with the drug product manufactured, filled and release tested at F. Hoffmann-La Roche Ltd., Basel, Switzerland and packaged at [redacted]. If approval is granted, this will assure that a commercial launch can quickly follow, regardless of the inspection status of your Nutley, NJ facility.

2. Please amend your application with a commitment to undertake these recommendations, or with a discussion of alternate plans.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Grace N. Carmouze
Regulatory Project Manager
Division of Antiviral Drug Products

Concurrence
HFD-530/ChemTL/Miller
HFD-530/Chem/Boring
HFD-530/RPM/Carmouze-[illegible]-Sep-00

cc:
Original NDA 21-246
Division File
HFD-530/MO/Lewis
HFD-530/ChemTL/Mille-
HFD-530/Chem/Boring
HFD-530/RPM/Carmouze

Facsimile

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