

21087/SE1-002

K2.1

NDA 21-087/SE1-002

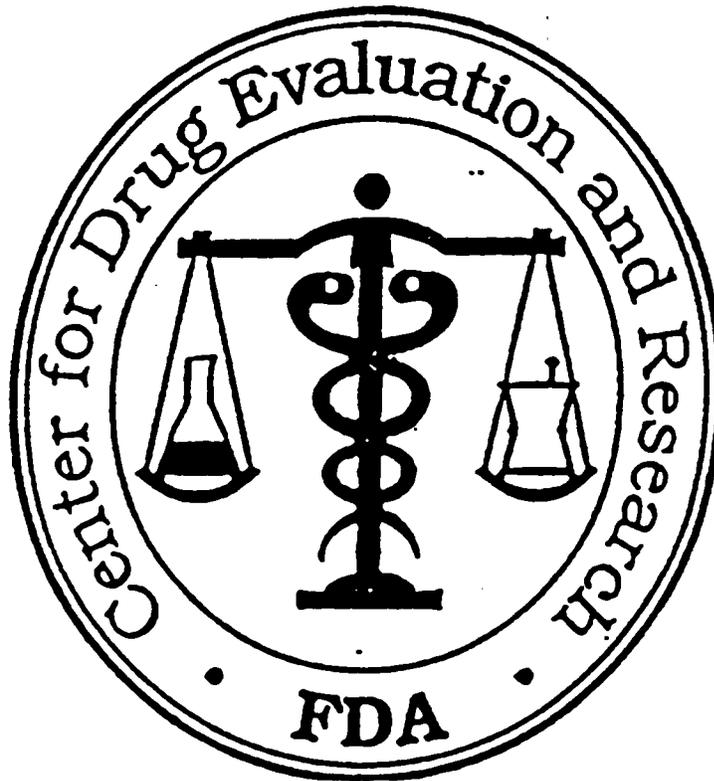
N21087



Tamiflu™ (oseltamivir phosphate)
75mg Capsule



REC.
1-4-01
8:45AM



DIVISION OF ANTIVIRAL DRUG PRODUCTS
HFD-530

Teresa Wu M.D., Ph.D.
Medical Officer

Grace N. Carmouze
Regulatory Project Manager

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-087</u> / SE <u>1</u> - <u>002</u>	
Drug <u>Hoffmann-La Roche</u>	Applicant <u>Hoffmann-La Roche, Inc.</u>
RPM <u>Grace N. Carmouze</u>	Phone <u>301/827-2335</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input type="checkbox"/> S <input checked="" type="checkbox"/> P	
Pivotal IND(s) <u>53,093</u>	
Application classifications: Chem Class <u>6</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>November 22, 2000</u> Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
 User Fee Waiver (attach waiver notification letter)
 User Fee Exemption

- ◆ Action Letter..... AP AE NA

- ◆ Labeling & Labels
 - FDA revised labeling and reviews..... _____
 - Original proposed labeling (package insert, patient package insert) _____
 - Other labeling in class (most recent 3) or class labeling..... _____
 - Has DDMAC reviewed the labeling? Yes (include review) No
 - Immediate container and carton labels N/A
 - Nomenclature review N/A

- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.
 - Exception for review (Center Director's memo)..... N/A
 - OC Clearance for approval..... N/A



- ◆ Status of advertising (if AP action) Reviewed (for Subpart H – attach review) ✗ Materials requested in AP letter

- ◆ Post-marketing Commitments
 - Agency request for Phase 4 Commitments..... ✗
 - Copy of Applicant’s commitments ✗

- ◆ Was Press Office notified of action (for approval action only)?..... ✗ Yes No
 Copy of Press Release or Talk Paper..... _____

- ◆ Patent
 - Information [505(b)(1)] ✗
 - Patent Certification [505(b)(2)]..... _____
 - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... _____

- ◆ Exclusivity Summary ✗

- ◆ Debarment Statement ✗

- ◆ Financial Disclosure
 - No disclosable information ✗
 - Disclosable information – indicate where review is located _____

- ◆ Correspondence/Memoranda/Faxes ✗

- ◆ Minutes of Meetings ✗
 - Date of EOP2 Meeting _____
 - Date of pre NDA Meeting _____
 - Date of pre-AP Safety Conference N/A _____

- ◆ Advisory Committee Meeting N/A
 - Date of Meeting _____
 - Questions considered by the committee _____
 - Minutes or 48-hour alert or pertinent section of transcript _____

- ◆ Federal Register Notices, DESI documents N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Summary memoranda (e.g., Office Director’s memo, Division Director’s memo, Group Leader’s memo) ✗

- ◆ Safety Update review(s) See MO review
- ◆ Pediatric Information
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred
Pediatric Page..... X
 - Pediatric Exclusivity requested? Denied Granted Not Applicable No
- ◆ Statistical review(s) and memoranda X
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) N/A
Recommendation for scheduling
- ◆ Microbiology (efficacy) review(s) and memoranda X
- ◆ DSI Audits
 Clinical studies bioequivalence studies

CMC INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

- ◆ CMC review(s) and memoranda X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability X
- ◆ DMF review(s) X
- ◆ Environmental Assessment N/A
- ◆ Micro (validation of sterilization) review(s) and memoranda See CMC review
- ◆ Facilities Inspection (include EES report)
Date completed See Original NDA Acceptable Not Acceptable
- ◆ Methods Validation Completed Not Completed
April 11, 2000

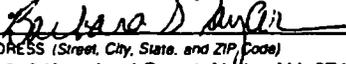
PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

- ◆ Pharm/Tox review(s) and memoranda X
- ◆ Memo from DSI regarding GLP inspection (if any) X N/A

- ◆ Statistical review(s) of carcinogenicity studies § N/A
- ◆ CAC/ECAC report § N/A

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		Form Approved OMB No 0910-0338 Expiration Date April 30, 2000 See OMB Statement on page 2
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE (Title 21, Code of Federal Regulations, 314 & 601)		FOR FDA USE ONLY
		APPLICATION NUMBER
APPLICANT INFORMATION		
NAME OF APPLICANT Hoffmann-La Roche Inc		DATE OF SUBMISSION May 22, 2000
TELEPHONE NO. (Include Area Code) (973) 562-3664		FACSIMILE (FAX) Number (Include Area Code) (973) 562-3700/3554
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 340 Kingsland Street Nutley, New Jersey 07110-1199		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Barbara S. Taylor, Ph.D. Program Director Drug Regulatory Affairs
PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		NDA 21-087
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) oseltamivir phosphate		PROPRIETARY NAME (trade name) IF ANY TAMIFLU
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) <small>(3R,4R,5S)-4-Acetylamino-5-amino-3-(1-ethoxypropoxy)-1-cyclohexane-1-carboxylic acid, ethyl ester phosphate (1:1)</small>		CODE NAME (if any) R0 64-0796
DOSAGE FORM Capsules	STRENGTHS 75 mg (free base equivalent)	ROUTE OF ADMINISTRATION Oral
(PROPOSED) INDICATION(S) FOR USE Treatment of Influenza		
APPLICATION INFORMATION		
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507		
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRE-SUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
REASON FOR SUBMISSION Supplemental New Drug Application		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED 116		THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION		
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready).		
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)		

This application contains the following items. (Check all that apply)		
<input checked="" type="checkbox"/>	1	Index
<input checked="" type="checkbox"/>	2	Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input checked="" type="checkbox"/>	3	Summary (21 CFR 314.50 (c))
	4	Chemistry section
		A Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
		B Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
		C Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
<input checked="" type="checkbox"/>	5	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
<input checked="" type="checkbox"/>	6	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
<input checked="" type="checkbox"/>	7	Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
<input checked="" type="checkbox"/>	8	Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
<input checked="" type="checkbox"/>	10	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
<input checked="" type="checkbox"/>	11	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
<input checked="" type="checkbox"/>	12	Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
<input checked="" type="checkbox"/>	13	Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
<input checked="" type="checkbox"/>	14	A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
<input checked="" type="checkbox"/>	15	Establishment description (21 CFR Part 600, if applicable)
<input checked="" type="checkbox"/>	16	Debarment certification (FD&C Act 306 (k)(1))
	17	Field copy certification (21 CFR 314.50 (k) (3))
<input checked="" type="checkbox"/>	18	User Fee Cover Sheet (Form FDA 3397)
	19	OTHER (Specify) Phase IV Commitments
CERTIFICATION		
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:		
<ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202. 5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81. 7. Local, state and Federal environmental impact laws. 		
If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.		
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.		
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Barbara S. Taylor, Ph.D., Program Director, DRA	May 22, 2000
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
340 Kingsland Street, Nutley NJ 07110 HLR 2000-773		(973) 562-3664
Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to		
DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0338) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W. Washington, DC 20201		An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Please DO NOT RETURN this form to this address.		



NDA 21-087/S-002

Hoffmann-La Roche, Inc
Attention: Barbara S. Taylor, Ph.D.
Program Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Dr. Taylor:

Please refer to your supplemental new drug application dated May 22, 2000, received May 22, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tamiflu® (oseltamivir phosphate) Capsules 75mg.

We acknowledge receipt of your submissions dated:

July 21, 2000	October 11, 2000
July 25, 2000	October 18, 2000
August 8, 2000	October 19, 2000
August 10, 2000	October 20, 2000
August 18, 2000	November 6, 2000 (2)
August 22, 2000	November 10, 2000
August 31, 2000	November 14, 2000
September 1, 2000	November 16, 2000
September 28, 2000	

This supplemental new drug application provides for the use of Tamiflu (oseltamivir phosphate) 75 mg for the prophylaxis of influenza virus in adults and adolescents 13 years and older.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (package insert dated November 16, 2000, patient package insert dated November 16, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-087/S-002." Approval of

this submission by FDA is not required before the labeling is used.

We remind you of your post marketing commitments specified in your submission dated November 16, 2000. These commitments, along with estimated completion dates, are listed below.

1. Please investigate the effectiveness and safety of oseltamivir for the treatment and prevention of influenza infection in immunocompromised patients. In this population the emergence of resistant viruses should be closely monitored. {Fourth quarter 2003}
2. Please study the pharmacokinetics and safety of oseltamivir, given at the proposed dosing regimens based on simulations, in end-stage renal dialysis subjects. {Fourth quarter 2003}
3. Please submit a final study report for the completed study of oseltamivir in subjects with impaired hepatic function. {Second quarter 2001}
4. Please submit a final study report for the completed long-term carcinogenicity studies in mice and rats. {July 31, 2002 (for mice) ; December 19, 2001 (for rats)}
5. Please explore the isolation, characterization and clinical implications of oseltamivir-dependent influenza virus variants. {To be discussed with the Agency second quarter 2001}

In addition, we remind you of the post marketing commitments for the treatment of influenza virus, previously agreed upon on October 25, 1999.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your post marketing commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these post marketing commitments must be clearly designated "Post Marketing Commitments."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that at this time you have fulfilled the requirements of 21 CFR 314.55 for adolescents. We are deferring the requirement for studies in pediatric patients under 12 years of age for the indication of prophylaxis of influenza until December 31, 2004.

Please refer to the Written Request issued by this Division on March 1, 2000 for the study of Tamiflu in pediatric patients for the indication of treatment of influenza virus.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Ms. Grace N. Carmouze, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

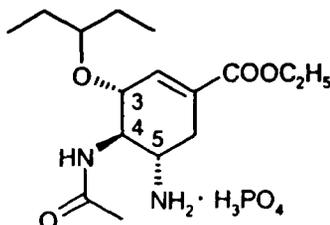
Debra B. Birnkrant, M.D.
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure



TAMIFLU™
(oseltamivir phosphate)
CAPSULES

DESCRIPTION: TAMIFLU (oseltamivir phosphate) is available as a capsule containing 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate. In addition to the active ingredient, each capsule contains pregelatinized starch, talc, povidone K 30, croscarmellose sodium, sodium stearyl fumarate, ethanol, and purified water. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide. Each capsule is printed with blue ink, which includes FD&C Blue #2 as the colorant. Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is $C_{16}H_{28}N_2O_4$ (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt. The structural formula is as follows:



MICROBIOLOGY: Mechanism of Action: Oseltamivir is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate. The proposed mechanism of action of oseltamivir is via inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

Antiviral Activity In Vitro: The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of oseltamivir carboxylate required for inhibition of influenza virus were highly variable depending on the assay method used and the virus tested. The 50% and 90% inhibitory concentrations (IC₅₀ and IC₉₀) were in the range of 0.0008 μ M to >35 μ M and 0.004 μ M to >100 μ M, respectively (1 μ M=0.284 μ g/mL). The relationship between the in vitro antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established.

Drug Resistance: Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have been recovered in vitro by passage of virus in the presence of increasing concentrations of oseltamivir carboxylate. Genetic analysis of these isolates showed that reduced susceptibility to oseltamivir carboxylate is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both.

In challenge studies in the treatment of human subjects infected with influenza virus, 3% (3/102) of the post-treatment isolates showed emergence of influenza variants with decreased neuraminidase susceptibility to oseltamivir carboxylate. Genotypic analysis of these variants showed a specific mutation in the active site of neuraminidase compared to challenge virus.

In clinical studies of post-exposure and seasonal prophylaxis, determination of resistance was limited by the low overall incidence rate of influenza infection and prophylactic effect of TAMIFLU.

In clinical studies in the treatment of naturally acquired infection with influenza virus, 1.3% (4/301) of post-treatment isolates showed emergence of influenza variants with decreased neuraminidase susceptibility to oseltamivir carboxylate.

Genotypic analysis of these variants showed a specific mutation in the active site of neuraminidase compared to pretreatment isolates. The contribution of resistance due to alterations in the viral hemagglutinin has not been fully evaluated.

Cross-resistance: Cross-resistance between zanamivir-resistant influenza mutants and oseltamivir-resistant influenza mutants has been observed in vitro.

Due to limitations in the assays available to detect drug-induced shifts in virus susceptibility, an estimate of the incidence of oseltamivir resistance and possible cross-resistance to zanamivir in clinical isolates cannot be made. However, one of the three oseltamivir-induced mutations in the viral neuraminidase from clinical isolates is the same as one of the three mutations observed in zanamivir-resistant virus. Insufficient information is available to fully characterize the risk of emergence of TAMIFLU resistance in clinical use.

Immune Response: No influenza vaccine interaction study has been conducted. In studies of naturally acquired and experimental influenza, treatment with TAMIFLU did not impair normal humoral antibody response to infection.

Influenza Challenge Studies: Antiviral activity of TAMIFLU was supported for influenza A and B by experimental challenge studies in volunteers who received intranasal inoculations of challenge strains of influenza virus. These subjects received TAMIFLU either 24 hours following or 24 hours before virus challenge.

CLINICAL PHARMACOLOGY: PHARMACOKINETICS:

Absorption and Bioavailability: Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure after oral dosing (Table 1).

Table 1. Mean (% CV) Pharmacokinetic Parameters of Oseltamivir and Oseltamivir Carboxylate After a Multiple 75 mg Twice Daily Oral Dose (n=20)

Parameter	Oseltamivir	Oseltamivir Carboxylate
C _{max} (ng/mL)	65.2 (26)	348 (18)
AUC _{0-12h} (ng·h/mL)	112 (25)	2719 (20)

Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily (see DOSAGE AND ADMINISTRATION).

Coadministration with food has no significant effect on the peak plasma concentration (551 ng/mL under fasted conditions and 441 ng/mL under fed conditions) and the area under the plasma concentration time curve (6218 ng·h/mL under fasted conditions and 6069 ng·h/mL under fed conditions) of oseltamivir carboxylate.

Distribution: The volume of distribution (V_d) of oseltamivir carboxylate, following intravenous administration in 24 subjects, ranged between 23 and 26 liters.

The binding of oseltamivir carboxylate to human plasma protein is low (3%). The binding of oseltamivir to human plasma protein is 42%, which is insufficient to cause significant displacement-based drug interactions.

Metabolism: Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. Neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome P450 isoforms.

Elimination: Absorbed oseltamivir is primarily (>90%) eliminated by conversion to oseltamivir carboxylate. Plasma concentrations of oseltamivir declined with a half-life of 1 to 3 hours in most subjects after oral administration. Oseltamivir carboxylate is not further metabolized and is eliminated in the urine. Plasma concentrations of oseltamivir carboxylate declined with a half-life of 6 to 10 hours in most subjects after oral administration. Oseltamivir carboxylate is eliminated entirely (>99%) by renal excretion. Renal clearance (18.8 L/h) exceeds glomerular filtration rate (7.5 L/h) indicating that tubular secretion occurs, in addition to glomerular filtration. Less than 20% of an oral radiolabeled dose is eliminated in feces.

Special Populations: Renal Impairment: Administration of 100 mg of oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. Oseltamivir carboxylate exposures in patients with normal and abnormal renal function administered various dose regimens of oseltamivir are described in Table 2.

Table 2. Oseltamivir Carboxylate Exposures in Patients With Normal and Reduced Serum Creatinine Clearance

Parameter	Normal Renal Function			Impaired Renal Function			
	75 mg qd	75 mg bid	150 mg bid	Creatinine Clearance <10 mL/min		Creatinine Clearance >10 and <30 mL/min	
				CAPD	Hemodialysis		
				75 mg weekly	75 mg alternate HD cycle	75 mg daily	75 mg alternate days
C _{max}	259*	348*	705*	1885*	2131*	1638	1175
C _{min}	39*	138*	288*	155	120	864	209
AUC ₀₋₄₈	7476*	10876*	21864*	43451	31073	62636	21999

*Observed values. All other values are predicted.

Geriatric Patients: Exposure to oseltamivir carboxylate at steady-state was 25% to 35% higher in geriatric patients (age range 65 to 78 years) compared to young adults given comparable doses of oseltamivir. Half-lives observed in the geriatric patients were similar to those seen in young adults. Based on drug exposure and tolerability, dose adjustments are not required for geriatric patients for either treatment or prophylaxis (see DOSAGE AND ADMINISTRATION: *Special Dosage Instructions*).

INDICATIONS AND USAGE:

Treatment of Influenza: TAMIFLU is indicated for the treatment of uncomplicated acute illness due to influenza infection in adults who have been symptomatic for no more than 2 days. This indication is based on studies of naturally occurring influenza in which the predominant infection was influenza A, and influenza challenge studies in which antiviral activity of TAMIFLU was supported for influenza A and B (see *Description of Clinical Studies* and PRECAUTIONS).

Prophylaxis of Influenza: TAMIFLU is indicated for the prophylaxis of influenza in adults and

adolescents 13 years and older.

TAMIFLU is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee.

Description of Clinical Studies: Studies in Naturally Occurring Influenza:

Treatment of Influenza: Adults: Two phase 3 placebo-controlled and double-blind clinical trials were conducted: one in the USA and one outside the USA. Patients were eligible for these trials if they had fever >100°F, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache) and influenza virus was known to be circulating in the community. In addition, all patients enrolled in the trials were allowed to take fever-reducing medications.

Of 1355 patients enrolled in these two trials, 849 (63%) patients were influenza-infected (age range 18 to 65 years; median age 34 years; 52% male; 90% Caucasian; 31% smokers). Of the 849 influenza infected patients, 95% were infected with influenza A, 3% with influenza B, and 2% with influenza of unknown type.

TAMIFLU was started within 40 hours of onset of symptoms. Subjects participating in the trials were required to self-assess the influenza-associated symptoms as "none," "mild," "moderate" or "severe". Time to improvement was calculated from the time of treatment initiation to the time when all symptoms (nasal congestion, sore throat, cough, aches, fatigue, headaches, and chills/sweats) were assessed as "none" or "mild". In both studies, at the recommended dose of TAMIFLU 75 mg twice daily for 5 days, there was a 1.3 day reduction in the median time to improvement in influenza-infected subjects receiving TAMIFLU compared to subjects receiving placebo. Subgroup analyses of these studies by gender showed no differences in the treatment effect of TAMIFLU in men and women.

In the treatment of influenza, no increased efficacy was demonstrated in subjects receiving treatment of 150 mg TAMIFLU twice daily for 5 days.

Prophylaxis of Influenza: The efficacy of TAMIFLU in preventing naturally occurring influenza illness has been demonstrated in three seasonal prophylaxis studies and a post-exposure prophylaxis study in households. The primary efficacy parameter for all these studies was the incidence of laboratory confirmed clinical influenza. Laboratory confirmed clinical influenza was defined as oral temperature • 99.0°F/37.2°C plus at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one constitutional symptom (aches and pain, fatigue, headache, chills/sweats), all recorded within 24 hours, plus either a positive virus isolation or a fourfold increase in virus antibody titers from baseline.

In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults (aged 13 to 65 years), TAMIFLU 75 mg once daily taken for 42 days during a community outbreak reduced the incidence of laboratory confirmed clinical influenza from 4.8% (25/519) for the placebo group to 1.2% (6/520) for the TAMIFLU group.

In a seasonal prophylaxis study in elderly residents of skilled nursing homes, TAMIFLU 75 mg once daily taken for 42 days reduced the incidence of laboratory confirmed clinical influenza from 4.4% (12/272) for the placebo group to 0.4% (1/276) for the TAMIFLU group. About 80% of this elderly population were vaccinated, 14% of subjects had chronic airway obstructive disorders, and 43% had cardiac disorders.

In a study of post-exposure prophylaxis in household contacts (aged • 13 years) of an index case, TAMIFLU 75 mg once daily administered within 2 days of onset of symptoms in the index case and continued for 7 days reduced the incidence of laboratory confirmed clinical influenza from 12% (24/200) in the placebo group to 1% (2/205) for the TAMIFLU group. Index cases did not receive TAMIFLU in the study.

CONTRAINDICATIONS: TAMIFLU is contraindicated in patients with known hypersensitivity to any of the components of the product.

PRECAUTIONS: General: There is no evidence for efficacy of TAMIFLU in any illness caused by agents other than influenza viruses Types A and B. Data on treatment of influenza B are limited (see INDICATIONS AND USAGE: *Description of Clinical Studies*).

Use of TAMIFLU should not affect the evaluation of individuals for annual influenza vaccination in accordance with guidelines of the Center for Disease Controls and Prevention Advisory Committee on Immunization Practices.

Efficacy of TAMIFLU in patients who begin treatment after 40 hours of symptoms has not been established.

Efficacy of TAMIFLU in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population. No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalization.

Safety and efficacy of repeated treatment or prophylaxis courses have not been studied.

Efficacy of TAMIFLU for treatment or prophylaxis has not been established in immunocompromised patients.

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. TAMIFLU has not been shown to prevent such complications.

Hepatic Impairment: The safety and pharmacokinetics in patients with hepatic impairment have not been evaluated.

Renal Impairment: Dose adjustment is recommended for patients with a serum creatinine clearance <30 mL/min (see DOSAGE AND ADMINISTRATION).

Information for Patients: Patients should be instructed to begin treatment with TAMIFLU as soon as possible from the first appearance of flu symptoms. Similarly, prevention should begin as soon as possible after exposure, at the recommendation of a physician.

Patients should be instructed to take any missed doses as soon as they remember, except if it is near the next scheduled dose (within 2 hours), and then continue to take TAMIFLU at the usual times.

TAMIFLU is not a substitute for a flu vaccination. Patients should continue receiving an annual flu vaccination according to guidelines on immunization practices.

Drug Interactions: Information derived from pharmacology and pharmacokinetic studies of oseltamivir suggests that clinically significant drug interactions are unlikely.

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases, located predominantly in the liver. Drug interactions involving competition for esterases have not been extensively reported in literature. Low protein binding of oseltamivir and oseltamivir carboxylate suggests that the probability of drug displacement interactions is low.

In vitro studies demonstrate that neither oseltamivir nor oseltamivir carboxylate is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases.

Cimetidine, a non-specific inhibitor of cytochrome P450 isoforms and competitor for renal tubular secretion of basic or cationic drugs, has no effect on plasma levels of oseltamivir or oseltamivir carboxylate.

Clinically important drug interactions involving competition for renal tubular secretion are unlikely due to the known safety margin for most of these drugs, the elimination characteristics of oseltamivir carboxylate (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. Coadministration of probenecid results in an approximate twofold increase in exposure to oseltamivir carboxylate due to a decrease in active anionic tubular secretion in the kidney. However, due to the safety margin of oseltamivir carboxylate, no dose adjustments are required when coadministering with probenecid.

Coadministration with amoxicillin does not alter plasma levels of either compound, indicating that competition for the anionic secretion pathway is weak.

In six subjects, multiple doses of oseltamivir did not affect the single-dose pharmacokinetics of acetaminophen.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term carcinogenicity tests with oseltamivir are underway but have not been completed. However, a 26-week dermal carcinogenicity study of oseltamivir carboxylate in FVB/Tg.AC transgenic mice was negative. The animals were dosed at 40, 140, 400 or 780 mg/kg/day in two divided doses. The highest dose represents the maximum feasible dose based on the solubility of the compound in the control vehicle. A positive control, tetradecanoyl phorbol-13-acetate administered at 2.5 µg per dose three times per week gave a positive response.

Oseltamivir was found to be non-mutagenic in the Ames test and the human lymphocyte chromosome assay with and without enzymatic activation and negative in the mouse micronucleus test. It was found to be positive in a Syrian Hamster Embryo (SHE) cell transformation test. Oseltamivir carboxylate was non-mutagenic in the Ames test and the L5178Y mouse lymphoma assay with and without enzymatic activation and negative in the SHE cell transformation test.

In a fertility and early embryonic development study in rats, doses of oseltamivir at 50, 250, and 1500 mg/kg/day were administered to females for 2 weeks before mating, during mating and until day 6 of pregnancy. Males were dosed for 4 weeks before mating, during and for 2 weeks after mating. There were no effects on fertility, mating performance or early embryonic development at any dose level. The highest dose was approximately 100 times the human systemic exposure (AUC_{0-24h}) of oseltamivir carboxylate.

Long-term carcinogenicity tests with oseltamivir have not been completed.

Pregnancy: Pregnancy Category C: There are insufficient human data upon which to base an evaluation of risk of TAMIFLU to the pregnant woman or developing fetus. Studies for effects on embryo-fetal development were conducted in rats (50, 250, and 1500 mg/kg/day) and rabbits (50, 150, and 500 mg/kg/day) by the oral route. Relative exposures at these doses were, respectively, 2, 13, and 100 times human exposure in the rat and 4, 8, and 50 times human exposure in the rabbit. Pharmacokinetic studies indicated that fetal exposure was seen in both species. In the rat study, minimal maternal toxicity was reported in the 1500 mg/kg/day group. In the rabbit study, slight and marked maternal toxicities were observed, respectively, in the 150 and 500 mg/kg/day groups. There was a dose-dependent increase in the incidence rates of a variety of minor skeletal abnormalities and variants in the exposed offspring in these studies. However, the individual incidence rate of each skeletal abnormality or variant remained within the background rates of occurrence in the species studied.

Because animal reproductive studies may not be predictive of human response and there are no adequate and well-controlled studies in pregnant women, TAMIFLU should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: In lactating rats, oseltamivir and oseltamivir carboxylate are excreted in the milk. It

is not known whether oseltamivir or oseltamivir carboxylate is excreted in human milk. TAMIFLU should, therefore, be used only if the potential benefit for the lactating mother justifies the potential risk to the breast-fed infant.

Pediatric Use: The safety and efficacy of TAMIFLU in children (<18 years) have not been established.

Geriatric Use: In an ongoing treatment study in otherwise healthy elderly patients, >65 years (n=168), given the recommended dosing regimen of TAMIFLU, there was a reduction in the median time to improvement in the subjects receiving TAMIFLU similar to that seen in younger adults. No overall difference in safety was observed between these subjects and younger adults. Safety and efficacy have been demonstrated in elderly residents of nursing homes who took TAMIFLU for up to 42 days for the prevention of influenza. Many of these individuals had cardiac and/or respiratory disease, and most had received vaccine that season (see *Description of Clinical Studies*).

ADVERSE REACTIONS: Treatment Studies: A total of 1171 patients who participated in adult phase 3 controlled clinical trials for the treatment of influenza were treated with TAMIFLU. The most frequently reported adverse events in these studies were nausea and vomiting. These events were generally of mild to moderate degree and usually occurred on the first 2 days of administration. Less than 1% of subjects discontinued prematurely from clinical trials due to nausea and vomiting.

Adverse events that occurred with an incidence of $\geq 1\%$ in 1440 patients taking placebo or TAMIFLU 75 mg twice daily in adult phase 3 treatment studies are shown in Table 3. This summary includes 945 healthy young adults and 495 "at risk" patients (elderly patients and patients with chronic cardiac or respiratory disease). Those events reported numerically more frequently in patients taking TAMIFLU compared with placebo were nausea, vomiting, bronchitis, insomnia, and vertigo.

Table 3. Most Frequent Adverse Events in Studies in Naturally Acquired Influenza

Adverse Event	Treatment		Prophylaxis	
	Placebo N=716	Oseltamivir 75 mg bid N=724	Placebo N=1434	Oseltamivir 75 mg qd N=1480
Nausea (without vomiting)	40 (5.6%)	72 (9.9%)	56 (3.9%)	104 (7.0%)
Vomiting	21 (2.9%)	68 (9.4%)	15 (1.0%)	31 (2.1%)
Diarrhea	70 (9.8%)	48 (6.6%)	38 (2.6%)	48 (3.2%)
Bronchitis	15 (2.1%)	17 (2.3%)	17 (1.2%)	11 (0.7%)
Abdominal pain	16 (2.2%)	16 (2.2%)	23 (1.6%)	30 (2.0%)
Dizziness	25 (3.5%)	15 (2.1%)	21 (1.5%)	24 (1.6%)
Headache	14 (2.0%)	13 (1.8%)	251 (17.5%)	298 (20.1%)
Cough	12 (1.7%)	9 (1.2%)	86 (6.0%)	83 (5.6%)
Insomnia	6 (0.8%)	8 (1.1%)	14 (1.0%)	18 (1.2%)
Vertigo	4 (0.6%)	7 (1.0%)	3 (0.2%)	4 (0.3%)
Fatigue	7 (1.0%)	7 (1.0%)	107 (7.5%)	117 (7.9%)

Adverse events included are: all events reported in the treatment studies with frequency $\geq 1\%$ in the oseltamivir 75 mg bid group.

Additional adverse events occurring in <1% of patients receiving TAMIFLU for treatment included unstable angina, anemia, pseudomembranous colitis, humerus fracture, pneumonia, pyrexia, and peritonsillar abscess.

Prophylaxis Studies: A total of 3434 subjects (adolescents, healthy adults and elderly) participated in phase III prophylaxis studies, of whom 1480 received the recommended dose of 75 mg once daily for up to 6 weeks. Adverse events were qualitatively very similar to those seen in the treatment studies, despite a longer duration of dosing (Table 3). Events reported more frequently in subjects receiving

TAMIFLU compared to subjects receiving placebo in prophylaxis studies, and more commonly than in treatment studies, were aches and pains, rhinorrhea, dyspepsia and upper respiratory tract infections. However, the difference in incidence between TAMIFLU and placebo for these events was less than 1%. There were no clinically relevant differences in the safety profile of the 942 elderly subjects who received TAMIFLU or placebo, compared with the younger population.

Observed During Clinical Practice for Treatment: The following adverse reactions have been identified during post-marketing use of TAMIFLU. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to TAMIFLU exposure.

General: Rash, swelling of the face or tongue

Cardiac: Arrhythmia

Neurologic: Seizure, confusion

Metabolic: Aggravation of diabetes

OVERDOSAGE: At present, there has been no experience with overdose. Single doses of up to 1000 mg of TAMIFLU have been associated with nausea and/or vomiting. A complete pack of ten capsules of TAMIFLU contains a total of 750 mg of oseltamivir.

DOSAGE AND ADMINISTRATION: TAMIFLU may be taken with or without food (see *PHARMACOKINETICS*). However, when taken with food, tolerability may be enhanced in some patients.

Standard Dosage – Treatment of Influenza: The recommended oral dose of TAMIFLU for treatment of influenza is 75 mg twice daily for 5 days. Treatment should begin within 2 days of onset of symptoms of influenza.

Standard Dosage – Prophylaxis of Influenza: The recommended oral dose of TAMIFLU for prophylaxis of influenza following close contact with an infected individual is 75 mg once daily for at least 7 days. Therapy should begin within 2 days of exposure. The recommended dose for prophylaxis during a community outbreak of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks. The duration of protection lasts for as long as dosing is continued.

Special Dosage Instructions: Hepatic Impairment: The safety and pharmacokinetics in patients with hepatic impairment have not been evaluated.

Renal Impairment: For plasma concentrations of oseltamivir carboxylate predicted to occur following various dosing schedules in patients with renal impairment, see *CLINICAL PHARMACOLOGY: PHARMACOKINETICS: Special Populations*.

Treatment of Influenza: Dose adjustment is recommended for patients with creatinine clearance between 10 and 30 mL/min receiving TAMIFLU for the treatment of influenza. In these patients it is recommended that the dose be reduced to 75 mg of TAMIFLU once daily for 5 days. No recommended dosing regimens are available for patients undergoing routine hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

Prophylaxis of Influenza: For the prophylaxis of influenza, dose adjustment is recommended for patients with creatinine clearance between 10 and 30 mL/min receiving TAMIFLU. In these patients it is recommended that the dose be reduced to 75 mg of TAMIFLU every other day. No recommended dosing regimens are available for patients undergoing routine hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

Pediatric Patients: The safety and efficacy of TAMIFLU in children have not been established.

Geriatric Patients: No dose adjustment is required for geriatric patients (see *PHARMACOKINETICS: Special Populations* and *PRECAUTIONS*).

HOW SUPPLIED: TAMIFLU is supplied as 75-mg (75 mg free base equivalent of the phosphate salt) grey/light yellow hard gelatin capsules. "ROCHE" is printed in blue ink on the grey body and "75 mg" is printed in blue ink on the light yellow cap. Available in blister packages of 10 (NDC 0004-0800-85).

Storage: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled

Room Temperature]

Manufactured by:

F. Hoffmann-La Roche Ltd.

Basel, Switzerland

Distributed by:



Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

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Gilead Sciences, Inc.

Foster City, California 94404

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Revised: November 2000

Printed in USA

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Patient Information

TAMIFLU™ (oseltamivir phosphate)

This leaflet contains important information about TAMIFLU (TAM-ih-flew). Read it well before you begin treatment. This information does not take the place of talking with your health care professional about your medical condition or your treatment. This leaflet does not list all the benefits and risks of TAMIFLU. If you have any questions about TAMIFLU, ask your health care professional. Only your health care professional can determine if TAMIFLU is right for you.

What is TAMIFLU?

TAMIFLU attacks the influenza virus and stops it from spreading inside your body. TAMIFLU treats flu at its source, by attacking the virus that causes the flu, rather than simply masking symptoms.

TAMIFLU is for treating adults with the flu whose flu symptoms started within the last day or two. TAMIFLU can also reduce the chance of getting the flu in people age 13 and older who have a higher chance of getting the flu because they spend time with someone who has the flu. TAMIFLU can also reduce the chance of getting the flu if there is a flu outbreak in the community.

What is “Flu”?

“The flu” is an infection caused by the influenza virus. Flu symptoms include fever (usually 100°F to 103°F in adults, and sometimes higher in children) and problems such as cough, sore throat, runny or stuffy nose, headaches, muscle aches, fever, and extreme tiredness. Many people use the term “flu” to mean any combination of these symptoms, such as the common cold, but true influenza infection is often worse and may last longer than a cold.

Flu outbreaks happen about once a year, usually in the winter, when the influenza virus spreads widely in the community. Outside of those outbreaks, only a very tiny number of respiratory infections are caused by the influenza virus.

Should I get a flu shot?

TAMIFLU is not a substitute for a flu vaccination. You should continue to get a flu vaccination every year, according to your health care professional’s advice.

Who should not take TAMIFLU?

Do not take TAMIFLU if you are allergic to the main ingredient, oseltamivir phosphate, or to any other ingredients of TAMIFLU. Before starting treatment, make sure your health care professional knows if you take any other medicines, or are pregnant, planning to become pregnant, or breastfeeding. TAMIFLU is normally not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.

Tell your health care professional if you have any type of kidney disease, heart disease, respiratory disease, or any serious health condition.

How should I take TAMIFLU?

It is important that you begin your treatment with TAMIFLU as soon as possible from the first appearance of your flu symptoms or soon after you are exposed to the flu. If you feel worse or develop new symptoms during treatment with TAMIFLU, or if your flu symptoms do not start to get better, you should contact your health care professional.

If you have the flu: Take TAMIFLU twice a day for 5 days, once in the morning and once in the evening. You should complete the entire treatment of 10 capsules, even if you feel better.

To prevent the flu: If someone in your home has the flu, take TAMIFLU once a day for at least 7 days or for as long as prescribed. You can take TAMIFLU for up to 6 weeks if you are exposed to the flu because of an outbreak in your community. Follow your health care professional's advice on how long to take TAMIFLU.

You can take TAMIFLU with food or without food. There is less chance of stomach upset if you take it with a light snack, milk, or a meal.

If you forget to take your medicine, take the missed dose as soon as you remember, except if it is 2 hours or less before your next dose. Then continue to take TAMIFLU at the usual times. Do not take 2 doses at a time to make up for a missed dose. If you miss several doses, tell your health care professional and follow the advice given to you.

What are the possible side effects of TAMIFLU?

The most common side effects of TAMIFLU are nausea and vomiting. These are usually mild to moderate. They usually happen in the first 2 days of treatment. Taking TAMIFLU with food may reduce the chance of getting these side effects.

If you notice any side effects not mentioned in this leaflet, or if you have any concerns about the side effects you get, tell your health care professional.

How and where should I store TAMIFLU?

TAMIFLU capsules should be stored at room temperature below 77°F (25°C) and kept in a dry place. Keep this medication out of reach of children.

General advice about prescription medicines:

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TAMIFLU for a condition for which it was not prescribed. Do not give TAMIFLU to other people, even if they have the same symptoms you have. It may not be right for them.

This leaflet summarizes the most important information about TAMIFLU. If you would like more information, talk with your health care professional. You can ask your pharmacist or health care professional for information about TAMIFLU that is written.

/s/

Debra Birnkrant
11/17/00 03:33:50 PM
NDA 21-087/S-002

16 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

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

Form Approved OMB No 0910-0297
Expiration Date 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199	3. PRODUCT NAME Tamiflu™ (oseltamivir phosphate) capsules 4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. YES IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA)
2. TELEPHONE NUMBER (Include Area Code) (973) 562-3664	
5. USER FEE I.D. NUMBER 3916	6. LICENSE NUMBER / NDA NUMBER NDA 21-087

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

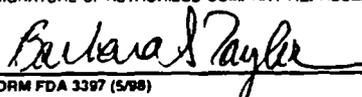
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Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Barbara S. Taylor, Ph.D. Program Director, DRA	DATE May 22, 2000
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May 18, 2000

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, Pennsylvania 15259-0001

Ladies and Gentlemen:

RE: NDA 21-087 - TAMIFLU™ (oseltamivir phosphate) CAPSULES
HUMAN DRUG APPLICATION FEE - I.D. No. 3916

Enclosed please find a check in the amount of \$142,870.00 made payable to the U.S. Food and Drug Administration. This payment represents the user fee required for our Supplemental New Drug Application for Tamiflu™ (oseltamivir phosphate), which is planned for submission on May 22, 2000.

Should you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

A handwritten signature in cursive script, appearing to read "Jill M. Serra", written over a horizontal line.

Jill M. Serra
Coordinator, Regulatory Submissions Group
Drug Regulatory Affairs
(973) 562-3726 (telephone)
(973) 562-3700/3554 (fax)

/JS
HLR 2000-772
Enclosure: Check No. 01342957

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

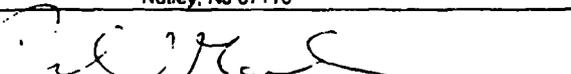
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Donald Maclean, Ph.D.	TITLE Vice President of Drug Regulatory Affairs
FIRM/ORGANIZATION Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, NJ 07110	
SIGNATURE 	DATE May 19, 2000

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Investigators & Sub-Investigators For Tamiflu – Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
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Principal Investigator: Dr. G. Achyuthan Sub-investigators:	Regina Medical Centre Suite 203 2550 12 th Avenue Regina, Saskatchewan S4P 3X1	Canada	WV15799 22952
Principal Investigator: Dr. L. Alwine Sub-investigators:	Downtown Medical Center 77 Manor Avenue Dowington, PA 19335	United States	WV15799 22959
Principal Investigator: Dr. O. Amzil Sub-investigators:	Espoonlahden sosiaali- ja Terveyskeskus Merikansantie 4 FIN 02320 Espoo	Finland	WV15799 23019
Principal Investigator: Dr. J. Anttila	Myyrmaen Sosiaali- ja Terveyskeskus Iskoste 5 FIN 01600, Vantaa	Finland	WV15799 23018
Principal Investigator: Dr. F. Aoki Sub-investigators:	Health Sciences Center 730 William Avenue Winnipeg, Manitoba R3E 0W3	Canada	WV15799 22938
Principal Investigator: Dr. T. Aronkyto	Tapiolan Terveysasema Kauppamiehentie 4 FIN 02100 Espoo	Finland	WV15799 23013

Investigators & Sub-Investigators For Tamiflu - Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. R. Barbarash Sub-investigators: 	St. Louis Pharmaceutical Research 12401 Olive Boulevard Suite 100 St. Louis, MO 63141	United States	WV15799 22960
Principal Investigator: Dr. R. Bettis Sub-investigators: 	Edmonds Family Medicine Clinic 7315 212 nd St. SW, Suite 101 Edmonds, WA 98026	United States	WV15799 22961

Investigators & Sub-Investigators For Tamiflu - Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. A.J.M. Boermans	Lutterstraat 2a 7581 BV Losser	Netherlands	WV15799 23024
Principal Investigator: Dr. V. Bralow Sub-investigators: Dr. P. Gross	Clincopts Inc. 732 So 8 th Street Philadelphia, PA 19147	United States	WV15799 22962
Principal Investigator: Dr. D. Brandon Sub-investigators:	California Research Foundation 2800 Third Avenue San Diego, CA 19147	United States	WV15799 22963
Principal Investigator: Dr. P. Buitenhuis Sub-investigators:	Stetweg 14 1901 JE Castricum	Netherlands	WV15799 23037
Principal Investigator: Dr. O. Carewicz	Im Breiten Wingert 5 69221 Dossenheim	Germany	WV15799 22536
Principal Investigator: Dr. A. Carr Sub-investigators:	Southern Clinical Research and Management 1501 Anthony Road Augusta, GA 30904	United States	WV15799 22965
Principal Investigator: Dr. T. Casale Sub-investigators:	Allergy, Asthma, and Immunology 401 East Gold Coast Road, #124 Papillon, NE 68046	United States	WV15799 22966
Principal Investigator: Dr. A. Ceulemans	Neerstraat 17 3980 Tessenderlo Belgium	Belgium	WV15799 23014
Principal Investigator: Dr. J. Champlin Sub-investigators:	Clinical Research, Inc. 6651 Madison Avenue Carmichael, CA 95608	United States	WV15799 22968

Investigators & Sub-Investigators For Tamiflu - Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. W.I.C. Clark Sub-investigators:	Horn Street Surgery 24 Horn Street Winslow Buckinghamshire MK 18 3AJ	United Kingdom	WV15799 22934
Principal Investigator: Dr. C. Cone	NW Physicians Network 2831 Fort Missoula Road Suite 301 Missoula, MT 59804	United States	WV15799 22971
Principal Investigator: Dr. R. Cook Sub-investigators:	Saltash Health Centre Callington Road Saltash Cornwall PL2 6DL	United Kingdom	WV15799 22931
Principal Investigator: Dr. F. Currie	The Medical Centre Caledonian Road Perth Scotland PH2 8HH	United Kingdom	WV15799 22935
Principal Investigator: Dr. M. Davidson Sub-investigators:	2 Gomersal Lane Dronfield Sheffield S18 1RU	United Kingdom	WV15799 22936
Principal Investigator: Dr. F. Diaz-Mitoma	Herridge Community Health Clinic 59 Herridge Street Ottawa, Ontario K1S 0G8	Canada	WV15799 22940
Principal Investigator: Dr. T. Fiel Sub-investigators:	Tempe Primary Care 5030 South Mill Avenue Suite D12 Tempe, AZ 85282	United States	WV15799 22972

Investigators & Sub-Investigators For Tamflu - Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. P. Fletcher Sub-investigators: _____	Woolwell Medical Centre School Drive Woolwell Plymouth Devon PL6 7 TH	United Kingdom	WV15799 22928
Principal Investigator: Dr. S. Galant Sub-investigators: _____ _____ _____	Clinical Trials of Orange County 2501 E. Chapman Avenue Suite 407 Orange, CA 92869	United States	WV15799 22974
Principal Investigator: Dr. K. Gillespie Sub-investigators: _____	Knowle House Surgery 4 Meavy Way Crownhill Devon PL5 3JB	United Kingdom	WV15799 22929
Principal Investigator: Dr. H. Gjessing	Tasenveien Legekantor Tasenv 49 0180 Oslo	Norway	WV15799 23209
Principal Investigator: Dr. A. Golding-Cook Sub-investigators: _____	The Ridgeway Practice Plympton Health Centre Mudge Way Plympton Devon PL7 1AD	United Kingdom	WV15799 22937
Principal Investigator: Dr. W. Gooch III. Sub-investigators: _____	Hilltop Research 420 E. South Temple, Suite 200 Salt Lake City, UT 84111	United States	WV15799 22975
Principal Investigator: Dr. H. Hassman Sub-investigators: _____	Clinical Managed Care Research, Inc. 7808 Claremont Mesa Boulevard Suite E San Diego, CA 92111	United States	WV15799 22979

Investigators & Sub-Investigators For Tamiflu - Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. M. Hassman Sub-investigators:	Berlin Medical Associates 160 S. White Horse Pike Berlin, NJ 08009	United States	WV15799 22980
Principal Investigator: Dr. J. Hedrick Sub-investigators:	Kentucky Pediatric and Adult Research 201 South 5 th Street Suite 3 Bardstown, KY 40004	United States	WV15799 22981
Principal Investigator: Dr. R. Hellebo	Sorum Legescenter Kuskerudv 2 1920 Sorum	Norway	WV15799 23025
Principal Investigator: Dr. L. Hergel Sub-investigators:	Laegehuset Buddingevej 54 2800 Kgs. Lyngby	Denmark	WV15799 23038
Principal Investigator: Dr. W. Jannetti Sub-investigators:	Hana Research Medical Center 8615 Knott Avenue Suite 8 Buena Park, CA 90620	United States	WV15799 22984

Investigators & Sub-Investigators For Tamiflu - Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. T. Jung Sub-investigators:	Dietzenbacher Str 33 73326 Deggingen	Germany	WV15799 22541
Principal Investigator: Dr. S. Junnila	Salon Seudun Terveyskeskus Sairaalanne 9 FIN 24130 Salo	Finland	WV15799 23020
Principal Investigator: Dr. E. Kurra Sub-investigators:	Poriin Terveyskeskus Maantienkatu 31 FIN 28120 Pori	Finland	WV15799 23015
Principal Investigator: Dr. R. Lebmeier Sub-investigators:	Private Practice Wilhelmstrasse 25 66894 Bechhofen	Germany	WV15799 22545
Principal Investigator: Dr. Dr. Lew Sub-investigators:	Hospital Cantonal University Maladies Infectieuses 24 Rue Micheli-Du-Crest 1211 Geneve	Switzerland	WV15799 23491
Principal Investigator: Dr. T. Littlejohn Sub-investigators:	Piedmont Medical Research 1901 S. Hawthorne Suite 306 Winston Salem, NC 27103	United States	WV15799 22985

Investigators & Sub-Investigators For Tamiflu - Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. M.D. Macleod Sub-investigators:	Aldershot Health Centre Wellington Avenue Aldershot GU11 1PA	United Kingdom	WV15799 22930
Principal Investigator: Dr. F. Maggiano Sub-investigators:	New England Center for Clinical Research	United States	WV15799 22986
Principal Investigator: Dr. J. McCarty Sub-investigators:	Hilltop Research, Inc. 6079 North Fresno Bullard Park Suite 101 Fresno, CA 93710	United States	WV15799 22987
Principal Investigator: Dr. D. McCluskey Sub-investigators:	Hilltop Research, Inc. 754 South Cleveland Avenue Suite 200 Mogadore, OH 44260	United States	WV15799 22988
Principal Investigator: Dr. C. McKeever Sub-investigators:	Health Advance Institute 902 Frostwood Suit 315 Houston, TX 77024	United States	WV15799 22990
Principal Investigator: Dr. T. Menke	Gartenstr 4 47574 Goch	Germany	WV15799 22537

Investigators & Sub-Investigators For Tamiflu - Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. M. Nosan <u>Sub-investigators:</u> 	San Carlos Medical Group 8881 Fletcher Parkway La Mesa, CA 91942	United States	WV15799 22982
Principal Investigator: Dr. M. Noss <u>Sub-investigators:</u> 	Bethesda Family Practice 4411 Montgomery Road Cincinnati, OH 45212	United States	WV15799 22982
Principal Investigator: Dr. P. Patel <u>Sub-investigators:</u> 	2000 Credit Valley Road, Suite 410 Mississauga, Ontario L5M 4N4	Canada	WV15799 22942
Principal Investigator: Dr. A. Patron <u>Sub-investigators:</u> 	South Florida Clinical Research Center 6448 Pembroke Road Hollywood, FL 33023	United States	WV15799 22994

Investigators & Sub-Investigators For Tamiflu - Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. D. Peterson Sub-investigators: 	Research Memphis 5240 Poplar Avenue Memphis, TN 38119	United States	WV15799 22995
Principal Investigator: Dr. K. Piispanen	Hakunilan Sosiaali-Ja Terveyskeskus Laukkarinne 6 FIN 01200 Vantaa	Finland	WV15799 23022
Principal Investigator: Dr. N. Pool Sub-investigators: 	Research Testing Laboratories, Inc 90 W. Franklin Street Hackensack, NJ 07601	United States	WV15799 23039
Principal Investigator: Dr. Dr. C. Raddatz	Bahnhofstr 1 55435 Gau-Algesheim	Germany	WV15799 22538
Principal Investigator: Dr. K. Reisinger Sub-investigators: 	Pittsburgh Pediatric Research 1580 McLaughlin Run Road, Suite 210 Pittsburgh, PA 15241	United States	WV15799 22997
Principal Investigator: Dr. Dr. F. Rudolt	Karlstr 17 89568 Hermaringen	Germany	WV15799 22540
Principal Investigator: Dr. E. Schatteman	Varendrieskouter 151 9031 DRONGEN Belgium	Belgium	WV15799 23017

Investigators & Sub-Investigators For Tamiflu - Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. H. Schwartz <u>Sub-investigators:</u>	Miami Research Associates 7500 SW 87 th Avenue Suite 202 Miami, FL 33173	United States	WV15799 22999
Principal Investigator: Dr. R. Schwartz <u>Sub-investigators:</u>	Vienna Pediatrics 410 Maple Avenue West Vienna, VA 22180	United States	WV15799 23000
Principal Investigator: Dr. V. Senikas <u>Sub-investigators:</u>	Scaforth Medical Building 3550 Cote-des-Neiges, Suite 550 Montreal, Quebec H3H 1V4	Canada	WV15799 23494
Principal Investigator: Dr. D. Shu <u>Sub-investigators:</u>	Gain Medical Centre 1199 Austin Avenue Coquitlam, British Columbia V3K 3P4	Canada	WV15799 22943
Principal Investigator: Dr. W. Smith <u>Sub-investigators:</u>	New Orleans Center for Clinical Research 2820 Canal Street New Orleans, LA 70119	United States	WV15799 23040

Investigators & Sub-Investigators For Tamiflu – Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. G. Tellier <u>Sub-investigators:</u> 	ZOOM International Hotel-Dieu de St. Jerome 290 Rue Montigny local F-19 St. Jerome, Quebec J7Z 5T3	Canada	WV15799 22944
Principal Investigator: Dr. M. S. Touger <u>Sub-investigators:</u>	Hilltop Research 516 Brookwood Boulevard Birmingham, AL 35209	United States	WV15799 23003
Principal Investigator: Dr. S. Trottier <u>Sub-investigators:</u>	Centre Hospitalier Universitaire Pavillon CHUL Laboratoire et Service d'Infectiologie 2705 Boul Laurier, local RC-709 Ste. Foy, Quebec G1V 4G2	Canada	WV15799 22945

Investigators & Sub-Investigators For Tamiflu – Protocol WV15799			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. N. van Mulders	Kloosterstaat 14 9390 MOORSEL Belgium	Belgium	WV15799 22954
Principal Investigator: Dr. J. Veerman	Ericaweg 26 7441 BN Nijverdal	Netherlands	WV15799 23027
Principal Investigator: Dr. M. Vichare Sub-investigators:	California State University-Chico Student Health Services Chico, CA 95929-0777	United States	WV15799 23004
Principal Investigator: Dr. P. Vohora	6682 Fraser Street Vancouver, B.C. V5H 3T5	Canada	WV15799 22946
Principal Investigator: Dr. E. Wang Sub-investigators:	Clinical Epidemiology Unit Hospital for Sick Children 555 University Avenue Toronto, Ontario M5G 1X8	Canada	WV15799 22947
Principal Investigator: Dr. R. Welliver Sub-investigators:	Children's Hospital Division of Infectious Diseases 219 Bryant Street Buffalo, NY 14222	United States	WV15799 23011
Principal Investigator: Dr. P. Whitsitt Sub-investigators:	Optimum Clinical Research 171 King Street Inc. Oshawa, Ontario L1H 1B8	Canada	WV15799 22948
Principal Investigator: Dr. M. Wukelic Sub-investigators:	Rockwood Clinical, Research Department 400 East 5 th Avenue Spokane, WA 99202	United States	WV15799 23006

Investigators & Sub-Investigators For Tamiflu – Protocol WV15825			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. L. Alwine	Downtown Medical Center 77 Manor Avenue Dowington, PA 19335	United States	WV15825 23673
Principal Investigator: Dr. M. Bari Sub-investigators:	Synergy Clinical Research Center 450 Fourth Ave #300 Chula Vista, CA 91910	United States	WV15825 23672
Principal investigator: Dr. G. Berrehi	Associated Psychotherapy Centers 8915 Shady Grove Court Ganthersburg, MD 20877	United States	WV15825 23628
Principal Investigator: Dr. S. Carnein Sub-investigators:	Centre Départemental de Repos et de Soins 40 Rue Stauffen F-68000 COLMAR	France	WV15825 23655
Principal Investigator: Dr. Christiaanse	GCP Walenburgerweg 33 3039 AC Rotterdam	Netherlands	WV15825 23703
Principal Investigator: Dr. A. Cutler Sub-investigators:	Co-ordinated Research of Florida Inc 807 W. Morse Blvd. Suite 101 Winter Park, FL	United States	WV15825 23677
Principal investigator: Dr. De Bock Sub-investigators:	Eeuwfeestkliniek Harmoniestraat 68 2018 Antwerpen	Belgium	WV15825 23696
Principal Investigator: Dr. J. Dixon	Gulf Coast Clinical Research 253 St. Anthony Street Mobile, AL 36603	United States	WV15825 23623
Principal Investigator: Dr. T. Gavardin Sub-investigators:	Les maisonnées Centre Hospitalier 10 Rue des Champs Gaillard 78300 POISSY	France	WV15825 23706
Principal Investigator: Dr. T. Gooding Sub-investigators:	The Atherstone Surgery 1 Ratcliffe Road Atherstone Warks CV9 1EU	United Kingdom	WV15825 23650

Investigators & Sub-Investigators For Tamiflu - Protocol WV15825			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. W. Harper Sub-investigators:	Wake Research Associates 3100 Blue Ridge Road, Suite 100 Raleigh, NC 27612	United States	WV15825 23687
Principal Investigator: Dr. A. Jacobson Sub-investigators:	Jene's Retirement Home 1595 N.E. 145 Street No. Miami, FL 33161 Intcramerican Rest Home 240 East 5 Street Hialeah, FL 33010 Family Rest Home 182 West 9 th Street Hialeah, FL 33010 Florida Club Care Center 390 N.E. 135 Street No. Miami, FL 33160 Pinecrest Convalescent Center 13650 N.E. Third Court No. Miami, FL 33161 Greynolds Park Manor Inc. 17400 West Dixie Highway No. Miami Beach, FL 33160	United States	WV15825 23638 WV15825 23639 WV15825 23640 WV15825 23642 WV15825 23644 WV15825 23645
Principal Investigator: Dr. P. Katz Sub-investigators:	Monroe Community Hospital 435 East Herieth Road Rochester, NY 14620	United States	WV15825 23686
Principal Investigator: Dr. D. Miller Sub-investigators:	Clinical Studies Ltd. 49 State Road Watuppa Building No. Dartmouth, MA 02747	United States	WV15825 23674

Investigators & Sub-Investigators For Tamiflu – Protocol WV15825			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. R. Moreines Sub-investigators: _____	ClinSearch Inc One Prospect Street Summit, NJ 07901	United States	WV15825 23665
Principal Investigator: Dr. J. Morley Sub-investigators: _____	St. Louis University Health Services 1402 S Grand Boulevard, M238 St. Louis, MO 63104	United States	WV15825 23669
Principal Investigator: Dr. D. Munoz Sub-investigators: _____	PC3 Inc. 316 Martin Luther King Jr Way Suite 304 Tacoma, WA 98405	United States	WV15825 23667
Principal Investigator: Dr. J. Nahlik Sub-investigators: _____	Family Medicine Research Center 6125 Clayton Avenue Suite 201 St. Louis, MO 63139	United States	WV15825 23632
Principal Investigator: Dr. R. Nett Sub-investigators: _____	The Institute for Clinical Research Inc. 8122 Datapoint Drive Suite 1010 San Antonio, TX 78229	United States	WV15825 23675
Principal Investigator: Dr. P. Norwood	1313 E. Herndon Avenue Fresno, CA 93720	United States	WV15825 23625
Principal Investigator: Dr. Reekers	GCP Groot Hertoginnelaan 34 2517 EH Den Haag	Netherlands	WV15825 23710
Principal Investigator: Dr. M. Salom Sub-investigators: _____	Centre de Gérontologie Leopold Bellan I Place Leopold Bellan 78200 Magnanville	France	WV15825 23707
Principal Investigator: Dr. P. Sauvage Sub-investigators: _____	Hopital de Jour Geriatrique/RdC Hopital Jean Robeyrol Avenue de Buisson 87042 Limoges Cedex	France	WV15825 23649

Investigators & Sub-Investigators For Tamiflu - Protocol WV15825			
Investigator & Address	Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. T. Scharold Sub-investigators:	Alliance Primary Care 6659 Greenfield Woods Cincinnati, OH 45224	United States	WV15825 23624
Principal Investigator: Dr. v. d. Graaf	GCP Soestdijkseweg Zuid 261	Netherlands	WV15825 21702
Principal Investigator: Dr. Van Couter Sub-investigators:	St Jan Hospital, Rudderhove 10, 8000 Brugge	Belgium	WV15825 21634

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.

EXHIBIT A

PATENT INFORMATION FOR SUPPLEMENT TO NDA NO. 21-087

1)	Active Ingredient(s)	oseltamivir phosphate
2)	Strength(s)	75 mg
3)	Trade Name	TAMIFLU™
4)	Dosage Form and Route of Administration	capsule for oral administration
5)	Applicant (Firm) Name	Hoffmann-La Roche Inc.
6)	NDA Supplement Number	NDA 21-087, S-001
7A)	First Approval Date of original NDA	October 27, 1999
7B)	First Approval Date of Supplemental NDA	Not yet approved*
8)	Exclusivity: Date first ANDA could be approved	ANDA for change covered by pending NDA Supplement can not be approved for at least three (3) years from the date pending NDA Supplement is approved
9)	Patent Information	See Attachment

CONFIDENTIAL INFORMATION

*Since the New Drug Application Supplement 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 Supplement has been approved.

Rev. 12/97

97077

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) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. | Drug Product (Composition/Formulation) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. | Method of Use | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | 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:

Prophylaxis 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:

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

OR

the subject of this application for which approval is being sought (prophylaxis of influenza).

By: 
Name: Briana C. Buchholz
Date: April 10, 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) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. Drug Product (Composition/Formulation) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. Method of Use | <input type="checkbox"/> | Y | <input type="checkbox"/> | 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:

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

OR

the subject of this application for which approval is being sought (prophylaxis of influenza).

By: *Briana C. Buchholz*
Name: Briana C. Buchholz
Date: April 10, 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) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 2. Drug Product (Composition/Formulation) | <input checked="" type="checkbox"/> | Y | <input type="checkbox"/> | N |
| 3. Method of Use | <input type="checkbox"/> | Y | <input type="checkbox"/> | 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:

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

OR

the subject of this application for which approval is being sought (prophylaxis of influenza).

By: 

Name: Briana C. Buchholz

Date: April 10, 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

Trade Name Tamiflu Generic Name oseltamivir phosphate

Applicant Name Hoffmann-La Roche, Inc. HFD- 530

Approval Date November 17, 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/___/ NO /X/

b) Is it an effectiveness supplement? YES /X/ NO /___/

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

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 /___/

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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /___/

- (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 15673/WV 15697

Investigation #2, Study # WV 15825

Investigation #3, Study # WV 15799

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 15673/WV 15697

Investigation #2, Study # WV 15825

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 # <u>53093</u> 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: _____

(

/S/
Signature of Preparer
Title: Regulatory Project Manager

17-Nov-00
Date

/S/)
Signature of Acting Division Director

11-17-00
Date

cc:
Archival NDA
HFD- /Division File

Group Leader's Memorandum
Tamiflu
Oseltamivir 75 mg capsules

Roche submitted this supplemental application to support the approval of Tamiflu for the prophylaxis of clinical influenza in adults and adolescents (>13 years). I concur with the review prepared by Teresa Wu, the primary clinical reviewer for this supplemental application. I also concur with her conclusions that Tamiflu 75 once daily (for 7 days to 6 weeks) should be approved for the indication proposed.

Studies Submitted

Roche submitted the results from four completed phase 3 studies to support the safety and efficacy of Tamiflu for the prophylaxis of Influenza. Two seasonal prophylaxis studies with the same design were conducted in healthy unvaccinated adults in the Northern Hemisphere. With concurrence from the division, these studies were pooled in a single analysis to increase statistical power. Another seasonal prophylaxis study was conducted in elderly residents of skilled nursing homes. About 80% of these study participants were vaccinated. The fourth study was a post-exposure prophylaxis study in household contacts (age > 13 years) of an index case.

In the two seasonal prophylaxis studies in healthy unvaccinated adults, two doses of Tamiflu were studied, 75 mg qd and 75 mg bid. Since no differences in treatment effect were observed for the two dosing regimens, the once daily regimen was studied in the other two studies that followed. In the three seasonal prophylaxis studies, Tamiflu was given for 6 weeks while in the post-exposure prophylaxis in households, Tamiflu was given daily for seven days.

Efficacy

Overall

For all three study analyses, the incidence of confirmed clinical influenza was lower among participants receiving Tamiflu compared to those receiving placebo. Although the overall attack rate among patients receiving placebo was relatively low, ranging from 4-12%, there was a substantial and unambiguous reduction in influenza among patients administered Tamiflu. These results were robust to analyses that utilized alternative definitions for confirmed clinical influenza.

Influenza Virus Infection with Type A vs. B

For the seasonal prophylaxis studies the predominant influenza virus type was A; consequently, there were too few cases of type B to analyze separately for efficacy. In contrast to the seasonal prophylaxis studies, influenza type B occurred more frequently in the post-exposure prophylaxis study. In the intent-to-treat analysis of this study, which included all contacts regardless of whether the index case had laboratory confirmed influenza or not, there was a statistically significant reduction in the number of cases of confirmed influenza type B.

Secondary Complications

Although the applicant conducted analyses comparing the number of secondary complications (e.g., sinusitis, bronchitis, and lower respiratory tract infections) between treatment arms, there were too few definitive cases to make any conclusions. In addition, these cases were not uniformly or rigorously substantiated as bacterial infections. Some of the symptoms presented as complications of influenza may have been related to the primary infection itself.

Vaccination

Although Tamiflu is not a substitute for early vaccination as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee, the prophylactic effect of Tamiflu was evident even among elderly individuals who had been vaccinated. The vaccine was considered to be a good match for the season studied.

In addition, prophylaxis with Tamiflu did not appear to attenuate an antibody response to influenza among patients who were confirmed to acquire the circulating strain.

Safety

In this safety data base of over 3000 individuals, the most common adverse events following administration of Tamiflu 75 mg once daily were nausea, vomiting, and headache. These adverse events occurred at a slightly lower frequency than observed in studies of the treatment of influenza, in which patients received the same dose twice daily.

The safety and tolerability profile was similar for elderly and younger study participants.

Resistance

Due to the low overall infection rate in these studies and the prophylactic effect of Tamiflu, determination of viral resistance was limited. Fewer than 10 isolates from subjects who had culture positive influenza after receiving Tamiflu were evaluable. However, among these few isolates neuraminidase susceptibility appeared to be similar to that reported for wild-type virus strains.

Special Populations

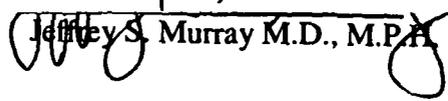
The use of Tamiflu for the treatment of influenza in children has been studied in separate clinical trials.

Elderly patients, including those with stable uncomplicated chronic obstructive airways disease or cardiac disorders, tolerated Tamiflu similarly to healthy adults.

The applicant has studied Tamiflu plasma exposure measures in patients with renal insufficiency. To date, dosing recommendations have been devised for treatment of influenza in patients with all degrees of renal impairment and for prophylaxis of influenza in patients with a creatinine clearance as low as 10 mL/min.

Conclusions

The safety and efficacy of Tamiflu for the prophylaxis of Influenza A and B has been sufficiently demonstrated. This supplemental NDA should be approved for the proposed indication.

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 Jeffrey S. Murray M.D., M.P.H.

DIVISION OF ANTIVIRAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-087

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 10/31/00

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE

SE1-002

5/22/00

5/22/00

6/1/00

NAME & ADDRESS OF SPONSOR:

Hoffman-LaRoche, Inc
340 Kingsland St
Nutley, NJ 07110

DRUG PRODUCT NAMES:

Proprietary
Nonproprietary
Code Name

Tamiflu®
oseltamivir capsules
Ro 64-0796

PHARMACOLOGICAL CATEGORY:

Viral neuraminidase inhibitor

INDICATION:

Prophylaxis of influenza's A and B

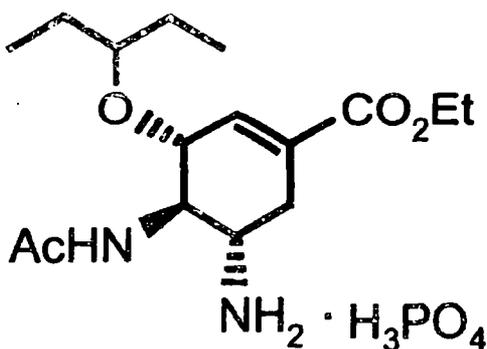
DOSAGE FORM/STRENGTH:

Capsule/75 mg

ROUTE OF ADMINISTRATION:

Oral

CHEMICAL NAME/STRUCTURAL FORMULA:



(3R,4R,5S)-4-Acetylamino-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1)

Mol. Form. - C₁₆H₂₈N₂O₄

SUPPORTING DOCUMENTS:

NDA 21-087 Hoffman-LaRoche, Inc. oseltamivir capsules Chemist's review 1

—— Hoffman-LaRoche, Inc. oseltamivir capsules Chemist's review 1

RELATED DOCUMENTS:

None

CONCLUSIONS & RECOMMENDATIONS:

This application is in conformance with section 505(b) of the Food, Drug and Cosmetic Act (as amended) in relation to chemistry manufacturing and controls procedures and may be approved from this standpoint.

Dan Boring, R.Ph., Ph.D., Review Chemist for HFD-530

Concurrence:

HFD-530-/SMiller

cc:

NDA 21-087 Original
HFD-530 Division File
HFD-830/CChen
HFD-530/JZheng

HFD-530/DBoring
HFD-530/SMiller
HFD-530/JMurray
HFD-530/NBattula

HFD-530/GCarmouze
HFD-530/TWu
HFD-530/IYuen

REMARKS/COMMENTS:

Tamiflu (Oseltamivir phosphate capsules) was approved for the treatment of influenzas A and B on 10/27/1999. It is a viral neuraminidase inhibitor that curtails viral shedding. The product is a hard gelatin capsule that is dosed as one 75 mg capsule taken twice daily for 5 days.

This efficacy supplement provides information to support approval of a prophylaxis regimen consisting of one 75 mg Tamiflu capsule taken daily for at least 7 days. This may be repeated every 2 weeks as needed, if exposed to influenza.

The supplement contained no changes to chemistry, manufacturing and controls (CMC). Therefore, there are no CMC approval issues.

/s/

Dan Boring
11/2/00 12:25:55 PM
CHEMIST

prophylaxis indication for capsules

Stephen Paul Miller
11/2/00 04:52:52 PM
CHEMIST
I concur - caveat lector

STATISTICAL REVIEW AND EVALUATION

NDA#: 21-087/S-002
APPLICANT: Hoffman-La Roche Inc.
NAME OF DRUG: Oseltamivir
INDICATION: Prophylaxis of Influenza Infection
TYPE OF REVIEW: Clinical
DOCUMENTS REVIEWED: Volumes 3, 18, 27, 42, 76, 94
MEDICAL INPUT: Teresa Wu, M.D. (HFD-530)

STATISTICAL REVIEW AND EVALUATION

NDA#: 21-087/S-002

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 - 1.2 Summary of Study Designs
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 - 1.2.2 Trials 15673 and 15697: Community Studies
 - 1.2.3 Trial 15799: Family Study
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1. Background

1.1 Objectives in Trials

The applicant submitted four pivotal randomized, double blind, placebo controlled clinical trials with oseltamivir, trial 15825, trials 15673 and 15697 pooled into one, trial 15708, and trial 15799.

The primary objective of these studies was to compare the clinical and antiviral efficacy of oseltamivir at doses of 75 mg qd or 75 mg bid to that of placebo in prophylaxis of influenza. The study population in trials 15673 and 15697 was healthy unvaccinated adults in Northern hemisphere communities experiencing an influenza outbreak. The study populations in trials 15825 and 15708, respectively, were nursing home residents in the Southern and Northern hemispheres, respectively, during influenza outbreaks at the home. The study population in trial 15799 was family members of influenza patients who were not themselves receiving oseltamivir.

1.2 Summary of Study Designs

1.2.1 Trials 15825 and 15708: Nursing Home Studies

Both studies were double-blind, randomized, two-arm, parallel, placebo-controlled, multi-center trials carried out in residential homes for elderly people. A local outbreak was defined as two cases in immediate vicinity within 7 days or one case in the home itself. When a local outbreak was detected, subjects were randomized in a 1:1 ratio to either 75 mg oseltamivir or placebo qd for 6 weeks. Randomization was stratified by vaccination status and pre-existing chronic obstructive airways disease (COAD). Trial 15825 was conducted in the US (16 investigators), the UK (1 investigator), France (4 investigators), Belgium (2 investigators), and the Netherlands (3 investigators). Trial 15708 was conducted in the Australia (6 investigators), New Zealand (2 investigators), South Africa (2 investigators), and Brazil (1 investigator).

1.2.2 Trials 15673 and 15697: Community Studies

Both studies were double-blind, randomized, three-arm, parallel, placebo-controlled, multi-center trials with healthy unvaccinated adults recruited from communities near the participating centers at the beginning of the influenza season. A local outbreak was defined as increased frequency of pneumonia, respiratory illness, and isolation of influenza virus at local labs. When a local outbreak was detected, subjects were randomized in a 1:1:1 ratio to either 75 mg oseltamivir bid, 75 mg oseltamivir qd plus placebo qd, or placebo bid for 6 weeks. Trial 15673 was conducted at 3 centers in Virginia. Trial 15697 was conducted at 2 centers in Texas and 1 in Kansas City.

1.2.3 Trial 15799: Family Study

This study was a double-blind, cluster randomized, two-arm, parallel, placebo-controlled, multi-center trial recruiting families of 3 to 8 members. After a local influenza outbreak and the occurrence of coryza plus cough in an index case within the family, the family was randomized in a 1:1 ratio to either 75 mg oseltamivir or placebo qd for 7 days. The index case received only paracetamol/acetaminophen for symptom relief. The remaining family members received the randomly assigned treatment for 7 days. These treated subjects had to live in the house for at least 2 days before and 3 days after the identification of the index case and had to maintain daily contact with the index case.

The trial was conducted at 35 centers in the US, 11 centers in Canada, 1 center in Denmark, 6 centers in Finland, 6 centers in Germany, 3 centers in the Netherlands, 2 centers in Norway, 1 center in Switzerland, and 8 centers the UK.

1.3 Subject Accounting and Baseline Characteristics

1.3.1 Trial 15825: Nursing Home Study

572 subjects were enrolled in the trial 15825. Of these, 548 received treatment. The subjects were enrolled at centers in the US and Europe. The treated population was 69% female with an age range of 64 to 96 years (mean age 82 years). They were 92% white, 4% black and 4% Hispanic. 80% were vaccinated for influenza; 14% had COAD.

**APPEARS THIS WAY
ON ORIGINAL**

Table 1.3.1 A summarizes the subject status in trial 15825.

TABLE 1.3.1 A
SUBJECT STATUS IN TRIAL 15825

	Oseltam	
	75 mg	Placebo
Randomized, Received Drug	276	272
Completed Study	244	249
Discontinued	32	23
Adverse Event	19	11
Lost to Follow-up	13	12

1.3.2 Trial 15708: Nursing Home Study

385 subjects were enrolled in the trial 15708. Of these, 372 received treatment. The subjects were enrolled at 14 residential homes in all three continents of the southern hemisphere. The treated population was 59% female with an age range of 65 to 95 years (mean age 79 years). They were 99% white. 69% were vaccinated for influenza; 12% had COAD.

Table 1.3.2 A summarizes the subject status in trial 15708.

TABLE 1.3.2 A
SUBJECT STATUS IN TRIAL 15708

	Oseltam	
	75 mg	Placebo
Randomized, Received Drug	190	182
Completed Study	163	162
Discontinued	27	20
Adverse Event	5	7
Lost to Follow-up	22	13

1.3.3 Trials 15673 and 15697: Community Studies

1562 subjects were randomized in the trials 15673 and 15697 pooled. The subjects were enrolled at centers in the US. The treated population was 63% female with a mean age of 34 years. They were 80% white, 11% black and 3% Hispanic.

Table 1.3 B summarizes the subject status in trials 15673 and 15697.

TABLE 1.3 B
SUBJECT STATUS IN TRIALS 15673+15697

	Oseltam 75 mg qd	Oseltam 75 mg bid	Placebo
Randomized	520	521	521
Trial 15673	268	268	268
Trial 15697	252	253	253
Started Drug	520	520	519
Completed Study	503	504	498
Discontinued	17	17	23
Adverse Event	8	7	10
Refused	4	4	9
Lost to Follow-up	5	6	4

1.3.4 Trial 15799: Family Study

Trial 15799 randomized 962 contact cases associated with 377 index cases. 464 contacts were randomized to placebo and 498 to 75 mg oseltamivir qd. The subjects were enrolled at 76 centers in North America and Europe. The treated population was 51% female with a mean age of 33 years. They were 86% white and 9% Hispanic.

Table 1.3 C summarizes the subject status in trials 15799, as reported by the sponsor. The reader will note that there are 7 fewer index cases in this table than in the preceding paragraph. These are the numbers which are reported by the sponsor in adjacent tables in their report. The sponsor also does not document how withdrawals were distributed relative to infected and non-infected index cases.

TABLE 1.3 C
SUBJECT STATUS IN TRIAL 15799

	Oseltam 75 mg	Placebo
Randomized Total		
Index Cases	193	177
Contact Cases	498	464
Randomized Non Infected Index		
Index Cases	109	98
Contact Cases	288	262
Randomized Infected Index Cases		
Index Cases	84	79
Contact Cases	205	200
Randomized Total		
Completed Study	486	458
Discontinued	12	6
Adverse Event	5	0
Refused Treatment	5	6
Lost to Follow-up	2	0

1.4 Summary of Methods of Assessment

1.4.1 Schedule of Measurements

1.4.1.1 Trials 15825 and 15708: Nursing Home Studies and Trials 15673 and 15697: Community Studies

Upon detection of influenza in the local community, subjects were asked if they still consented to be in the study and, if so, were given diary cards on which they recorded oral temperature and 7 influenza symptoms, (cough, sore throat, nasal symptoms, headache, myalgia, sweats/chills, fatigue). This was done daily for six weeks. In the community trials, 15673 and 15697, the diary cards also recorded use of concomitant medicine to treat symptoms. In the nursing home trials, 15825 and 15708, baseline concomitant medicines were recorded on the case report form. The subjects recorded new concomitant medications on the diary cards.

Subjects were seen by their doctor or nurse at baseline, week 3, week 6, week 8, and on any occasion when they felt ill or

had a fever. Nose and throat swabs for viral culture were taken at baseline and at illness visit. Viral antibody titer was measured at baseline and at week 8. In the nursing home trials, 15825 and 15708, the health care examiner also recorded five illnesses secondary to influenza (sinusitis, otitis media, pneumonia, lower respiratory tract infection, bronchitis) if they occurred at any time.

1.4.1.2 Trial 15799: Family Study

Within 48 hours of the diagnosis of influenza-like illness in any family member, the family returned to the clinic and were given diary cards. The contact cases recorded oral temperature and 7 influenza symptoms, (cough, sore throat, nasal symptoms, headache, myalgia, sweats/chills, fatigue) and use of concomitant medicine to treat symptoms. This was done daily for seven days.

Index cases were seen by their doctor or nurse at baseline and at day 10-25. Throat and nasal swabs for viral culture were taken at baseline, blood for viral antibodies at baseline and day 10-25. Contact cases were seen at baseline, at first occurrence of any influenza-like illness, at day 8, and at 21 + 4 days. Nose and throat swabs for viral culture were taken at every visit. Viral antibody titer was measured at baseline, day 8, and day 21 + 4.

1.4.2 Assessment of Treatment Effects

In all five trials, the primary endpoint was occurrence of laboratory confirmed clinical influenza. This was defined as fever (temperature > 99°) plus one respiratory symptom (cough, sore throat, nasal symptoms) plus one constitutional symptom (headache, myalgia, sweats/chills, fatigue) confirmed by either virus shedding within 2 days of symptom onset or four-fold increase in influenza antibody.

In the four community or nursing home studies, two sensitivity analyses were also conducted. In the first analysis, all subjects in all arms who discontinued early were considered to contract influenza. In the more challenging analysis, all

subjects who discontinued early were considered to contract influenza in the oseltamivir arms only.

In the nursing home trials, 15825 and 15708, the incidence rate of the five secondary illnesses listed above in section 1.3 was a secondary endpoint.

1.5 Summary of Statistical Analysis

1.5.1 Trials 15825 and 15708: Nursing Home Studies

The primary endpoint of laboratory confirmed influenza incidence was analyzed using a Fisher exact test. This endpoint was also analyzed separately for the two strata of vaccination status and for the two strata of presence of COAD in trial 15825.

1.5.2 Trials 15673 and 15697: Community Studies

The primary endpoint of laboratory confirmed influenza was analyzed using the Fisher exact test. The sponsor claimed to use a bootstrap adjustment for multiple comparisons but the FDA statistical reviewer notes that there is no such thing.

1.5.4 Trial 15799: Family Study

The primary endpoint was occurrence of laboratory confirmed clinical influenza in contacts of the index case. Two analyses were done. In one analysis, every contact case was considered as a separate chance to get influenza. A method published by Donner in Applied Statistics, 1998 was used to adjust for the clustered randomization of contact cases. In the second analysis, every household was considered as a unit with either no influenza in the contact cases or at least one influenza contact case. In this analysis, the Fisher exact test was used. It does not appear that this test was stratified by number of contact cases, although one would expect that the risk of any influenza among the contacts would increase as the number of contact cases increases.

2. Summary of Applicant's Results
 2.1 Trial 15825: Nursing Home Study

Results for the primary endpoint, incidence of laboratory confirmed influenza, for all subjects are summarized in table 2.1 A. Table 2.1 B contains the results for the two sensitivity analyses in which early discontinuers are considered as influenza cases, either in both arms or on oseltamivir only. Results for the subsets defined by vaccination status and presence of COAD, are summarized in table 2.1 C.

TABLE 2.1 A
 Incidence of Confirmed Influenza, Trial 15825

	Placebo	Osel. 75 mg
N (Treated)	272	276
Confirmed Influenza	12	1
Rate	4.4%	0.4%
95% Con Int for Difference	1.5% - 6.5%	
p-value	.002	

TABLE 2.1 B
 Incidence of Confirmed Influenza + Discontinuation,
 Trial 15825

	Placebo	Osel. 75 mg	p-value
All Discontinue = Influenza	21/272	14/276	.23
Oseltam Only = Influenza	12/272	14/276	.84

TABLE 2.1 C
 Incidence of Confirmed Influenza, Trial 15825
 By Vaccination Status and Presence of COAD
 Placebo Osel. 75 mg

Vaccinated		
Influenza/N	11/218	1/222
Rate	5.0%	0.5%
Unvaccinated		
Influenza/N	1/54	0/54
Rate	1.9%	0%
With COAD		
Influenza/N	3/39	1/39
Rate	7.7%	2.6%
Without COAD		
Influenza/N	9/233	0/237
Rate	3.9%	0%

There was a statistically significant difference of 1.5% to 6.5% in incidence rate of confirmed influenza in the oseltamivir arm compared to placebo. The treatment effect was qualitatively the same in subjects with and without COAD. The treatment effect was not observed to be reduced in vaccinated subjects.

(The FDA reviewer notes that the higher incidence rate of influenza in vaccinated placebo subjects than in unvaccinated placebo subjects was not statistically significant, Fisher exact p-value of .47).

There was also a statistically significant increase in the incidence of complications of influenza (sinusitis, otitis media, pneumonia, lower respiratory tract infection, bronchitis). The results on this secondary analysis are summarized in table 2.1 D.

TABLE 2.1 D
Incidence of Influenza Complications, Trial 15825

	Placebo	Osel. 75 mg
N (Treated)	272	276
Confirmed Influenza	7	1
Rate	2.6%	0.4%
95% Con Int for Difference	0.2% - 4.2%	
p-value	.037	

2.2 Trial 15708: Nursing Home Study

There was too little incidence of influenza in the nursing homes included in this trial for any statistically significant results to be possible. Results for the primary endpoint, incidence of laboratory confirmed influenza, for all subjects are summarized in table 2.2 A.

TABLE 2.2 A
Incidence of Confirmed Influenza, Trial 15708

	Placebo	Osel. 75 mg
N (Treated)	182	190
Confirmed Influenza	1	1
Rate	0.5%	0.5%
p-value	NS	

2.3 Trial 15673+15697: Pooled Community Studies

Results on the primary endpoint are summarized in table 2.3 A. Sensitivity analyses in which early discontinuations in all or only oseltamivir arms are given in table 2.3 B. These sensitivity analyses were only done for the qd arm, since that arm is the preferred dose.

TABLE 2.3 A
Incidence of Confirmed Influenza, Trials 15673+15697

	Placebo	Oseltam 75 mg qd	Oseltam 75 mg bid
N (Treated)	519	520	520
Confirmed Influenza	25	6	7
Rate	4.8%	1.2%	1.3%
95% Con Interval for Difference from Placebo		1.6% - 5.7%	1.4% - 5.6%
p-value		.001	.001

TABLE 2.3 B
**Incidence of Confirmed Influenza + Discontinuation,
Trials 15673+15697**

	Placebo	Oselt. 75 mg qd	p-value
All Discontinue = Influenza	35/519	16/520	.006
Oseltam Only = Influenza	25/519	16/520	.16

There was a statistically significant difference of 1.5% - 5.5% in the incidence rate of confirmed influenza in both oseltamivir arms compared to placebo.

Incidence rates for three other endpoints are summarized in table 2.3 C. These are laboratory confirmed virus with URTI (upper respiratory tract illness with symptoms not meeting the definition of clinical influenza), asymptomatic laboratory confirmed virus, and adverse events.

TABLE 2.3 C
Incidence of Other Endpoints, Trials 15673+15697

		Oseltam	Oseltam
	Placebo	75 mg qd	75 mg bid
N (Treated)	519	520	520
Confirmed URTI	11	9	8
Asymptomatic Virus	19	13	12
Adverse Events	384	414	408
p-value	.073		
Nausea	37	63	76
p-value	.001		
Vomiting	4	13	14
p-value	.051		

There was no statistically significant difference among the arms in incidence rates of laboratory confirmed influenza virus with non-clinical symptoms or asymptomatic. There were more adverse events with oseltamivir. The main source of these extra adverse events were gastro-intestinal events, particularly nausea and vomiting. The sponsor did not report any tests for statistical significance of these results. The p-values for adverse event rates in this table were calculated by the FDA reviewer, using a Pearson chi-square for equality of rates among the arms.

2.4 Trial 15799: Family Study

The results on the primary endpoint are summarized in table 2.4 A. Two analyses are presented. The first analyzed incidence rate by contact cases, adjusting for the clustered randomization.

The second analyzed incident rate by clusters. The results of sensitivity analyses counting early discontinuers as influenza cases are given in table 2.4 B.

TABLE 2.4 A
Incidence of Confirmed Influenza, Trial 15799
Placebo Osel. 75 mg

By Contact Cases		
N (Infected Index Case)	200	205
Confirmed Influenza	24	2
Rate	12%	1.0%
p-value	.0001	
By Clusters		
N (Infected Index Case)	79	84
Confirmed Influenza	17	2
Rate	22%	2.4%
95% Con Int for Difference	9.5% - 29%	
p-value	.0001	

The incidence of influenza was statistically significantly lower in the subjects given prophylactic oseltamivir, regardless of the method of analysis. The results of sensitivity analyses counting early discontinuers as influenza cases are given in table 2.4 B.

TABLE 2.1 B
Incidence of Confirmed Influenza + Discontinuation,
Trial 15825

	Placebo	Osel. 75 mg	p-value
All Discontinue = Influenza	25/200	8/205	.012
Oseltam Only = Influenza	24/200	8/205	.018

3. Summary of Applicant's Conclusions

The applicant concluded that use of 75 mg qd oseltamivir resulted in significant reduction in influenza incidence compared to placebo for the period for which it is taken. Furthermore, there was no statistically or practically significant increase in side effects, compared to oseltamivir for influenza treatment. This was true even for elderly subjects with high rates of co-morbidity taking oseltamivir for up to six weeks.

4. Statistical Reviewer's Comments and Analyses

There are three issues that the applicant does not discuss in detail. These are 1) the early discontinuations, 2) the increased incidence of nausea and vomiting, and 3) the statistical significance of the observed reduced incidence of influenza complications in trial 825.

4.1 Early Discontinuations

The applicant reports a sensitivity analysis in which all early discontinuers considered to have been confirmed influenza cases. There was no statistically significant difference between the arms in this analysis. The applicant makes no comment on the loss of statistical significance in this analysis.

The FDA reviewer notes that it seems unreasonable to assume that all subjects lost to follow-up actually had influenza. Only 5-12% of subjects on the placebo arm had influenza in the various trials. Furthermore, the subjects discontinuing the study were observed for at least a portion of the prophylaxis period, often a substantial fraction. Even allowing for the possibility that subjects discontinuing early were at higher risk than those observed to the end, it is unlikely that they all had influenza.

The FDA reviewer did a sensitivity analysis in which all subjects who discontinued early had a higher risk of influenza from the time of drop-out to the scheduled end of the study. The risk was assumed to be a multiple of the estimated risk for placebo subjects. The results may be briefly summarized. Even if discontinuing subjects were at a risk of influenza that was six times higher than that for observed placebo subjects, the imputed difference in incidence rates between oseltamivir and placebo would be statistically significant.

4.2 Increased Risk of Nausea and Vomiting

The applicant mentioned that there was an increased rate of nausea and vomiting observed with oseltamivir compared to placebo. The applicant did not mention that this increase was statistically significant.

The FDA reviewer computed the mean number of days on which subjects reported nausea or vomiting on each arm and compared that with the mean duration of episodes of lab confirmed influenza starting during prophylaxis on each arm. An episode of influenza was assumed to last until the subject was afebrile and symptom free. In computing these means, subjects who had no nausea or no influenza were included with durations of zero. The mean durations for each arm in each trial as well as the differences between the placebo and tamiflu arms are given in table 4.2 A.

TABLE 4.2 A
DURATIONS OF NAUSEA/VOMITING & INFLUENZA
ALL TRIALS

Trial, Arm	Nausea/Vomiting		Confirmed Influenza	
	Duration	Compared to Placebo	Duration	Compared to Placebo
Trial 673+697				
Placebo	.2 days	.	.54 days	
Tamiflu BID	.9 days	+.7 days**	.09 days	-.5 days**
Tamiflu QD	.5 days	+.4 days	.04 days	-.5 days**
Trial 799				
Placebo	.08 days	.	.68 days	
Tamiflu QD	.19 days	+.1 days*	.08 days	-.6 days**
Trial 708				
Placebo	.1 days	.		
Tamiflu QD	.8 days	+.7 days**		
Trial 825				
Placebo	.43 days	.	.18 days	
Tamiflu QD	.30 days	-.1 days	.03 days	-.2 days

** statistically significant at level < .05

* statistically significant at level <.10 but > .05

Trial 708 had only two cases on influenza, one in each arm,

so mean durations of influenza in that trial were not included. The overall impression is that the 75 mg qd dose of oseltamivir increased days with nausea or vomiting by .3 days over placebo and decreased influenza duration by .5 days. This comparison says nothing about the comparative risks of influenza versus drug induced nausea.

4.3 Incidence of Influenza Complications

In table 2.1 D above, the applicant reported that the incidence rates of influenza complications in trial 825 were 2.6% = 7/272 in the placebo arm and .4% = 1/276 in the oseltamivir arm, a difference which was statistically significant at level .037.

This is a statistically valid assertion about an unconditional probability. A subject is at lower risk of influenza complications when given oseltamivir prophylaxis. The reduced risk of influenza infection is part of the reason for the reduced of complications.

Proposed wording in the labelling may also appear to make a claim about a conditional probability, namely, _____

_____ The appropriate table for examination of this conditional claim is one in which the total for each arm is all subjects with laboratory confirmed influenza, not all subjects enrolled. For this claim, the incidence rates of influenza complications were 30% = 7/23 in the placebo arm and 7% = 1/15 in the oseltamivir arm. A Fisher exact test with this table shows that the difference was not statistically significant, with a p-value of .11.

It would therefore be inappropriate to make any label claim that _____

5. Statistical Reviewer's Summary

The applicant has shown that oseltamivir at 75 mg bid is an effective prophylactic against influenza, both for short term prophylaxis against intra-family transmission and for long term (6 weeks) prophylaxis against community based influenza in a high risk population. The only observable increased risk was an increase in nausea/vomiting of about 1/3 day during long term prophylaxis. There is reduced incidence of complications of influenza which appears to be entirely attributable to the reduced of influenza.

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Soon

cc:
Archival NDA #21-087/S-002

HFD-530
HFD-530/Dr. Jolson
HFD-530/Dr. Birnkrant
HFD-530/Ms. Carmouze
HFD-530/Dr. Murray
HFD-530/Dr. Wu
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HFD-725/Dr. Soon
HFD-725/Dr. Huque
HFD-725/Ms. Robinette

/s/

Thomas Hammerstrom
11/21/00 12:02:51 PM
BIOMETRICS

signature needed

Greg Soon
12/5/00 12:16:46 PM
BIOMETRICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-087 (Supplement SE1-002)
TYPE: P
DRUG: Oseltamivir (Tamiflu) 75 mg capsule
APPLICANT: Hoffmann-La Roche
REVIEWER: Jenny H. Zheng, Ph.D.
Prabhu Rajagopalan, Ph.D.
TEAM LEADER: Kellie Reynolds, Pharm.D.
CLINICAL DIVISION: 530
SUBMISSION DATE: May 22, 2000
PDUFA GOAL DATE: November 22, 2000
Briefing: Not required

Executive Summary

Oseltamivir phosphate (Tamiflu, Ro 64-0796) 75 mg BID for 5 days has been previously approved for treatment of influenza in adults. Oseltamivir is an ethyl ester prodrug of oseltamivir carboxylate (Ro 64-0802), a potent and specific inhibitor of the neuraminidase enzyme of influenza virus. This NDA supplement seeks approval of oseltamivir for the prevention of influenza using 75 mg QD for at least 7 days.

Pharmacokinetics were well characterized in original NDA, and are supportive in this NDA. Approval of this NDA supplement will be based on safety and efficacy data from studies in naturally acquired influenza (N=3434). The pharmacokinetic portion of this NDA supplement consists of four studies:

- (1) Pharmacokinetics of Ro 64-0796 and Ro 64-0802 in ESRD subjects on hemodialysis & peritoneal dialysis (Study PP 15974, Volumes 9-10, review – Pages 3-9),
- (2) Pharmacokinetic drug interaction of Ro 64-0796 and amoxicillin in healthy volunteers (Study NP15901, Volumes 11-12, review – Pages 10-12)
- (3) Pharmacokinetics of Ro 64-0796 and Ro 64-0802 in the prophylaxis of influenza in volunteers experimentally inoculated with the human influenza B virus (NP15757, Volume 13, review – Pages 13-14)
- (4) Pharmacokinetics of oral Ro 64-0796 and Ro 64-0802 in the prophylaxis against experimental inoculation with human influenza virus (GS 97-802, Volume 14, review – Pages 15-16).

PP15974 and NP15901 were conducted in compliance with post-marketing commitments made by the applicant. Pharmacokinetics of Ro 64-0796 and Ro 64-0802 were studied during the prophylaxis against experimental inoculation with human influenza viruses to confirm that the pharmacokinetics of Ro 64-0796 and Ro 64-0802 are similar between healthy volunteers and subjects with experimentally induced and naturally acquired influenza.

This review addresses oseltamivir dose adjustments in patients with creatinine clearance (CLcr) < 30 ml/min, including those on dialysis, when oseltamivir is administered for treatment or prophylaxis of influenza.

The original approved label for treatment of influenza indicates that patients with CLcr between 10-30 ml/min should receive oseltamivir 75 mg QD for 5 days rather than 75 mg BID. Although this regimen produces Ro 64-0796 and Ro 64-0802 concentrations much higher than those observed in patients with normal renal function who receive 75 mg BID, the safety profiles for oseltamivir supported this higher exposure for 5 days.

Because the prophylaxis regimen involves treatment for up to 6 weeks, patients with CLcr between 10-30 ml/min require a dose reduction: 75 mg every other day. The adjusted regimen will provide similar exposure as observed in adults with normal renal function who received 150 mg BID.

Study PP15974 shows that drug exposure for 4 days after single 75 mg of Ro-64-0796 oral dose in ESRD subjects on hemodialysis & peritoneal dialysis is more than 5-fold higher compared to that in subjects with normal renal function after 75 mg of Ro-64-0796 BID, but is comparable to that in subjects with CLcr between 10 to 30 ml/min after 75 mg of Ro 64-0796 QD. The applicant has provided simulations using different 30 mg dosing regimens, but does not want to recommend dosing regimens for treatment or prophylaxis of influenza for ESRD subjects on dialysis at this time. The sponsor would prefer to conduct another clinical study as a Phase IV commitment.

Study NP15901 indicates that amoxicillin does not affect the pharmacokinetics of Ro 64-0796 and its metabolite Ro 64-0802. Concomitant administration of oseltamivir and amoxicillin does not affect the pharmacokinetics of this antibiotic. Therefore, these two drugs can be administered concomitantly. In general, Ro 64-0796 and Ro 64-0802 appear to be weak competitors for drugs that undergo renal tubular secretion via the anionic pathway.

Studies NP15757 and GS 97-802 demonstrate that pharmacokinetics of Ro 64-0796 and Ro 64-0802 administered for the prophylaxis against experimental inoculation with human influenza viruses are comparable to the previous studies in treatment of influenza in healthy volunteers and subjects with experimentally induced and naturally acquired influenza.

Individual reviews are attached.

A single oral dose, multi-center study of the PK, safety and tolerability of Ro 64-0796/GS4104 in ESRD subjects on hemodialysis & peritoneal dialysis
(Protocol PP15974, Volumes 9-10)

Background: A previous study (WP 15648) has shown that total exposure for both Ro 64-0796 and Ro 64-0802 increases as renal clearance decreases. Dialysis subjects were not enrolled in the previous study, and are now studied separately as a Phase IV commitment.

Objective: To assess the pharmacokinetics of oseltamivir and its active metabolite in hemodialysis and peritoneal dialysis subjects; and to evaluate the safety and tolerability of oseltamivir in hemodialysis and peritoneal dialysis subjects.

Investigator and study location:

Subjects: 24 male or female ESRD subjects aged between 18 and 66 years (12 on hemodialysis and 12 on peritoneal dialysis).

Study design: This is a multi-center, single oral dose, open label study in ESRD subjects on hemodialysis and peritoneal dialysis. Hemodialysis subjects had routine dialysis three times a week. Subjects received a single oral 75mg dose of oseltamivir (Ro 64-0796) 48 hours prior to their next dialysis, and 30 minutes after receiving a standard meal. Subjects were dialyzed over the 48-52 hour time period. Peritoneal dialysis subjects had the dialysate changed 4 times per day. Immediately preceding the commencement of the morning peritoneal dialysis procedure, and 30 minutes after receiving a standard meal, subjects received a single oral 75mg dose of Ro 64-0796. The dialysate was changed at 5 hours, 10 hours, 15 hours and 24 hours post dose.

Formulations: Capsule containing 75mg Ro 64-0796 (V14, Market Formulation).

Sample collection for PK analysis: Blood samples were taken for the analysis of Ro 64-0796 and its metabolite Ro 64-0802. For hemodialysis patients, samples were taken at: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 36, 48, 48.5, 49, 49.5, 50, 51, 52, and 53 hours post dose, and just prior to the subjects next scheduled dialysis. During dialysis (48-52 hr), samples were taken from both 'arterial' (blood inflow) and 'venous' site (blood outflow) of the dialyzer.

For peritoneal dialysis patients, samples were taken before dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 36, 48 and 72 hours post-dose. Dialysate samples were collected at 5, 10, 15 and 24 hours post dose.

All urine samples were collected over 0-12, 12-24, 24-36, and 36-48 hours post dose.

Analytical methodology: Plasma and urine samples were assayed for concentrations of Ro 64-0796 and its active metabolite Ro 64-0802 by a HPLC/MS/MS analytical method.

Pharmacokinetic data analysis: Pharmacokinetic parameters were estimated by noncompartmental methods.

Pharmacokinetic results and discussions:

4.1. Pharmacokinetics

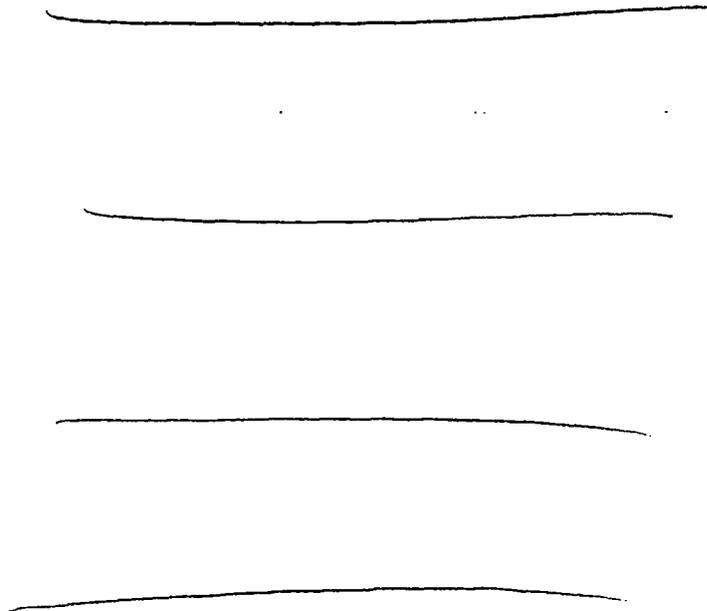


Figure 1 shows the plasma concentrations of Ro 64-0796 and Ro 64-0802 in hemodialysis patients. Figure 2 shows the plasma concentrations of Ro 64-0796 and Ro 64-0802 in peritoneal dialysis patients. Table 1 Compares Ro 64-0802 mean (SD) pharmacokinetic parameters in dialysis subjects with patients with different renal function.

The data show that, compared to subjects with severe renal impairment (creatinine clearance (CLcr) between 10 to 30 ml/min) after 75 mg of Ro 64-0796 OD, C_{max} of Ro 64-0802 is not higher and AUC is up to 30% higher over 2 days in hemodialysis and peritoneal dialysis patients. However, compared to subjects with normal renal function (CLcr > 90 ml/min) after 75 mg of Ro 64-0796 BID for 5 days, C_{max} is about 10-fold higher, and AUC is 7 to 8-fold higher over 2 days and 5-fold higher over 4 days in hemodialysis and peritoneal dialysis patients after a single 75 mg dose of Ro 64-0796. The increased drug exposure is due to reduction of total clearance and renal clearance in this group of patients (Table 1). The results show that drug exposures, measured by Ro

64-0802, are comparable between ESRD subjects (CLcr < 10 ml/min) on hemodialysis or peritoneal dialysis after single 75 mg of Ro 64-0796 and subjects with severe renal impairment (CLcr between 10 to 30 ml/min) after 75 mg of Ro 64-0796 OD (approved regimen for treatment). However, this drug exposure level is much greater than that in subjects with normal renal function after 75 mg of Ro 64-0796 BID (approved regimen for treatment).

75 mg dose	Hemodialysis	Peritoneal dialysis	Creatinine clearance >90 ml/min	Markedly reduced creatinine clearance 10-30 ml/min	Creatinine clearance >90 ml/min	Markedly reduced creatinine clearance (10-30 ml/min)*
	Single	Single	Single	Single	Multiple BID	Multiple QD
C _{max}	2131 (533)	1885 (475)	225 (49)	1102 (283)	348 (64)	3,039
T _{max} (hr)	27.3 (6.9)	18.0 (6.6)	3.8 (1.0)	8.4 (1.7)	3.0 (0.7)	5.2 (1.1)
AUC _{0-∞} (ng.hr/ml)	NA	152,081 (72,393)	2227 (410)	30,125 (10,905)	NA	NA
AUC ₀₋₄₈ (ng.hr/ml)	82,527 (20,239)	68,358 (20,857)	NA	NA	10,800 ^a	62,636 ^a
AUC ₀₋₉₆ (ng.hr/ml)	106,314 (26,029) (92 h)	108,998 ^b (37,807)	NA	NA	21,752 ^a	125,272 ^a
CL/F (ml/min) ^c	14.5 (3.2) ^d	19.0 (9.1)	532 (118)	42.3 (16.5)	438.3 (111.7)	41.2
CLr (ml/min) ^e	0.4 (0.7)	2.4 (5.8)	297 (65)	31 (10)	281(45)	26 (9.4)
t _{1/2} (h)	159 ^d	43.5	5.5 (1.4)	14.0 (4.5)	5.8 (6.0)	16.(2.7)

Table 1

- * Normalized to 75 mg dose
- ^d Prior to initiation of hemodialysis at 48 hours
- ^a Based on AUC₀₋₁₂, assuming no accumulation.
- ^b AUC was estimated from 72 h to 96 hr.
- ^c 48 hr clearance

(2) Dosing regimens:

A 75 mg of Ro 64-0796 QD for 5 days for treatment of influenza in patients with creatinine clearance between 10 to 30 ml/min was approved in NDA 21-087. Although this regimen produces Ro 64-0796 and Ro 64-0802 concentrations much higher than those observed in patients with normal renal function who receive 75 mg BID, the safety profiles for oseltamivir supported this higher exposure for 5 days (see Dr. Rajagopalan's review for NDA 21-087). In addition, the drug exposure in this group was only 40% higher than that in adults with moderate renal impairment (CLcr between 30 and 60 ml/min) after 75 mg BID of Ro 64-0796 (approved regimen for treatment) (Table 2).

In the prophylaxis of influenza, the dosing regimen allows treatment for up to 6 weeks. We recommend that patients with CLcr between 10-30 ml/min require a dose reduction to avoid possibility of increased adverse events due to accumulation:

75 mg every other day, if taking the capsule; or
30 mg per day, if taking the suspension.

These adjusted regimens will provide similar exposure as observed in adults with normal renal function who received 150 mg BID and observed in adults with CLcr between 30 and 60 ml/min after 75 mg daily (Table 2).

Parameter	Normal Renal Function		Impaired Renal Function				
	75 mg BID	150 mg BID	CLcr between 10 and 30 ml/min			CLcr between 30 and 60 ml/min	
			75 mg daily	75mg alternate days	30 mg daily	75 mg daily	75 mg BID
C_{max}			1,638	1,175	655	707	1,063
C_{min}			864	209	346	197	707
AUC_{0-18}	10,876	21,864	62,636	21,999	25,054	21,978	43,948
$AUC/5\ days^*$	27,190	54,660	156,590	-	62,635	54,945	109,870
$AUC/week^*$	38,066	76,524	219,226	-	87,689	76,923	153,818

Table 2

* Based on AUC_{0-18} , assuming no accumulation.

For adults with CLcr <10 ml/min who are on hemodialysis or peritoneal dialysis, a 75 mg single dose produces Ro 64-0802 concentrations similar to that in adults with CLcr between 10 and 30 ml/min after a single 75 mg dose (approved regimen for treatment) (Table 1). Therefore, a 75 mg single dose is acceptable for treatment of influenza in ESRD subjects on hemodialysis or peritoneal dialysis.

For prophylaxis of influenza in ESRD subjects on hemodialysis or peritoneal dialysis, the sponsor provided simulations of Ro 64-0802 exposure after receiving different dosing regimens of 30 mg of oseltamivir oral suspension.

Table 3 presents the projected steady-state exposure in subjects on peritoneal dialysis (CAPD) after receiving weekly 30 mg doses. The data show that the drug exposure (C_{max} and AUC) is up to 6 fold higher compared to that in subjects with normal renal function after a 75 mg QD of Ro 64-0796 (Table 3), but is comparable to that in subjects with CLcr between 30 and 60 ml/min after a 75 mg QD of Ro 64-0796 (Table 2). Figure 3 shows the simulated oseltamivir concentration following administration of a 30 mg oseltamivir dose once a week in subjects on peritoneal dialysis and following administration of 75 mg once daily in healthy volunteer.

Ro 64-0802	CAPD; 30mg per week	Normal: 75mg QD	Difference
C_{max}	_____		
C_{min}	_____		
$AUC/week$	60,832	13,083	5-6 fold

Table 3

In subjects on hemodialysis, if hemodialysis is scheduled every 48 hours, Ro 64-0802 concentrations after the second dialysis session (96-100 hours) would be low (~40 to 60 ng/mL), but still around the trough level observed during effective prophylaxis. However the concentrations following the second session would be below this minimum level. The applicant proposed a dosing regiment that requires a supplemental 30 mg dose after each alternate hemodialysis session to maintain plasma concentrations above the

minimum trough level observed with the 75mg daily dose in prophylaxis studies. Figure 4 compares Ro 64-0802 concentration profiles following administration of 30mg dose of oseltamivir every other hemodialysis in hemodialysis patient and following administration of 75mg QD dose of oseltamivir in healthy volunteer. Table 4 shows the simulated steady-state drug exposure in hemodialysis patients following administration of 30mg dose of oseltamivir every other dialysis session, compared to that in healthy volunteers following administration of 75mg QD oseltamivir. The data show that the drug exposure (C_{max} and AUC) is up to 4 fold higher compared to that in subjects with normal renal function after a 75 mg QD of Ro 64-0796 (Table 4), but is comparable to that in subjects with CLcr between 30 and 60 ml/min after a 75 mg QD of Ro 64-0796 (Table 2).

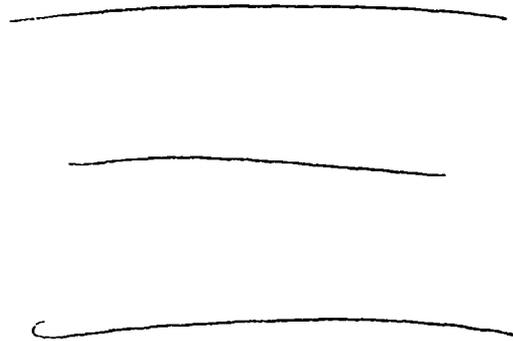


Figure 3

The applicant does not feel comfortable using the simulated results to recommend dosing regimens for treatment or prophylaxis in ESRD subjects on peritoneal dialysis or hemodialysis at this time. The sponsor would prefer to conduct another clinical study as a Phase IV commitment.

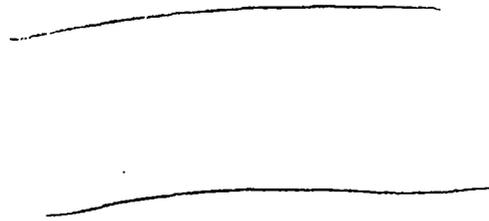


Figure 4

(3) The efficiency of dialyses:

The efficiency of dialyses was measured by dialysis clearance and fraction eliminated during dialysis. In this submission, the reviewer realized that the sponsor has defined some of parameters inappropriately.

Hemodialysis clearance CL_{HD} was defined as: $CL_{HD} = BFR * (1-Hct) * (A-V)/A$, where BFR is the dialysis blood flow rate; Hct is the hematocrit; A is the 'arterial' (inflow to dialyzer) concentration of Ro 64-0802 and V is the 'venous' concentration (outflow from dialyzer) of Ro 64-0802. The reviewer noticed that the sponsor assume inflow rate was the same as outflow rate, which might not be true due to fluid loss (often 2 to 3 liters during a typical 3 to 4 hr dialysis period). The correct equation should be $CL_{HD} = (1-Hct) * (A * Q_{b,in} - V * Q_{b,out})/A$, where $Q_{b,in}$ and $Q_{b,out}$ are in and out blood flow rates, respectively. Another method to estimate CL_{HD} , which is more accurate, is using the amount of drug in dialysate: $CL_{HD} = \text{amount of drug in dialysate} / \int_0^t A dt$. However, the amount of drug in dialysate was not determined in this study.

Fraction eliminated in hemodialysis was defined as: $(\text{mean } C_{48} - \text{mean theoretical } C_{52}) / \text{mean } C_{48}$, where C_{48} and C_{52} are concentrations at the beginning of the dialysis and the end of the dialysis, respectively. Theoretical C_{52} in this study was determined by back extrapolation of the observed concentration at 92 h to 52 h, assuming mono-exponential decline. The reviewer noticed that Fraction eliminated in hemodialysis needs to be estimated individually and be summarized, instead of using the mean value to calculate it. The reviewer also noticed that the subtractor should be theoretical C_{48} instead of theoretical C_{52} . Theoretical C_{48} is determined by back extrapolation of the observed concentration at 92 h to 48 h, assuming mono-exponential decline. The accurate equation should be: fraction eliminated in hemodialysis = $(C_{48} - \text{theoretical } C_{48}) / C_{48}$.

Fraction eliminated in peritoneal dialysis was defined as: $\text{mean } CL_{HD} / \text{mean } CL/F$. As mentioned for hemodialysis, the individual data should be used in the equation.

Secondly, there is a typo in the equation, CL_{PD} instead of CL_{HD} should be used. CL_{PD} needs to be defined as: amount of drug in dialysate/AUC.

Conclusion:

The proposed doses are acceptable for treatment in subjects with creatinine clearance < 30 ml/min. However, for prophylaxis of influenza, patients with CL_{Cr} between 10-30 ml/min require a dose reduction: 75 mg every other day.

Upon request, the applicant provided pharmacokinetic simulation to compare different dosing regimens using 30 mg dose. However, the applicant does not feel comfortable to use the simulated results to recommend dosing regimens for treatment or prophylaxis in ESRD subjects on dialysis.

An open-label, two-way crossover randomized pharmacokinetic drug interaction study of neuraminidase inhibitor of Ro 64-0796 and amoxicillin in healthy volunteers
(Protocol NP15901, Volumes 11-12)

Background: A previous study conducted by the Sponsor had indicated that Ro 64-0802 was eliminated by the kidneys via the anionic transport process. The Sponsor has conducted a study to assess the pharmacokinetic interaction between Ro 64-0802 and amoxicillin, which is also eliminated by the anionic pathway of renal tubular excretion and may be used for the treatment of respiratory tract infection during treatment of influenza infection.

Objective: To determine the effect of Ro 64-0796 on the pharmacokinetics of amoxicillin and the effect of amoxicillin on the pharmacokinetics of Ro 64-0796.

Subjects: 12 healthy subjects (6 males and 6 females, mean age: 24 years, mean weight: 68 kg) completed the study.

Study design: The subjects received the following treatments in a randomized crossover fashion.

Treatment A: Single oral dose of 500 mg of amoxicillin

Treatment B: Ro 64-0796 75 mg BID for four days

Treatment C: Ro 64-0796 75 mg + 500 mg of amoxicillin administered in the morning

The treatments were administered according to one of two sequences: ABC or BCA. Treatment C immediately followed Treatment B. Treatments A and BC were separated by a washout period of 3 days. Pharmacokinetic assessments were made on Days 1, 8 and 9 (sequence ABC) or Days 4, 5 and 9 (sequence BCA).

Formulations: Ro 64-0796 capsules (75 mg, /V14, batch number GMZ0134/03) and amoxicillin capsules (500 mg) were used in this study.

Sample collection: Blood samples were obtained at predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hours after drug administration on pharmacokinetic assessment days. Urine samples were collected during 0-4, 4-8 and 8-12 hours after drug administration.

Pharmacokinetic data analysis: Pharmacokinetic parameters of amoxicillin, Ro 64-0796 and Ro 64-0802 were estimated by non-compartment methods. The mean plasma concentration-time profiles of amoxicillin are shown in Figure 1 and the pharmacokinetic parameters of amoxicillin are summarized in Table 1.

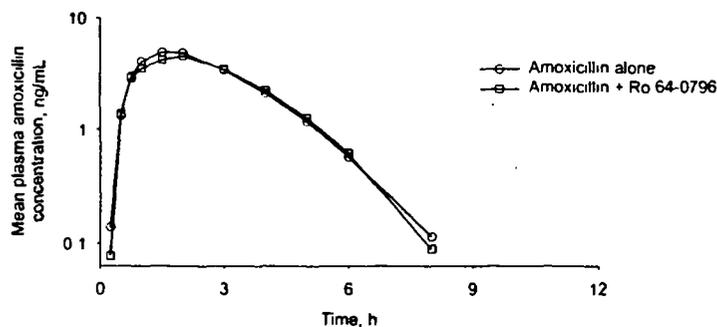


Figure 1

Table 1. Mean (%CV) amoxicillin pharmacokinetic parameters

PK parameter	Treatment A	Treatment C
C_{max} , $\mu\text{g/ml}$	5.5 (36)	5.5 (33)
AUC_{0-12} , $\mu\text{g}\cdot\text{h/ml}$	16.1 (22)	15.7 (29)
CL/F, ml/min	516 (21)	523 (22)
% UR	49.1 (23)	53.6 (30)

The pharmacokinetics of amoxicillin were not affected by concomitant administration of Ro 64-0796. The point estimates [90% CI] for log transformed C_{max} and AUC for Treatment C with respect to Treatment A were 1.01 [0.86 – 1.12] and 0.97 [0.89 – 1.06], respectively.

The mean plasma concentration - time profiles of Ro 64-0796 and Ro 64-0802 are shown in Figure 2 and the pharmacokinetic parameters of these species are summarized in Table 2.

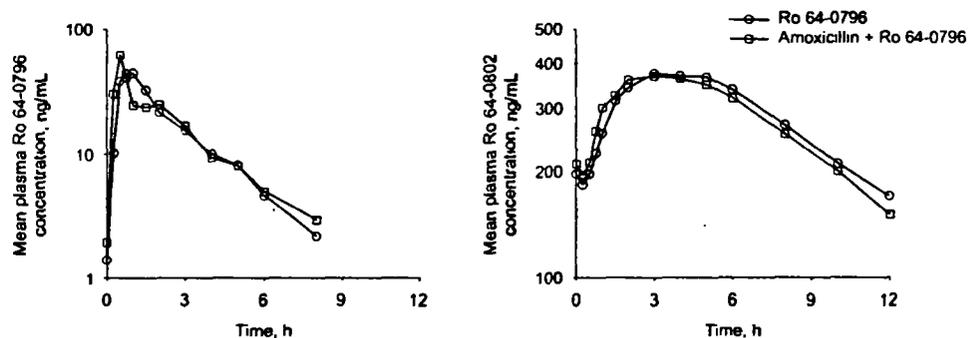


Figure 2

Table 2. Mean (%CV) Ro 64-0796 and Ro 64-0802 pharmacokinetic parameters

Species	Ro 64-0796		Ro 64-0802	
	Treatment B	Treatment C	Treatment B	Treatment C
C_{max} , ng/ml	59.4 (41)	79.1 (46)	389 (15)	397 (19)
AUC_{0-12} , ng·h/ml	115 (31)	115 (24)	3438 (13)	3330 (13)
CL/F, L/min	11.8 (29)	11.4 (22)	0.336 (13)	0.347 (13)
% UR (0-12h)	4.1 (20)	4.2 (29)	83.1 (7)	84.9 (7)

The 90% confidence intervals for log transformed C_{max} and AUC for the metabolite Ro 64-0802 were within [0.80 – 1.25]. The 90% confidence interval for Ro 64-0796 AUC was within [0.80 – 1.25], however the 90% confidence interval for Ro 64-0796 C_{max} was [0.94 – 1.81]. The average increase in Ro 64-0796 C_{max} was 30%, which is not considered to be clinically significant.

Conclusions: The results of this study indicate that amoxicillin does not affect the pharmacokinetics of Ro 64-0796 and its metabolite Ro 64-0802. Concomitant administration of oseltamivir and amoxicillin does not affect the pharmacokinetics of this antibiotic. Therefore, these two drugs can be administered concomitantly. In general, Ro 64-0796 and Ro 64-0802 appear to be weak competitors for drugs that undergo renal tubular secretion via the anionic pathway.

Study of the Pharmacokinetics and Pharmacodynamics of the Neuraminidase Inhibitor
Ro 64-0796 (GS4104) in the Prophylaxis of Influenza in Volunteers Experimentally
Inoculated with the Human Influenza B Virus
(Protocol NP15757, Volume 13)

Investigators and cen

Objectives: To evaluate the pharmacokinetics and antiviral effect of prophylactic doses of Ro 64-0796 in subjects experimentally inoculated with influenza B virus, and to assess the safety and tolerability of Ro 64-0796.

Subjects: 58 healthy male or female volunteers.

Study design: This is a single center, double blind, placebo-controlled oral dose study. Subjects were randomized to one the three groups:

Group A: 75 mg of Ro 64-0796 BID starting on Day 1 for 7 days

Group B: 75 mg of Ro 64-0796 OD starting on Day 1 for 7 days, received one capsule of 75mg Ro 64-0796 in the morning followed by one placebo capsule in the afternoon

Group C: Placebo BID starting on Day 1 for 7 days.

Subjects were inoculated with 10^7 TCID₅₀ of influenza B/Yamagata/16/88 virus by nasal drops on the morning of Day 2.

Formulations: 75mg Ro 64-0796/V01-00 capsules and matching placebo capsules for Ro 64-0796/V02-00

Analytical methodology: Plasma samples were assayed for concentrations of Ro 64-0796 and its active metabolite Ro 64-0802 by a HPLC/MS/MS analytical method.

Pharmacokinetic data analysis: Pharmacokinetic parameters were estimated by noncompartmental methods.

Mean (SD) pharmacokinetic parameters for Ro 64-0796 after multiple doses of Ro 64-0796 are summarized in the table below.

Ro 64-0796 Parameter	Study Day	75 mg o.d. (n=19)	75 mg b.i.d. (n=20)
C _{max} (ng/ml)	1	38.2 (14.1)	45.0 (22.8)
	7	51.0 (27.7)	58.5 (27.5)
t _{max} (h)	1	2.02 (0.87)	1.58 (0.64)
	7	1.69 (0.84)	1.64 (0.99)
AUC ₀₋₁₂ (ng.h/ml)	1	114 (28.5)	113 (39.3)
	7	116 (27.5)	132 (37.9)
t _{1/2} observed (h)	1	2.22 (1.21)	1.81 (0.95)
	7	1.63 (0.47)	2.62 (1.57)
t _{1/2} effective (h)	1-7	nc*	6.25 (3.77)**

nc* : not calculated in >10 subjects

** : n=14

The table below shows the mean (SD) pharmacokinetic parameters for Ro 64-0802.

Parameter	Study Day	75mg o.d. (n=19)	75mg b.i.d. (n=20)
C _{max} (ng/mL)	1	195 (50.8)	215 (76.9)
	7	259 (59.2)	367 (75.7)
t _{max} (h)	1	5.03 (1.11)	4.86 (1.33)
	7	4.21 (1.02)	3.94 (1.41)
AUC _{0-∞} (ng.h/mL)	1	1445 (326)	1563 (502)
	7	1869 (407)	2879 (558)
t _{1/2} observed (h)	1	7.17 (2.21)	8.98 (7.56)
	7	6.14 (1.42)	6.32 (1.48)
t _{1/2} effective (h)	1/7	10.80 (2.77)	11.5 (4.50)

Trough plasma concentration of Ro 64-0796 and Ro 64-0802 were determined from samples obtained on study Days 4, 6 and 7 as an assessment of steady state. The data indicated that steady state had been attained by Day 4 for both Ro 64-0796 and Ro 64-08. The table below lists the trough plasma concentrations (ng/ml) of Ro 64-0802.

Dose Regimen	Day 4	Day 6	Day 7
75 mg o.d.	39.3 ± 15.6	31.5 ± 12.5	32.7 ± 12.4
75 mg b.i.d.	183 ± 53.7	175 ± 45.3	201 ± 48.7

Conclusion: The pharmacokinetics parameters of Ro 64-0796 and Ro 64-0802 in this study are comparable to those in previous studies in adults.

Safety, tolerability and activity of oral Ro 64-0796 (GS4104) for prophylaxis against experimental inoculation with human influenza virus (Protocol GS 97-802, Volume 14)

Investigators and centers:

Objectives:

1. To assess the safety and tolerability of two oral doses of Ro 64-0796 compared to placebo.
2. To assess the prophylactic antiviral activity of two oral doses of Ro 64-0796 compared to placebo.
3. To assess trough plasma concentrations of Ro 64-0796 and Ro 64-0802.

Subjects: 37 healthy male or female volunteers aged 18-40 years.

Study design: This is a single center, double blind, placebo-controlled oral dose study.

Subjects were randomized to receive one the three groups:

Group A: 100 mg of Ro 64-0796 BID starting on Day 1 for 5 days

Group B: 100 mg of Ro 64-0796 OD starting on Day 1 for 5 days, received one capsule of 100mg Ro 64-0796 in the morning followed by one placebo capsule in the afternoon

Group C: Placebo BID starting on Day 1 for 5 days.

Subjects were inoculated with 10^6 TCID₅₀ of influenza virus A/Texas/91 (H1N1) by nasal drops 24-26 hours after the first dose.

Formulations: 100mg Ro 64-0796 capsules and matching placebo capsules

Analytical methodology: Plasma samples were assayed for concentrations of Ro 64-0796 and Ro 64-0802 by a HPLC/MS/MS analytical method.

Pharmacokinetic data analysis: Pharmacokinetic parameters were estimated by noncompartmental methods.

Following either once or twice daily administration, plasma levels of Ro 64-0796 at trough were generally below the limit of detection of the assay on all sampling days. Trough plasma concentrations of Ro 64-0802 (Mean \pm SD) on study Days 2, 4 and 5 are summarized in the table below.

	Plasma Concentration (ng/mL)			n
	Day 2	Day 4	Day 5	
100 mg o.d.	37 \pm 16	50 \pm 15	48 \pm 19	12
100 mg b.i.d.	144 \pm 56	191 \pm 78	173 \pm 70	12

The data show that plasma concentrations of the active species were similar on study Days 4 and 5 and approximately 30% higher than the levels observed on study day

2 in both groups. The data indicated that steady state was achieved by Day 4, but not by day 2.

Conclusion: The trough concentration of Ro 64-0796 and Ro 64-0802 in this study are similar to those in previous studies in adults.

Jenny H. Zheng, Ph.D.
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III, OCPB

Concurrence:

Kellie S. Reynolds, Pharm. D
Team Leader, Antiviral Drug Products Section
Division of Pharmaceutical Evaluation III, OCPB

cc: HFD-530 /NDA 21214
/MO/TWu
CSO/GCarmouze
HFD-880 /JHZheng
/TL/KReynolds

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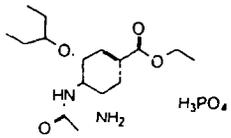
/s/

Jenny H. Zheng
12/15/00 02:05:22 PM
BIOPHARMACEUTICS

Kellie Reynolds
12/20/00 08:53:40 AM
BIOPHARMACEUTICS

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

REVIEWER NAME: Ita Yuen
 DIVISION NAME: Division of Antiviral Drug Products
 HFD#: 530
 REVIEW COMPLETION DATE: November 9, 2000
 ELECTRONIC FILE NUMBER: None
 NDA NUMBER: 21-087
 SERIAL #/DATE/TYPE OF SUBMISSION: 002/October 23, 2000/SE1-002/AP
 INFORMATION TO SPONSOR: Yes () No (X)
 SPONSOR (OR AGENT): Hoffmann-La Roche Inc.
 340 Kingsland Street
 Nutley, NJ 07110-1199
 MANUFACTURER OF DRUG SUBSTANCE: F. Hoffmann-La Roche Ltd.
 Grenzacherstrasse 124
 CH-4070 Basel, Switzerland
 DRUG:
Code Name: Free base: Ro 64-0796/000; GS-4104
 Phosphate salt: Ro 64-0796/002; GS-4104-02
Generic Name: Oseltamivir phosphate
Trade Name: Tamiflu®
Chemical Name: (3R,4R,5S)-4-(acetylamino)-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester, phosphate (1:1)
CAS Registry Number: 204255-11-8
Molecular Formula/Molecular Weight: C₁₆H₂₈N₂O₄ (free base)/M.W. = 312.41
 C₁₆H₂₈N₂O₄ 1:1 H₃PO₄ (phosphate salt)/410.408
Structure:



RELEVANT INDS/NDAS/DMFS: IND 53,093
 ..
 ..
 DRUG CLASS: Influenza viral neuraminidase inhibitor
 INDICATION: Prophylaxis of influenza
 CLINICAL FORMULATION: The drug product is being supplied as 75-mg (75 mg free base equivalent to 98.5 mg of the phosphate salt) gray/light yellow hard gelatin capsules. The excipients contain —, pre-gelatinized starch — Povidone K 30 —

Vol. 1, pp. 56-105).

3. Twenty-six week dermal oncogenicity study with Ro 64-0802/002 in Tg.AC hemizygous mice (FVB/N) (Draft report; Study # 6131-310; Lot # 00101B2438; GLP; Without QA report: Study dates 3/21/00-9/21/00; Vols. 1-3).

Study Reviews:

1. In vitro transformation of Syrian Hamster embryo (SHE) cells by 7-day exposure to Ro 64-0796/002 (Draft Report; Study # 21448-0-0485R; Lot # BS00020079). The neoplastic potential for the influenza neuraminidase inhibitor prodrug, Ro 64-0796, was assessed by its ability to induce a significant increase in the frequency of morphologically transformed colonies compared to vehicle control cultures in the SHE cell transformation system following a 7-day continuous exposure.

The assay was considered acceptable for evaluation if (1) an average of 25 to 45 colonies per dish were present per dose level; (2) total number of colonies per dose level should be at least 1000; (3) the positive control should induce a statistically significant increase in morphological transformation frequency compared to the concurrent vehicle control; (4) feeder cells must be present in stained dishes at all dose levels. One-sided Fisher's Exact Test was used to evaluate the results. The tested drug is considered positive if it caused a statistically significant increase in morphological transformation frequency for a least 2 dose levels compared to concurrent controls or if one dose showed statistical significant increase and the trend test was significant. The tested drug was considered negative if no statistically significant increase in morphological transformation was obtained and the highest dose caused a sufficient level of toxicity or the maximum applicable dose was achieved.

The results of 3 successful transformation assays are presented below:

Treatment	Total colonies scored ^a	Average colonies/dish ^b	# of MT ^c colonies	MT frequency ^d	Relative plating efficiency ^e	MT p value ^f
Ro 64-0796 – Trial 1						
100 µM	1265	32.4	8	0.632	82	0.1044
200 µM	1066	26.7	14	1.31	67	0.0014
300 µM	972	24.9	9	0.92	63	0.0227
400 µM	922	23.1	16	1.7	58	0.0001
600 µM	1035	25.9	2	0.19	43	0.5527
800 µM	1243	31.1	0	0	43	0.0979
1200 µM	951	23.8	5	0.526	24	0.2179
Culture medium	1579	39.5	4	0.253	100	-
B[a]P 2.5µg/ml	1739	43.5	15	0.863	110	0.0162
B[a]P 5.0µg/ml	1827	45.7	20	1.095	116	0.0023
Ro 64-0796 – Trial 2						
50 µM	1262	28.0	3	0.238	93	0.2838
300 µM	1166	25.9	9	0.772	51	0.0054
400 µM	1197	26.6	6	0.501	48	0.0435
500 µM	1210	26.9	5	0.413	45	0.0835
Culture medium	1364	30.3	1	0.07	100	-
B[a]P 2.5µg/ml	1592	35.4	12	0.754	117	0.0038
B[a]P 5.0µg/ml	1618	36.0	10	0.618	119	0.0122
Ro 64-0796 – Trial 3						
50 µM	1681	37.4	3	0.178	96	0.1023
100 µM	1586	35.2	5	0.315	90	0.0128
200 µM	1969	43.8	8	0.406	67	0.0017
300 µM	1829	40.6	3	0.16	57	0.1189
400 µM	1772	39.4	2	0.113	50	0.2614
500 µM	2079	46.2	3	0.17	50	0.1478
Culture medium	3518	39.1	1	0.02	100	-
DMSO (0.2%)	3846	43.7	2	0.05	112	-
B[a]P 2.5µg/ml	1546	35.1	7	0.4	131	0.0032
B[a]P 5.0µg/ml	1591	36.2	10	0.6	135	0.0002
a: Total colonies scored = total number of colonies from all dishes with the same drug concentration b: Average colonies per dish = Total colonies scored / total dishes c: MT = morphologically transformed d: MT frequency = total MT / total colonies scored * 100% e: Relative plating efficiency = Average plating efficiency / vehicle plating efficiency * 100% f: MT p value = probability of treatment-related effect using a one-tailed Fisher's exact test to compare to vehicle control group						

The results from all three trials indicated that the prodrug, Ro 64-0796, was positive for its ability to cause an increase in the number of morphologically transformed (MT) SHE cells as compared to the vehicle control. In 2 of the trials, the concentrations where a statistically significant increase in MT colonies were seen, were identical, i.e. 300 and 400 µM, while in one trial, a positive result occurred at concentrations of 100 and 200 µM. Despite of the differences, it's clear that prodrug is considered positive in this genotoxicity assay. This finding has ramifications for the pediatric population and patients with liver impairment. Toxicology studies in juvenile rats and in vitro studies using perfused liver and liver preparation from marmosets of various ages indicated that conversion of Ro 64-0796 to the active drug is about 7-10 fold slower in the juvenile animals than adults. It is not known if this hydrolysis process is also much slower in human neonates and infants resulting in higher exposure to the prodrug in that patient

population.

2. In vitro transformation of Syrian Hamster embryo (SHE) cells by 7-day exposure to Ro 64-0801/002 (Draft Report; Study # 21449-0-0485R; Lot # 00101B2438). The ability of the influenza neuraminidase inhibitor, Ro 64-0801, to induce an increased number of morphological transformed colonies were tested in the SHE cell assay. The methodology and criteria for positive or negative results were the same as described above. The results of 2 successful trials are presented in the following table:

Treatment	Total colonies scored ^a	Average colonies/dish ^b	# of MT ^c colonies	MT frequency ^d	Relative plating efficiency ^e	MT p value ^f
Ro 64-0801 - Trial 1						
200 µM	1069	24.3	1	0.094	83	0.5684
300 µM	1104	24.5	5	0.153	84	0.1691
500 µM	932	20.7	2	0.215	71	0.5601
700 µM	1163	25.8	6	0.516	62	0.1141
900 µM	897	20.4	5	0.557	45	0.1072
1100 µM	1008	22.4	2	0.198	42	0.5923
1300 µM	1209	26.9	3	0.248	40	0.4718
1500 µM	1098	24.4	6	0.546	33	0.0988
Culture medium	1284	29.2	2	0.156	100	-
B[a]P 2.5µg/ml	1813	40.3	8	0.141	138	0.1445
B[a]P 5.0µg/ml	1571	38.5	14	0.891	131	0.0065
Ro 64-0801 - Trial 2						
100 µM	1624	36.1	1	0.062	95	0.5320
200 µM	1504	33.4	0	0.000	87	0.7005
300 µM	1388	30.8	2	0.144	81	0.1948
500 µM	1639	37.5	2	0.122	58	0.2388
700 µM	1834	40.8	0	0.000	53	0.6573
800 µM	1815	42.2	4	0.220	50	0.0487
900 µM	1876	41.7	2	0.107	44	0.2787
1000 µM	1933	43.0	0	0.000	39	0.6454
Culture medium	3518	39.1	1	0.028	100	-
DMSO (0.2%)	3846	45.7	2	0.052	112	-
B[a]P 2.5µg/ml	1546	35.1	7	0.153	131	0.0032
B[a]P 5.0µg/ml	1591	36.2	10	0.629	135	0.0002
a: Total colonies scored = total number of colonies from all dishes with the same drug concentration b: Average colonies per dish = Total colonies scored / total dishes c: MT = morphologically transformed d: MT frequency = total MT / total colonies scored * 100% e: Relative plating efficiency = Average plating efficiency / vehicle plating efficiency * 100% f: MT p value = probability of treatment-related effect using a one-tailed Fisher's exact test to compare to vehicle control group						

Based on the criteria set for this assay, the active drug Ro 64-0801 is not considered positive for its ability to induce an increase in the number of morphologically transformed SHE cell colonies.

3. Twenty-six week dermal oncogenicity study with Ro 64-0802/002 in Tg.AC hemizygous mice (FVB/N) (Draft report; Study # 6131-310; Lot # 001 01B 2438 01). The oncogenic potential of the influenza neuraminidase inhibitor, Ro 64-0801, was studied in Tg.AC

hemizygous mice. The active metabolite rather than the prodrug was used in this carcinogenicity assay. Since the studied drug is applied to the skin of the transgenic mice, it is expected that very small amount of esterases will be present in the skin to convert the prodrug, Ro 64-0796, to active metabolite, Ro 64-0801. It was decided that, since the exposure to prodrug is less than 5% in the systemic circulation, it was more relevant to test the active metabolite, Ro 64-0801 in the Tg.AC assay. The vehicle (negative) control was 75% ethanol. The drug was applied topically to the dorsal skin of the animals twice daily, approximately 6 hours apart for 26 weeks. The dosing volume was 6.5 ml/kg with a maximum volume of 200 μ l/application. The highest dose represents the maximum feasible dose based on the highest solubility of Ro 64-0801 in 75% ethanol (60 mg/ml). The positive control used was 2.5 μ g tetradecanoyl phorbol-13-acetate (TPA) which was applied 3 times/week. Histopathological evaluation was performed for skin and any gross lesions.

Species/Strain: Tg.AC hemizygous mice of strain [FVB/NTaC-TgN(v-Ha-ras)] and background strain FVB/Ntac													
Route: dermal			Vehicle: 75% ethanol (v/v)			Age at initiation: 7 weeks old			Duration of Dosing: 26 weeks				
Dosing frequency: Twice daily 6 hours apart for vehicle and drug treatment groups; 3 times/wk for positive control													
Dose Volume: 6.5 ml/kg/dose not to exceed 200 μ l/application for vehicle and drug treatment group; 200 μ l for positive control								Positive control: 2.5 μ g of tetradecanoyl phorbol 13-acetate (TPA)					
Data collected		Frequency/Occasion					Data collected		Frequency/Occasion				
Moribundity/mortality		Twice daily					Gross pathology		Termination at week 26: premature deaths				
Clinical observation		Daily					Histopathology		Termination at week 27: skin and macroscopic lesions				
Physical exam		Weekly; include time of onset, location, size & appearance of visible or palpable masses					Toxicokinetics		Background strain used; 3 mice/sex/time point on day 28 at 0.5, 1, 2, 4, 6 (prior to 2 nd daily dose), 9, 12, & 24 hours post 1 st dose; each mouse was bled twice				
Body weight		Weekly											
Food consumption		Weekly											
Dermal irritation		Pretreatment & weekly after											
Important findings at week 26													
Sex		Males					Females						
Daily Dosage (mg/kg)		0	40	140	400	780	TPA	0	40	140	400	780	TPA
Number of animals:													
Main study		15	15	15	15	15	15	15	15	15	15	15	15
Toxicokinetic ^a		12	12	12	12	12	12	12	12	12	12	12	12
Premature deaths:													
Main study- # of deaths		8	7	5	2	3	6	3	2	3	5	2	4
% mortality		53	47	33	13	20	40	20	13	20	33	13	27
Visible/palpable masses:													
Number mice affected		1	1	0	0	2	15	1	0	0	1	0	12
Multiplicity		0.07	0.07	0	0	0.13	13.1	0.07	0	0	0.07	0	10.5

Species/Strain: Tg.AC hemizygous mice of strain [FVB/N ^{Tac} -TgN(v-Ha-ras)] and background strain FVB/N ^{Tac}													
Route: dermal	Vehicle: 75% ethanol (v/v)			Age at initiation: 7 weeks old			Duration of Dosing: 26 weeks						
Dosing frequency: Twice daily 6 hours apart for vehicle and drug treatment groups; 3 times/wk for positive control													
Dose Volume: 6.5 ml/kg/dose not to exceed 200 µl/application for vehicle and drug treatment group; 200 µl for positive control							Positive control: 2.5 µg of tetra-decanoyl phorbol 13-acetate (TPA)						
Data collected	Frequency/Occasion					Data collected	Frequency/Occasion						
Morbidity/mortality	Twice daily					Gross pathology	Termination at week 26: premature deaths						
Clinical observation	Daily					Organ weights	Termination at week 26						
Physical exam	Weekly; include time of onset, location, size & appearance of visible or palpable masses					Histopathology	Termination at week 27						
Body weight	Weekly					Toxicokinetics	Background strain used: 3 mice/sex/time point on day 28 at						
Food consumption	Weekly						0, 5, 1, 2, 4, 6 (prior to 2 nd daily dose), 9, 12, & 24 hours post dosing; each mice bled twice						
Important findings at Week 16													
Sex	Males						Females						
Daily Dosage (mg/kg)	0	40	140	400	780	TPA	0	40	140	400	780	TPA	
Number of animals:													
Main study	15	15	15	15	15	15	15	15	15	15	15	15	
Toxicokinetic [#]	12	12	12	12	12	12	12	12	12	12	12	12	
Premature deaths:													
Main study- # of deaths	4	0	5	0	1	1	2	1	2	4	2	3	
% mortality	27	0	33	0	7	7	13	7	13	27	13	20	
Visible/palpable masses:													
Number mice affected	1	0	0	1	3	15	1	0	1	2	1	12	
Average # of masses per affected mouse	1	0	0	1	1	>15	1	0	1	1	1	>8	

The cause of deaths cannot be determined from the necropsy findings. Many deaths were not associated with any necropsy findings. In males, distended fluid-filled urinary bladder was commonly seen in animals that died prematurely, while in females, enlarged liver and spleen were the common findings. In a female treated with 400 mg/kg/day Ro 64-802, a skin mass (probably papilloma) was detected a week before premature death. However, this mass was not reported in the gross pathology observations and presumably resolved at the time of death. Many papillomas were detected in all but 3 females treated with the positive control material, TPA. Papillomas were also detected in control and treated animals. Only a single mass was

seen per affected mice in the treatment groups while multiple masses were observed per affected mice in the positive control group.

CONCLUSION AND EVALUATION:

The present submission contains a draft final report for the short-term alternative carcinogenicity assay using the Tg.AC transgenic mouse model. The sponsor agreed to provide the Division with monthly updates starting on 4 months into the treatment on the number of papillomas and other palpable masses in all treatment groups. The results indicate that the 26-week carcinogenicity study was negative, and according to the results, oseltamivir has low carcinogenic potential. Some of the masses detected at 16 weeks were transient, i.e., not observable or palpable by 26 weeks of treatment. On the other hand, all but 3 mice treated with positive control, TPA, had at least 8 papillomas or palpable masses per affected animal by 16 weeks.

The results of the studies reviewed here will be placed into the label.

Assuming that the final audited reports will bear out the conclusions reached in the review of the above studies, there is no reason to preclude that the NDA is not approvable. The sponsor will be required to complete the 2-year ongoing carcinogenicity studies of oseltamivir in mice and rats and report the findings to the Division in a timely manner as a Phase 4 commitment.

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Jita Yuen, Ph.D.
Reviewing Pharmacologist

Concurrences:

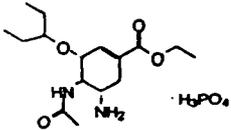
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cc:

HFD-530/NDA 21,087 (SE1.002)
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HFD-345
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HFD-530/NBattula
HFD-530/DBoring
HFD-530/PRajagopalan
HFD-530/Hammerstrom

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

REVIEWER NAME: Ita Yuen
 DIVISION NAME: Division of Antiviral Drug Products
 HFD#: 530
 REVIEW COMPLETION DATE: September 5, 2000
 ELECTRONIC FILE NUMBER: None
 NDA NUMBER: 21-087
 SERIAL #/DATE/TYPE OF SUBMISSION: 002/August 8, 2000/SE1
 INFORMATION TO SPONSOR: Yes () No (X)
 SPONSOR (OR AGENT): Hoffmann-La Roche Inc.
 340 Kingsland Street
 Nutley, NJ 07110-1199
 MANUFACTURER OF DRUG SUBSTANCE: F. Hoffmann-La Roche Ltd.
 Grenzacherstrasse 124
 CH-4070 Basel, Switzerland
 DRUG:
Code Name: Free base: Ro 64-0796/000; GS-4104
 Phosphate salt: Ro 64-0796/002; GS-4104-02
Generic Name: Oseltamivir phosphate
Trade Name: Tamiflu®
Chemical Name: (3R,4R,5S)-4-(acetylamino)-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester, phosphate (1:1)
CAS Registry Number: 204255-11-8
Molecular Formula/Molecular Weight: C₁₆H₂₈N₂O₄ (free base)/M.W. = 312.41
 C₁₆H₂₈N₂O₄ 1:1 H₃PO₄ (phosphate salt)/410.408
Structure:



RELEVANT INDS/NDAS/DMFS: IND 53,093
 DMF Type I #
 DMF Type III _____
 DMF Type IV

DRUG CLASS: Influenza viral neuraminidase inhibitor
 INDICATION: Prophylaxis of influenza
 CLINICAL FORMULATION: The drug product is being supplied as 75-mg (75 mg free base equivalent to 98.5 mg of the phosphate salt) gray/light yellow hard gelatin capsules. The excipients contain: _____ pre-gelatinized starch, _____ Povidone K 30 _____

croscarmellose sodium — Talc, —
sodium stearyl fumarate.

ROUTE OF ADMINISTRATION: Oral

PROPOSED CLINICAL USE: Prevention of influenza infection

DISCLAIMER: Some material may be taken directly from sponsor's submission

INTRODUCTION AND DRUG HISTORY:

Ro 64-0796 is an oral ethyl ester prodrug of an anti-influenza agent Ro 64-0802, which has poor bioavailability via the oral route of administration. Ro 64-0802 binds specifically to the active site of the neuraminidase enzyme on the surface of the influenza virus. The prodrug, also known as Tamiflu[®], was approved for marketing for the treatment of influenza infection on 10/27/99. The approved oral dosage is 75 mg twice daily for 5 days. At the time of original NDA submission, the sponsor also wanted to seek the marketing approval for the prophylaxis indication. However, because of a lack of long-term safety data, specifically, carcinogenic assessment studies in rats and mice, the indication in the original NDA was limited to the treatment claim. A 2-year rat carcinogenicity study was initiated in November, 1998 and a 2-year mouse carcinogenicity study was started in June 1999. Since the sponsor planned to submit a supplemental NDA for the prophylaxis indication in April, 2000, results from either carcinogenicity study would not be available for review prior to the decision date. The Division has worked with the sponsor to decide on an alternative plan to address the carcinogenic potential of Tamiflu. It was agreed that the sponsor could use a short-term (6 month) TG.AC transgenic mice carcinogenicity assay to assess the carcinogenic potential of Tamiflu in addition to the 2 two-year carcinogenicity studies in rats and mice. If the study results are submitted within the NDA review period and are negative, the Division would be willing to consider market approvability while waiting for the results from the 2-year carcinogenicity studies. However, the sponsor was asked to send monthly interim data starting at 16 weeks of dosing. The present submission contains an unaudited report containing 16 week data from the TG.AC transgenic mouse carcinogenicity study.

NONCLINICAL TOXICOLOGY STUDY REVIEW:

1. 16-week interim report: Twenty-six week dermal oncogenicity study with Ro 64-0802/002 in Tg.AC hemizygous mice (FVB/N) (Study # 6131-310;

Species/Strain: Tg.AC hemizygous mice of strain [FVB/NTaC-TgN(v-Ha-ras)] and background strain FVB/NTac													
Route: dermal		Vehicle: 75% ethanol (v/v)			Age at initiation: 7 weeks old			Duration of Dosing: 26 weeks					
Dosing frequency: Twice daily 6 hours apart for vehicle and drug treatment groups; 3 times/wk for positive control													
Dose Volume: 6.5 ml/kg/dose not to exceed 200 µl/application for vehicle and								Positive control: 2.5 µg of tetra-decanoyl phorbol 13-acetate (TPA)					
Dose Volume: 200 µl for positive control													
Data collected		Frequency/Occasion				Data collected		Frequency/Occasion					
Moribundity/mortality		Twice daily				Gross pathology		Termination at week 26; premature deaths					
Clinical observation		Daily				Organ weights		Termination at week 26					
Physical exam		Weekly; include time of onset, location, size & appearance of visible or palpable masses				Histopathology		Termination at week 27					
Body weight		Weekly				Toxicokinetics		Background strain used; 3 mice/sex/time point on day 28 at 0.5, 1, 2, 4, 6 (prior to 2 nd daily dose), 9, 12, & 24 hours post dosing; each mice bled twice					
Food consumption		Weekly											
Important findings at Week 16													
Sex		Males					Females						
Daily Dosage (mg/kg)		0	40	140	400	780	TPA	0	40	140	400	780	TPA
Number of animals:													
Main study		15	15	15	15	15	15	15	15	15	15	15	15
Toxicokinetic ^a		12	12	12	12	12	12	12	12	12	12	12	12
Premature deaths:													
Main study- # of deaths		4	0	5	0	1	1	2	1	2	4	2	3
% mortality		27	0	33	0	7	7	13	7	13	27	13	20
Visible/palpable masses:													
Number mice affected		1	0	0	1	3	15	1	0	1	2	1	12
Average # of masses/mouse		1	0	0	1	1	>15	1	0	1	1	1	>8

The cause of deaths cannot be determined from the necropsy findings. Many deaths were not associated with any necropsy findings. In males, distended/fluid-filled urinary bladder was commonly seen in animals that died prematurely, while in females, enlarged liver and spleen were the common findings. In a female treated with 400 mg/kg/day Ro 64-802, a skin mass (probably papilloma) was detected a week before premature death. However, this mass was not reported in the gross pathology observations and presumably resolved at the time of death. Many papillomas were detected in all but 3 females treated with the positive control material, TPA. It was also detected in control and treated animals. Only a single mass was seen per affected mice, however, more animals were affected in the higher dose groups. Many of the masses became undetectable by week 16. Thus, the significance of dose-relationship is unclear and awaits the full report at the end of the treatment period.

CONCLUSION AND EVALUATION:

The present submission contains an interim report for the short-term alternative carcinogenicity assay using the Tg.AC transgenic mouse model. The sponsor has agreed to provide the Division with monthly updates starting on 4 months into the treatment on the number of papillomas and other palpable masses in all treatment groups. The results so far indicate that oseltamivir has low carcinogenic potential. Although, slightly more mice were affected at the high dose groups, only one mass/mice was detected. Many of the masses were transient, i.e., not observable or palpable by 16 weeks of treatment. On the other hand, all but 3 mice treated with positive control, TPA, have at least 8 papillomas or palpable masses by 16 weeks. Thus, it is

reassuring so far that study is working as expected. Whether oseltamivir is carcinogenic or not awaits the final analysis at the end of 6 month treatment.

There are no regulatory action associated with this submission.

/S/

Ita^WYueh, Ph.D.
Reviewing Pharmacologist

Concurrences:

HFD-530/WDempsey ¹⁵¹ .. /00
HFD-530/JFarrelli ¹⁵¹ .. /00
V

cc:

HFD-530/NDA 21,087 (SE1.002)
HFD-530/Division File
HFD-530/GCarmouze
HFD-345
HFD-530/TWu
HFD-530/NBattula
HFD-530/DBoring
HFD-530/PRajagopalan
HFD-530/THammerstrom

Medical Officer Review
Of
NDA 21-087 Supplement (SE1-002)
Tamiflu™ (oseltamivir)
For
Prophylaxis of Influenza

Date Submitted: 05/22/00
Date Completed: 11/06/00
Reviewer: Teresa C. Wu, M.D., Ph.D.

Applicant: Hoffmann-La Roche Inc.
340 Kingland Street
Nutley, New Jersey 07110-1199

Product Names: Code: Ro 64-0796
Generic: oseltamivir phosphate
Trade: Tamiflu™

Formulation/Dosage: Capsule, 75-mg strength
Treatment: 75 mg twice daily for 5 days
Prophylaxis: 75 mg daily for at least 7 days to 6 weeks

Approved Indication: Treatment of uncomplicated influenza in adults

NDA Drug Classification: 1P

Related NDA: NDA 21-264, Tamiflu Oral Suspension for Treatment of Influenza in Pediatric Patients, FDA review ongoing.

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Executive Summary

I. Recommendations

A. Recommendation:

The applicant has demonstrated the effectiveness and safety of oseltamivir (Tamiflu™) for the prevention of influenza infection. From a clinical perspective, oseltamivir is recommended be approved for the prophylaxis of influenza A and B in adolescents and adults.

B. Phase 4 Commitments:

- The applicant is recommended to investigate the effectiveness and safety of oseltamivir for the treatment and prevention of influenza infection in immunocompromised patients. The applicant should closely monitor the emergence of resistant virus in this population.
- The applicant is recommended to study the pharmacokinetics and safety of oseltamivir, given at the proposed dosing regimens based on simulations, in end-stage renal dialysis subjects.
- The applicant should submit a final study report for the completed study of oseltamivir in subjects with impaired hepatic function.
- The applicant should submit a final study report for the completed long-term carcinogenicity studies in mice and rats.
- The applicant is requested to explore the isolation, characterization and clinical implications of oseltamivir-dependent influenza virus variants.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Oseltamivir is a neuraminidase inhibitor with activity against both influenza A and B viruses. It was approved for marketing in 1999 for treatment of uncomplicated influenza infection in adults. The approved treatment dosing regimen is 75 mg bid for 5 days. The applicant submitted this supplement seeking a new indication of oseltamivir given at 75 mg once daily for the prevention of influenza illness in subjects of ≥ 13 years of age.

The initial seasonal prophylaxis studies (WV15673 and WV15679), conducted during the season of 1997/98, were randomized, double blind, parallel group and placebo-controlled trials in healthy unvaccinated adults. A total of 1562 subjects were enrolled, of whom 1559 subjects received the study medication, i.e. 519 received placebo for 6 weeks and

two groups of 520 each received Tamiflu 75 mg once or twice a day for 6 weeks. At any time during the 6-week period that a subject became ill with symptoms of influenza, he/she attended the investigative site in order for symptoms to be assessed and for a nose/throat swab to be taken. All subjects had blood samples for determination of influenza virus antibody at baseline and at the end of the study.

In 1998 and 1999, two seasonal prophylaxis studies were conducted in elderly nursing home residents, one in Southern hemisphere (WV15708) and the other in Northern hemisphere countries (WV15825). Study WV15708 enrolled 385 subjects, of whom 372 subjects took study medication; Study WV15825 enrolled 572 subjects, of whom 548 subjects took study medication. The study designs for both studies were very similar to that of WV15673 and WV15679 with the exception that subjects were randomized according to two strata: vaccination status and presence or absence of chronic obstructive airway disease (COAD) at baseline. In both studies, approximately 80% of subjects had received influenza vaccination prior to receiving study medication.

In addition to the 6-week seasonal studies, a single short-term post exposure prevention study (WV15799) was conducted in Europe and North American during the 1998/99 influenza season. Study WV15799 was a multi-center, household-randomized, double blind, placebo-controlled study. Eligible subjects were contacts of an index case with a clinically diagnosed respiratory illness. The index case could be any individual, one year or older, and the contacts were adults and adolescents of 13 years and older. The study enrolled 962 subjects who were contacts of a total of 377 index cases. The index case did not receive any active treatment. Contacts were treated, within 2 days of onset of symptoms in the index case, with oseltamivir 75 mg or placebo once daily for 7 days. All members of a cluster received the same treatment. The study enrolled both vaccinated and unvaccinated individuals, although a higher proportion of healthy unvaccinated adults were recruited than that of vaccinated individuals.

The primary efficacy endpoint for the above studies was the incidence of laboratory-confirmed clinical influenza during the period of drug administration. Laboratory confirmation was defined as a positive culture of influenza virus within two days after the onset of influenza symptoms, or an antibody titer on hemagglutination-inhibition testing (HAI) or complement-fixation testing (CF) that was at least four times as high as the baseline titer, or both. Influenza symptoms included an oral temperature of 37.2° C or higher, at least one respiratory symptom (cough, sore throat, or nasal congestion) and at least one constitutional symptoms (aches, fatigue, headache, or chills or sweats) occurring on the same day.

For efficacy, an intent-to-treat (ITT) analysis was used for the seasonal prophylaxis studies, i.e. all subjects who were randomly assigned to a study group and who took at least one dose of the assigned study medication. The population used for the primary analysis for the post-exposure prophylaxis study was the Intent-to-Treat Index Infected Negative at Baseline (ITTINAB) population. The ITTINAB population included all contacts who had a negative influenza virus culture at baseline (day1), who received at

least one dose of study medication and in whom the index case was confirmed to be influenza infected.

A total of 3529 subjects were included in the safety evaluation, of whom 2063 took oseltamivir. The majority of subjects were from the clinical trials described above and a small number of subjects were from the 2 experimental challenge trials (GS97-802 and NP15757). The safety population was an intent-to-treat population which included all subjects who were randomized, who received at least one dose of study medication and for whom post-baseline safety data were available.

B. Efficacy

The number of laboratory confirmed clinical influenza cases observed in the placebo groups of studies WV15673 and WV15697 was lower than that might have been expected in many influenza seasons recorded in the literature, indicating that both studies were conducted during an outbreak of relatively low attack rate. Because of the low incidence of events, these two studies were pooled for the efficacy analysis. Both the once daily and twice daily doses of oseltamivir significantly reduced the incidence of laboratory confirmed clinical influenza from 25/519 (4.8%) in the placebo group to 6/520 (1.2%) in the oseltamivir once daily group ($p=0.00055$) and 7/520 (1.3%) in the twice daily oseltamivir group ($p=0.0013$). Both studies were not intended formally to compare the two dosage regimens of oseltamivir with either other. However, inspection of the results suggested that there was no difference between oseltamivir 75 mg qd and oseltamivir 75 mg bid in terms of efficacy.

Although there were 2 nursing home prophylaxis studies conducted, only study WV15825 was included in the applicant's efficacy analysis because study WV15708 had too few ($n=2$) cases of laboratory confirmed clinical influenza. Study WV15825 showed that 4.4% of the placebo patients (12/272) and 0.4% of oseltamivir patients (1/276) had laboratory confirmed clinical influenza. The reduction in the oseltamivir group is statistically significant ($p=0.0015$).

In the post-exposure prophylaxis study (WV15799) the proportion of contacts in the ITTINAB population with laboratory confirmed influenza infection was statistically significantly lower in the oseltamivir group than in the placebo group; 12% (24/200) in the placebo group compared with 1% (2/205) in the oseltamivir group ($p=0.000076$).

In study WV15799 sufficient contacts in the ITT population were exposed to influenza B. The number of subjects in the ITT population with laboratory confirmed clinical influenza B was statistically significantly lower in the oseltamivir group compared to the placebo group ($p=0.01$). This is the first clinical trial that has demonstrated the effectiveness of oseltamivir in the prevention of influenza B.

C. Safety

The adverse event profile of oseltamivir when used for influenza prophylaxis was generally similar to that seen in influenza treatment. The reported incidences of headache, nausea and vomiting were increased by oseltamivir administration and there was a trend towards higher incidences in the twice daily dosage of oseltamivir. The overall frequency of these events, with the exception of headache, was lower than in the treatment studies.

The reporting frequency of headache differed between the treatment and prophylaxis studies. Headache was approximately 10-fold more frequent in the prophylaxis studies, regardless of study medication, but the incidence was also higher in the oseltamivir group than in the placebo group (29% and 25%, respectively). In the 7-day post-exposure prophylaxis study, the incidence of headache was similar to that seen in the 5-day treatment studies (2.4% and 1.8 %, respectively), which suggested that the overall increase in reports of headache was probably a result of a longer study period.

Hyperglycemia and aggravation of pre-existing diabetes mellitus were reported in a small number of subjects (n=8) in the seasonal prophylaxis studies, all but one were oseltamivir treated subjects. These subjects were predominantly elderly subjects with a history of diabetes mellitus.

Adverse events for Tamiflu that were reported to the Agency's Adverse Event Reporting System (AERS) since the approval of the drug up through April 2000 have provided additional safety information. During the 1999-2000 winter season, a total of 5 patients with influenza-like symptoms, receiving Tamiflu treatment, were found to have developed septicemia (group A streptococcus, *Staphylococcus aureus*, *Streptococcus milleri*, *Streptococcus pneumoniae*, *Neisseria meningitidis*). Four of these patients died of sepsis. The temporal sequence of these cases suggested that the original influenza-like symptoms could have been the prodrome of a bacteremic illness in some and secondary bacterial infections in others. Because of these and similar cases reported for another approved neuraminidase inhibitor, Relenza, the Agency issued a Public Health Advisory on January 12, 2000 to alert the public to consider the possibility of bacterial infections in patients with influenza-like illnesses.

Also presented in the AERS, reports of arrhythmia, rash, angioedema, seizure, confusion and aggravation of diabetes were noted. Because they were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Because of their seriousness, frequency of reporting or potential association with the use of Tamiflu, the Division has recommended these events be described in the package insert of Tamiflu.

D. Special Populations

The efficacy of oseltamivir were explored by analyzing the primary efficacy parameter for several subgroups with respect to gender and age in both the long and short-term prophylaxis studies. In most subgroups oseltamivir 75 mg qd statistically significantly reduced the incidence of laboratory confirmed clinical influenza compared to the corresponding placebo group. In the male subgroup of the pooled seasonal prophylaxis

studies and in the adolescent subgroup (12-17 years) of the post-exposure prophylaxis study, there was a numerical but not statistically significant reduction in the incidence of laboratory confirmed clinical influenza in the oseltamivir treated subjects in both subgroups owing to insufficient sample sizes.

In both the seasonal prophylaxis studies and the post-exposure prophylaxis study, the increase in reports of nausea by oseltamivir recipients compared with placebo recipients was greater for female than for male subjects. Headache was also reported more frequently by women. The post-exposure prophylaxis study enrolled the highest number of adolescents aged 12 to 17. The pattern of adverse experiences in the adolescent subgroup was the same as that of adults aged at least 18 years, although the number of subjects reporting any adverse events in the adolescent group was small.

Since oseltamivir is eliminated primarily by renal excretion of the active metabolite (Ro64-0802) and reduced renal clearance causes increased exposure to the compound, the reporting frequency of adverse events was assessed according to estimated creatinine clearance in the pooled seasonal prophylaxis studies. There was no clear exposure-related difference in the incidence of nausea or headache. However, there was an increase in the incidence of vomiting in subjects with the most impaired renal function (<30 mL/min creatinine clearance). This observation was again seen in 2 open-label pharmacokinetic studies: study WP15648 in subjects with renal impairment and study PP15974 in subjects undergoing dialysis.

E. Emergence of Resistant Virus

The number of subjects shedding virus, while receiving oseltamivir, at sufficient level to allow for phenotypic assay of the neuraminidase was small in all prophylaxis studies. There were 5, 2, and 2 such individuals in study WV15799, WV15673 + WV15697, and WV15825, respectively. All neuraminidase samples from these patients had IC₅₀ values for inhibition by Ro 64-0802 consistent with wild type N2 neuraminidase. Because the number of samples was small, no conclusion can be made on the emergence of resistant virus from the prophylaxis studies of oseltamivir.

Clinical Review

I. Introduction and Background

Epidemics of influenza occur during the winter months nearly every year and are responsible for an average of approximately 20,000 deaths per year in the U.S. The principle means of preventing influenza, as has been recommended by the Advisory Committee on Immunization Practices (ACIP), is immunoprophylaxis with inactivated vaccine. The role of chemoprophylaxis with antiviral agents, according to a report issued by ACIP on April 14, 2000, is considered to be "an important adjunct to influenza vaccine for the control and prevention of influenza. However, they are not a substitute for vaccination."

Antiviral agents approved for influenza chemoprophylaxis have included amantadine and rimantadine. Amantadine (Symmetrel, Endo Labs) and Rimantadine (Flumadine, Forest) are chemically related antiviral drugs with activity against influenza A viruses but not influenza B viruses. Amantadine was initially approved in 1966 for prophylaxis of influenza A (H2N2) infection and was subsequently approved in 1976 for the treatment and prophylaxis of influenza A virus infections in adults and children aged ≥ 1 year. The original approval of amantadine for prophylaxis was based on the effectiveness of amantadine demonstrated in the experimental challenge studies, although the drug was ineffective in a field trial in adult prisoners. This regulatory approval, although based on a sub-optimal data package, was primarily a clinical judgement at a time when there was no alternative drug available for the prevention of influenza. Rimantadine was approved in 1993 for treatment and prophylaxis of influenza infection in adults, but was approved only for prophylaxis of infection in children aged ≥ 1 year. The approval of rimantadine was based on the results of 4 double-blind, either active- or placebo-controlled trials in which rimantadine for prophylaxis against influenza A demonstrated superior efficacy when compared to placebo and equivalent efficacy, with less toxicity, when compared to amantadine.

Zanamivir and oseltamivir are neuraminidase inhibitors with activity against both influenza A and B viruses. Both zanamivir and oseltamivir were approved by the Agency in 1999 for the treatment of uncomplicated influenza infections. Worldwide oseltamivir has been approved for the treatment indication in Switzerland, Canada, New Zealand, Brazil, Argentina, Mexico, and Peru. Given the considerations of the potential severe consequences of an influenza infection, the expanded antiviral activity of oseltamivir against both influenza A and B viruses, the favorable toxicity profile of oseltamivir, and potential advantages with regard to the emergence of virus resistance, this supplement was granted a priority review.

II. Clinically Relevant Findings from Other Review Disciplines

The lack of animal carcinogenicity assessment studies in this supplement has been deemed a major deficiency at the outset of this submission. The 2-year rat and mouse carcinogenicity studies were both initiated less than 2 years ago; thus, these data would not be available within the review timeframe. Prior to this submission, the division has worked with the applicant on an alternative plan to address the carcinogenic potential of oseltamivir. It was agreed that, for regulatory purposes, the applicant could use a short-term (6 months) TG.AC transgenic mouse carcinogenicity assay to preliminarily address the carcinogenic potential of oseltamivir while awaiting the completion of the two 2-year animal studies. It was also agreed that, starting at week 16 of dosing, the applicant would submit monthly interim data from the TG.AC transgenic mouse carcinogenicity study. Based on the first interim report dated 8/2/00, Dr. Ita Yuen, the Pharmacology Reviewer, concluded that oseltamivir had a low carcinogenic potential which is yet to be confirmed by the final report after the completion of the 6-month dosing. For details, please refer to Dr. Yuen's review dated 9/12/00.

III. Human Pharmacokinetics and Pharmacodynamics

For details, please refer to Dr. Jenny Zheng's review.

IV. Review Methods

A. Clinical Review

This review began with individual case verification according to the specified primary efficacy criteria. A list of 256 cases was generated based on either a positive virus culture or 4-fold increase in serology titers from baseline. Individual case review was conducted with the aid of Case Report Tabulations (CRTs) provided in electronic format. When necessary, original Case Report Forms (CRFs) were reviewed for further confirmation.

The above review process has confirmed that the applicant's identification of each of the laboratory confirmed clinical influenza cases was justified and the applicant's enumeration in the efficacy analysis was accurate.

B. Clinical Inspection

Three sites were selected for inspection. They were: H. Schwartz, M.D., Miami, FL, W. Harper, M.D., Raleigh, NC, and F. Hayden, M.D., Charlottesville, VA. Dr. El-Hage, Division of Scientific Investigations, concluded that no objectionable conditions were found which would preclude use of the data submitted in support of this application (11/14/00 memo).

V. Description of Data Source

The primary data source consisted of 7 placebo-controlled clinical studies. The secondary data source consisted of 2 human experimental challenge studies. The following table provides outlines for these studies:

Table 1: Data Source

Study	Description	Age (yr.)	Duration	Region	Period of study	# pts randomized
Primary Data Source						
WV15673 WV15697	Community prophylaxis	18-65	42 days	U.S.	Jan to Apr 1998	1562
WV15825 WV15708	Nursing home prophylaxis	≥ 65	42 days	N.Hemisphere S.Hemisphere	Jan to Apr 1999 July to Oct 1998	385 572
WV 15799	Family Transmission prophylaxis	≥ 13	7 days	U.S. and non U.S.	Dec to March 1999	962
Secondary Data Source						
GS97-802	Challenge study (Type A)	18-40	5 days	U.S.	May to Jun 1997	37
NP15757	Challenge study (type B)	18-65	7 days	U.S.	May to July, 1998	59

In addition, adverse events for Tamiflu that were reported to the agency's Adverse Event Reporting System (AERS) since the approval of the drug up through April 2000 were reviewed.

VI. Review of Efficacy

A. Study WV15673 and Study WV15697

I. Design

Both studies were multi-center, randomized, double blind, parallel group and placebo-controlled trials conducted during the season of 1997/98. Study WV15673 was carried out in three centers in Virginia, and study WV15697 was carried out in two centers in Texas and one in Kansas City.

All subjects were healthy adult volunteers and were identified before the start of influenza season. The eligible subjects were requested to return to the clinic when the principal investigators decided that influenza was present in the community, on the basis of local surveillance information. On the day of this return visit (day 1), subjects were assigned to treatment according to the randomization schedule and treatment was continued for 6 weeks. All subjects were to return to the clinic at week 3, week 6 and week 8. In addition, the subjects were instructed to return to the clinic for evaluation if they developed fever and symptoms of influenza.

The primary efficacy parameter was the incidence of laboratory confirmed clinical influenza. Laboratory confirmed clinical influenza was defined as: oral temperature $\geq 99.0^{\circ}$ F/ 37.2° C plus at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one constitutional system (aches and pain, fatigue, headache, chills/sweats), all recorded within 24 hours, plus laboratory confirmation of influenza infection. Laboratory confirmation was defined as a positive culture of influenza virus within two days after the onset of influenza symptoms, or an antibody titer on

hemagglutination-inhibition testing (HAI) or complement-fixation testing (CF) that was at least four times as high as the baseline titer, or both.

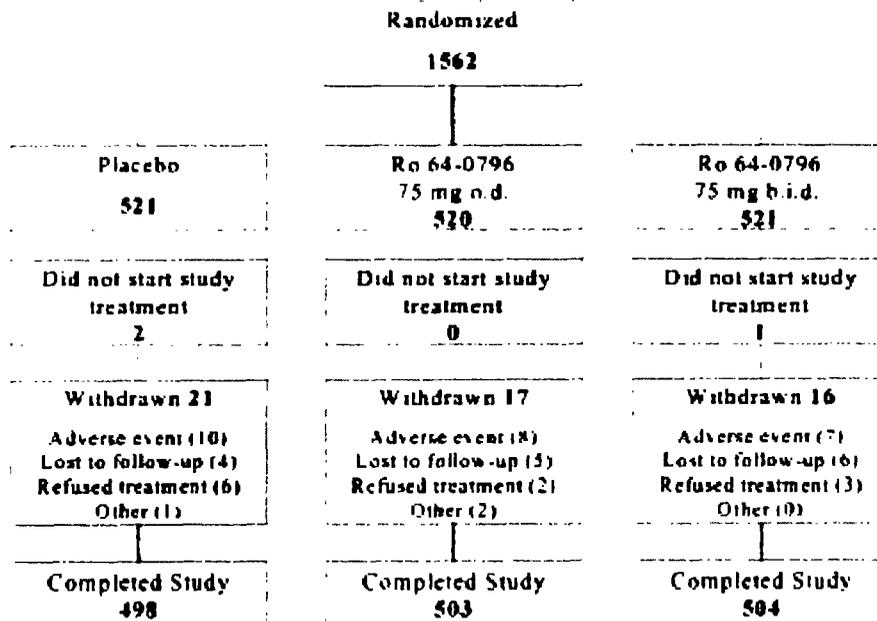
For the primary efficacy analysis, an intent-to-treat (ITT) population was used, i.e. all subjects who were randomly assigned to a study group and who took at least one dose of the assigned study medication.

Because the incidence of influenza in the 1997/1998 season was lower than expected (projected incidence: 10%), study WV15673 and WV 15697 were combined for analysis, as originally planned.

2. Patient Disposition, Demographics

A total of 1562 subjects were randomized in the two studies combined (521 to placebo, 520 to oseltamivir 75 mg q.d., 521 to oseltamivir 75 mg b.i.d.). The following figure summarizes the disposition of the randomized subjects.

Figure 1: Patient Disposition (WV15673, WV15679)



Refused Treatment = "refused treatment" + "withdrew consent" + "did not co-operate"

Source: Figure 2, vol.42, page 33

As shown in Fig. 1, the rates of study discontinuation across treatment groups were low and similar: 4%(21/519), 3.4%(17/520), and 3%(16/520), for placebo, oseltamivir 75 mg q.d., and oseltamivir 75 mg bid, respectively.

Demographic characteristics of the three treatment groups for the ITT population were similar. The group means for age were between 34 and 35 years. Eighty percent (80%) of the population were Caucasian. Sixty percent (60%) of the population were female subjects. Approximately 25% of population had detectable antibodies to the predominant circulating influenza virus strain (influenza A H3N2-Sydney).

3. Key Efficacy Results

The results of the primary efficacy analysis are shown in Table 2.

Table 2: Laboratory Confirmed Clinical Influenza
(ITT, WV15673+WV15697)

	Placebo (N=519)	Oseltamivir 75 mg qd (N=520)	Oseltamivir 75 mg bid (N=520)
Clinical Influenza	25 (4.8%)	6 (1.2%)	7 (1.3%)
	Treatment effect	P value	95% CI for difference
Placebo vs. 75 mg qd	76%	0.00055	1.6%-5.7%
Placebo vs. 75 mg bid	72%	0.00125	1.4%-5.6%
75 mg qd vs 75 mg bid	-	1	-2%-1.2%

Source: Table 18, vol. 42, page 54

Table 2 shows that the proportion of subjects with laboratory confirmed clinical influenza was statistically significantly lower in each of the active treatment groups than in the placebo group. There was no evidence of any difference in the treatment effect between the two active treatment groups, although the studies were not intended formally to compare the two dosage regimens of oseltamivir with each other.

When the incidence of non-clinical influenza was analyzed, the results are shown in Table 3.

Table 3: Non-Clinical Influenza (ITT, WV15673+WV15697)

	Placebo (N=519)	Oseltamivir 75 mg qd (N=520)	Oseltamivir 75 mg bid (N=520)
Non-Clinical Influenza	11 (2%)	9 (1.7%)	8 (1.5%)
	Treatment effect	P value	95% CI for difference
Placebo vs. 75 mg qd	18%	0.66	-1%-2.1%
Placebo vs. 75 mg bid	27%	0.49	-1%-2.2%
75 mg qd vs 75 mg bid	11%	1.00	-1%-1.7%

Source: Table 19, vol. 42, page 56

When the incidence of asymptomatic influenza was analyzed, the results are shown in Table 4.

Table 4: Laboratory Confirmed Asymptomatic Influenza
(ITT, WV15673+WV15697)

	Placebo (N=519)	Oseltamivir 75 mg qd (N=520)	Oseltamivir 75 mg bid (N=520)
Asymptomatic Influenza	19(3.7%)	13(2.5%)	12(2.3%)
	Treatment effect	P value	95% CI for difference
Placebo vs. 75 mg qd	31%	0.28	-0.9%-3.3%
Placebo vs. 75 mg bid	37%	0.20	-0.7%-3.4%
75 mg qd vs 75 mg bid	8%	1.00	-2%-2.1%

Source: Table 20, vol. 42, page 56

Tables 3 and 4 suggest that the proportion of subjects with non-clinical influenza or asymptomatic influenza, all laboratory confirmed, did not show statistically significant differences in the three treatment groups. However, the numbers were consistently lower in the active treatment groups compared with placebo.

Seven subjects (2 placebo, 1 oseltamivir 75 mg qd, 4 oseltamivir 75 mg bid) developed laboratory confirmed clinical influenza after the end of study treatment (Week 6) and before the final week 8 clinic visit. Given that plasma concentrations of oseltamivir declined with a half-life of 1 to 3 hours in most subjects after oral administration, it can be expected that the drug has been completely eliminated during this period. Thus the results suggested that the protective effect of oseltamivir did not persist after elimination of the drug from the body at the end of treatment.

B. Study WV15708 and WV15825

I. Design

Both studies were multi-center, randomized, double blind, parallel group and placebo-controlled trials in residential homes for elderly people conducted during the season of 1998/99. Study WV15708 was carried out in Australia, New Zealand, South Africa, Brazil. Study WV15825 was carried out in the U.S., United Kingdom, France, Belgium and the Netherlands.

Residents aged ≥ 65 years, with a Mental Status Questionnaire (MSQ) scores ≥ 7 , without presenting any evidence of unstable conditions of renal, cardiac, pulmonary, vascular, neurologic or metabolic disease were identified before the influenza season. The criterion for triggering the start of the study was when there was one confirmed case of influenza identified in the residential home.

The study design for these two studies was very similar to that of study WV15673 and WV15679 with the exception that subjects were randomized according to two strata: vaccination status and presence or absence of chronic obstructive airway disease (COAD) at baseline. The dose of 75 mg qd oseltamivir was selected for this study based on the results of study WV15673 and WV15679.

For this elderly population, 5 events were predefined as illnesses that could be secondary to influenza: sinusitis, otitis media, pneumonia, lower respiratory tract infection, and

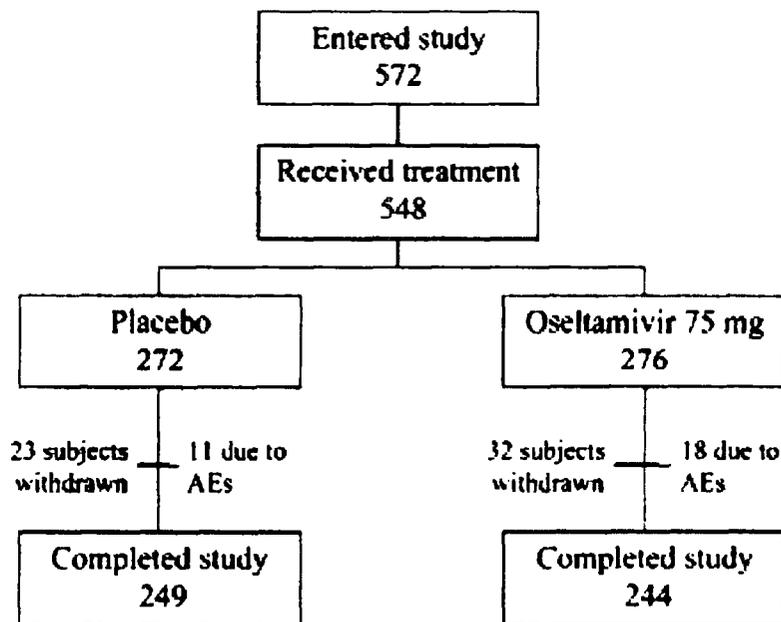
bronchitis. Although detailed diagnostic confirmation for each condition was pre-specified in the CRF (including symptoms/signs, radiologic studies, and microbiologic examinations), they were just recommendations, not requirements, to the investigator's assessment. The protocol stated that the diagnosis was in the judgement of the investigator on the basis of symptoms, signs, and results of additional examinations at investigator's discretion.

As the applicant explained, the timing of study WV15708 may have started after the peak of the influenza season, since there were only 2 cases of laboratory confirmed clinical influenza. Therefore, the applicant decided not to include study WV15708 in the efficacy analysis but included it in the safety analysis.

2. Patient Disposition, Demographics

Study WV15825 enrolled a total number of 572 subjects, of whom 548 received study treatment and 493 completed the study. The following figure shows the disposition of these subjects.

Figure 2: Patient Disposition (WV15825)



Source: Figure 2, vol. 76, page 32

As shown in Fig. 2, the rates of study discontinuation were slightly higher than that seen in young adult population. In this study 8.5% (23/272) and 11.6% (32/276) for the placebo and treatment groups, respectively, withdrew from the study prematurely. The most frequent reason given for withdrawal was for adverse events which were slightly higher in the oseltamivir group than in the placebo group (6.5% compared with 4%).

The demographic characteristics of the two treatment groups were similar. There were more female (~70%) than male subjects for both treatment groups. The subjects were aged between 64 and 96 years, with group means for age of 82 and 81 years. The great majority (92%) of subjects were Caucasian. Eighty percent (80%) of subjects had been vaccinated prior to the influenza season, and 14% had COAD. Approximately 70% and 80% of the subjects had an HAI titer $\geq 1:40$ for influenza A-H3N2 or influenza B, respectively. The virus types recommended for inclusion in the vaccine before this season were deemed well matched since it had included an influenza A H3N2 Sydney 97-like strain.

In these elderly nursing home residents, approximately 98% of the subjects in each treatment group had one or more concomitant illnesses. The most frequent disorder was hypertension (49% for both groups). The proportion of subjects with a past history of diabetes were slightly higher for the placebo group than the oseltamivir group (placebo=14%, oseltamivir=10%).

3. Key Efficacy Results

The results of the primary efficacy analysis are shown in Table 5.

Table 5: Laboratory Confirmed Clinical Influenza (ITT, WV15825)

	Placebo (N=272)	Oseltamivir 75 mg qd (N=520)	
Clinical Influenza	12(4.4%)	1(0.4%)	
Placebo vs. 75 mg qd	Treatment effect	P value	95% CI for difference
	92%	0.0015	1.5% to 6.6%

Source: Table 25, vol. 76, page 63

In the ITT population, the proportion of subjects with laboratory confirmed clinical influenza was statistically significantly lower in the active treatment groups than in the placebo group.

When the incidence of non-clinical influenza was analyzed, the results are shown in Table 6.

Table 6: Non-clinical Influenza (ITT, WV15625)

	Placebo (N=272)	Oseltamivir 75 mg qd (N=276)	
Non-Clinical Influenza	4(1.5%)	8(2.9%)	
Placebo vs. 75 mg qd	Treatment effect	P value	95% CI for difference
	-	0.382	-4% to 1%

Source: Table 29, vol. 76, page 66

When the incidence of asymptomatic influenza was analyzed, the results are shown in Table 7.

Table 7: Asymptomatic Influenza (ITT, WV15825)

	Placebo (N=272)	Oseltamivir 75 mg qd (N=276)	
Clinical Influenza	7(2.6%)	6(2.2%)	
Placebo vs. 75 mg qd	Treatment effect	P value	95% CI for difference
	16%	0.787	-2% to 2.9%

Source: Table 30, vol. 76, page 67

Tables 6 and 7 show that the proportions of subjects with either non-clinical symptomatic influenza or asymptomatic influenza virus infection were not statistically different between the two treatment groups. These results are consistent with that for the seasonal prophylaxis in younger adults.

4. Subgroup Analyses

- **Vaccination Status**

Eighty percent of subjects enrolled were vaccinated. An analysis of the incidence of laboratory confirmed clinical influenza in the vaccinated subgroup gave a similar result to the primary analysis as shown in Table 8.

Table 8: Laboratory Confirmed Clinical Influenza
(Vaccinated Subjects, ITT, WV15825)

	Placebo (N=218)	Oseltamivir 75 mg qd (N=222)	
Clinical Influenza	11(5%)	1(0.5%)	
Placebo vs. 75 mg qd	Treatment effect	P value	95% CI for difference
	91%	0.0028	1.6% to 7.6%

Source: Table 26, vol. 76, page 64

However, the numbers of unvaccinated subjects (n= 108) and incidence of laboratory confirmed clinical influenza (n=1) were too small to allow for a meaningful comparison with respect to the efficacy of oseltamivir between the vaccinated and unvaccinated groups. Thus, an assessment of potential treatment interactions (augmentation or reduction) between oseltamivir and vaccination status can not be made based on the data from study WV15825.

- **COAD**

Seventy-three percent (73%) of subjects enrolled were without COAD. The following Table shows the results of a primary efficacy analysis according to the presence or absence of COAD at baseline.

Table 9: Laboratory Confirmed Clinical Influenza according to COAD
(ITT, WV15825)

Clinical Influenza	With COAD		Without COAD	
	Placebo (n=39)	Oseltamivir (n=134)	Placebo (n=233)	Oseltamivir (n=237)
	3	1	9	0
P value	0.615		0.0017	
95% CI for the difference	-5% to 15%		1.5% to 6.3%	

Source: Table 27, vol. 76, page 65

As expected, for subjects without COAD oseltamivir administration was associated with statistically significant reduction in the incidence of laboratory confirmed clinical influenza compared with placebo. Although the numbers of subjects in the COAD group were small, there was a similar trend that oseltamivir reduced the number of cases of laboratory confirmed clinical influenza compared with placebo.

- **Cardiac Conditions**

There were 44% and 43% of subjects recorded to have either a history of or concomitant cardiac disorder at baseline in subjects randomized to placebo and oseltamivir, respectively. The most frequently recorded conditions were coronary artery disease, atrial fibrillation, and congestive heart failure. It should be pointed out that this protocol excluded subjects with unstable or uncontrolled cardiac conditions. In respond to this reviewer's request, the applicant performed a primary efficacy analysis according to the presence or history of a cardiac condition. The results are shown in Table 10.

Table 10: Laboratory Confirmed Clinical Influenza According
to the Presence of a Cardiac Condition
(ITT, WV15825)

Clinical Influenza	With Cardiac disorder		Without cardiac disorder	
	Placebo (n=132)	Oseltamivir (n=134)	Placebo (n=140)	Oseltamivir (n=142)
	7	1	5	0
P value	0.035		0.029	
95% CI for the difference	0.5% to 8.6%		0.5% to 6.6%	

Source: Roche's facsimile, dated 9/28/00

The results show that oseltamivir was associated with statistically significant reduction in the incidence of laboratory confirmed clinical influenza compared to placebo, regardless of the presence of a cardiac condition.

- **Secondary Complications of Influenza**

Otitis media, sinusitis, LRTI, bronchitis and pneumonia were defined in the protocol as complications secondary to influenza infection. A total of 8 cases were assessed by investigators to have one or two of these conditions. All but one were subjects in the placebo group; all but two had laboratory confirmed clinical influenza. These complications included 3 cases of pneumonia (all in placebo), 5 cases of bronchitis (4 placebo and 1 oseltamivir), and 1 placebo subject had both bronchitis and sinusitis. A summary of these cases is presented in Appendix 1.

To estimate the effectiveness of oseltamivir in preventing the occurrence of a secondary complication, the applicant took 2 approaches: by expressing the proportion within the ITT population as a whole, and by considering only those subjects proven to have been infected with influenza. Both results are shown in Table 11.

Table 11: Number (%) of Subjects with Influenza-Related Complications

Complications	For ITT population		For subjects who had influenza infection	
	Placebo (n=272)	Oseltamivir (n=276)	Placebo (n=23)	Oseltamivir (n=15)
	7(2.6%)	1 (0.4%)	7(30%)	1(6.6%)
Placebo vs. oseltamivir	P value	95% CI for the difference	P value	95% CI for the difference
	0.037	0.2% to 4.2%	0.114	-61% to 97%

Source: Table 32, vol.76 and Table 14, vol.18

The above Table shows that, within the entire ITT population, the proportion of influenza-related complications was statistically significantly reduced in subjects in the oseltamivir ($p=0.037$) group compared with subjects in the placebo group. However, when considering only those subjects infected with influenza, the proportion of the secondary complication was numerically but not statistically reduced in the oseltamivir group, owing to the smaller sample size.

Based on investigator's assessment, there appeared to be a consistent trend of reduction in the incidence of secondary complications associated with oseltamivir prophylaxis, irrespective of which population was used to derive the proportions. However, the data to support the clinical diagnoses of each of the 8 cases were deemed weak. Appendix 1 provides a summary of the data on which investigators' diagnoses were based. Three deficiencies were identified and are described below:

- ◆ The minimally required diagnostic criteria for sinusitis, bronchitis, and pneumonia were not predefined in the protocol. The lack of microbiologic evaluation in all 8 cases and insufficient radiographic evaluation in most cases have made a clinical review of the investigators' assessments problematic.
- ◆ It is questionable to consider acute bronchitis as a secondary bacterial complication of influenza, given that increased bronchial reactivity and decreased tracheobronchial clearance are both within the spectrum of uncomplicated influenza. In addition, no information on smoking was provided.
- ◆ Subject 23632/4710 presented a clinical diagnosis of 'pneumonia' on the same day of the onset of influenza. In the absence of any microbiologic evaluations, it is impossible to differentiate a non-viral pneumonia from a primary viral pneumonia due to influenza virus.

In conclusion, the applicant's claim of the effectiveness of oseltamivir in preventing influenza-related secondary complications can not be substantiated due to the uncertainty of the investigators' assessments.

C. Study WV15799

1. Design

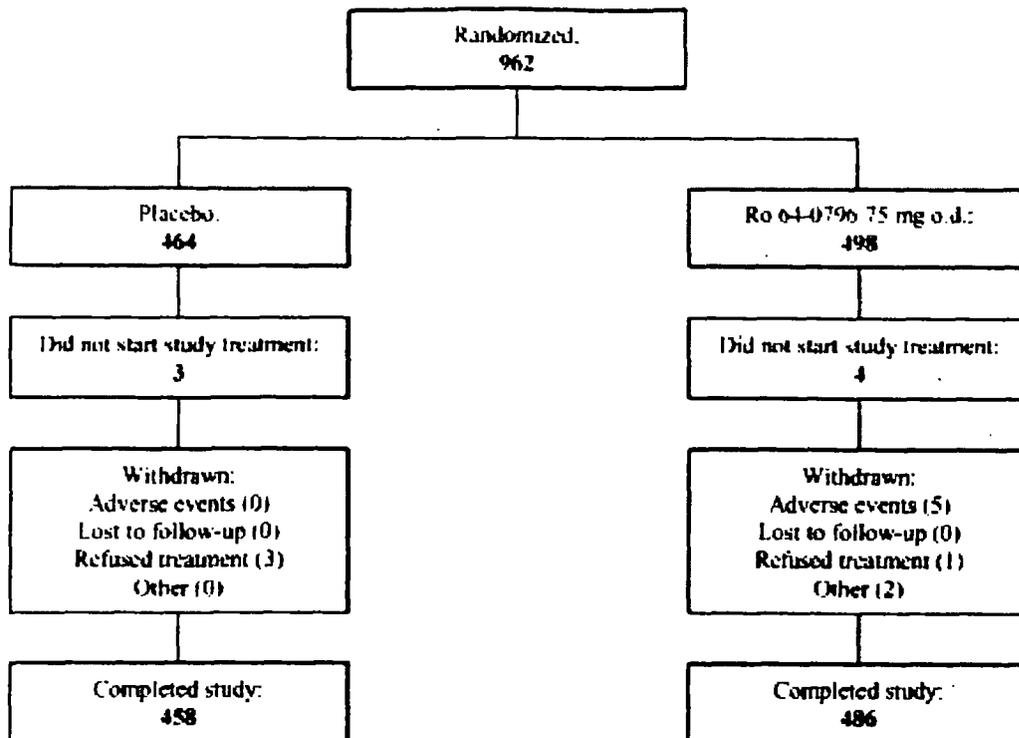
Study WV15799 was a multi-center, household-randomized, double blind, placebo-controlled study conducted in families in Europe and North American during the 1998/9 influenza season. Eligible subjects were contacts of an index case with clinically diagnosed respiratory illness. The index case could be any individual one year or older, and the contacts were adults and adolescents of 13 years and older. The index case was not allowed to receive any anti-viral treatment. Contacts, within 2 days of onset of symptoms in the index case, were treated with oseltamivir 75 mg or placebo once daily for 7 days. All members of a cluster received the same treatment. Although prior vaccination was allowed, the study population was predominantly healthy unvaccinated adults.

The primary efficacy analysis for this post-exposure prophylaxis study was the Intent-to-Treat Index Infected Negative at Baseline (ITTINAB) population which was defined as contacts who had a negative influenza virus culture at baseline (day1), who received at least one dose of study medication and in whom the index case was confirmed to be influenza infected. The ITT population was used for the safety analysis.

2. Patient Disposition, Demographics

A total of 962 contacts were randomized to this study (464 to placebo; 498 to 75mg oseltamivir qd). These individuals were contacts of a total of 377 index cases. Of the 377 index cases, 163 were subsequently confirmed to have influenza virus infection. The disposition of subjects who enrolled in the study is shown in the following figure.

Figure 3: Patient Disposition (WV15799)



Refused treatment = 'refused treatment' + 'withdrew consent' + 'did not cooperate'

Source: Figure 2, vol. 27, page 42

As shown in the above, the rates of premature study discontinuation were low for both treatment groups (placebo 0.9%, oseltamivir 1.6%).

The clusters were predominantly family groups (>90%). The majority of households comprised 3 to 4 individuals.

Contacts from both treatment groups were comparable with regard to gender, age, race, and influenza virus antibody titer at baseline. The age of contacts ranged from 13 years to 85 years; the age of index cases ranged from 1 year to 76 years. Approximately 13% of contacts were vaccinated. At least two third of contacts in the ITTNAB population had protective levels of antibody titers against at least one of the two predominant circulating strains of influenza: Types A H3N2 and B.

3. Key Efficacy Results

The results of the primary efficacy analysis are shown in Table 12.

Table 12: Laboratory confirmed clinical influenza (ITTINAB, WV15799)

# of contacts	Placebo (N=200)	Oseltamivir 75 mg qd (N=205)
Clinical Influenza	24(12%)	2(1%)
Placebo vs. 75 mg qd	P value	95% CI for difference
	0.000076	70.6% to 98.1%

Source: Table 9, vol. 27, page 49

In the ITTINAB population, the proportion of subjects with laboratory confirmed clinical influenza was statistically significantly lower in the oseltamivir treatment group than in the placebo group.

When the number of clusters¹ was used for the primary efficacy analysis, the proportion of subjects with laboratory confirmed clinical influenza was also statistically significantly lower in the oseltamivir group than in the placebo group as shown in Table 13.

Table 13: Laboratory confirmed clinical influenza (ITTINAB, WV15799)

# of clusters	Placebo (N=79)	Oseltamivir 75 mg qd (N=84)
Clinical Influenza	17(21.5%)	2(2.4%)
Placebo vs. 75 mg qd	P value	95% CI for difference
	<0.0001	9.5% to 29%

Source: Table 12, vol. 27, page 52

When the incidences of non-clinical influenza and asymptomatic influenza were analyzed, the results are summarized in Table 14 and Table 15.

Table 14: Non-clinical influenza (ITTINAB, WV15799)

	Placebo (N=200)	Oseltamivir 75 mg qd (N=205)
Non Clinical Influenza	10(5%)	5(2.4%)
Placebo vs. 75 mg qd	P value	95% CI for difference
	0.227	-20.2% to 87.7%

Source: Table 13, vol. 27, page 53

Table 15: Asymptomatic influenza (ITTINAB, WV15799)

	Placebo (N=200)	Oseltamivir 75 mg qd (N=205)
Asymptomatic Influenza	6(3%)	7(3.4%)
Placebo vs. 75 mg qd	P value	95% CI for difference
	0.835	-16.7% to 81.9%

Source: Table 14, vol.27, page 53

The numbers of contacts in the ITTINAB population with non-clinical influenza or asymptomatic influenza infection during the study treatment period were not statistically significantly different between the two treatment groups, despite the fact that the number of contacts with non-clinical influenza was numerically lower in the oseltamivir group compared to placebo.

¹ A cluster was defined as a family unit with at least one contact developed laboratory confirmed clinical influenza.

4. Subgroup Analyses

- Influenza Type

At the time of the approval for the original NDA, evidence for the effectiveness of oseltamivir against influenza B was limited, only 3% of the infected subjects in the entire database were diagnosed with influenza type B. Thus the approval for a broad treatment claim to include both influenza A and B was based on the totality of the information available then including *in vitro* data, animal models and human challenge trials.

During the 1998/9 winter season, influenza A H3N2 viruses predominated but influenza B viruses were also circulating. Since there were sufficient numbers of contacts infected with either type, primary efficacy analysis according to influenza type was performed. The applicant took 2 approaches:

- Using the ITT population to assess the effectiveness of oseltamivir in preventing laboratory confirmed clinical influenza. In this population, the sources of infection among the contacts included both index cases and the community. This approach was analogous to that for the seasonal prophylaxis studies.
- Using the ITTNAB population to assess the effectiveness of oseltamivir in preventing laboratory confirmed clinical influenza. This approach specifically aimed at a family post-exposure situation.

As shown in Table 16, the number of subjects in the ITT population with laboratory confirmed clinical influenza type A or type B was respectively statistically significantly lower in the oseltamivir group compared to the placebo group.

Table 16: Number of Laboratory Confirmed Clinical Influenza by Influenza Type (WV15799)

Influenza Type		Placebo	Oseltamivir	p-value
Type A	ITT	21/462	1/493	0.000134
	ITTNAB	18/200	0/205	0.001789
Type B	ITT	13/462	3/493	0.010122
	ITTNAB	6/200	2/105	0.153057

Source: Table 23, vol. 18. page 77

In the ITTNAB population, the number of contacts with laboratory confirmed clinical influenza type A was statistically significantly lower in the 75 mg oseltamivir qd group compared to the placebo group. There was not a statistically significant difference between the treatment groups with respect to clinical influenza type B, however, the number of contacts in the same population with laboratory confirmed clinical influenza type B was numerically lower in the oseltamivir group compared to placebo. In the ITT population, the number of contacts with laboratory confirmed clinical influenza type A or type B was statistically significantly lower in the oseltamivir group compared to placebo.

These results provided for the first time the clinical evidence of oseltamivir as an effective agent against influenza B.

- Post-treatment Prevention

In the ITTINAB population, the number of new cases of laboratory confirmed clinical influenza post-treatment (i.e. at any time from day 8 to 14 days post dose) was numerically lower in the oseltamivir group than in the placebo group (5 in placebo, 1 in oseltamivir). The applicant concluded that this short-term prophylaxis of 7 days duration might have afforded protection from clinical influenza illness well beyond the treatment duration for up to 2 weeks following the cessation of the drug. The applicant named it as a 'hang-over' effect. They further speculated that the effect could be attributed by the interruption of viral replication during the incubation period in subjects who became infected with influenza virus late in the 7-day treatment period.

Upon review, among the 5 placebo subjects, 4 contacts were found to have clinical influenza on day 8 which coincided with the first scheduled visit day. In this 7-day short course prophylaxis, it is conceivable that subjects who developed a clinical case of influenza late during the course opted to postpone an illness visit until the scheduled one on day 8. Thus there is insufficient data to distinguish a potential 'hang-over' effect of oseltamivir from a possible artifact as a result of the protocol design.

D. Challenge Studies: Study GS 97-082 and NP15757

Studies GS 97-082 and NP15757, both being experimental challenge studies, are considered supportive data. Both were single-center, double blind, randomized, placebo-controlled studies. The main objective of these two studies was to assess the safety, tolerability and prophylactic antiviral activity of oseltamivir in healthy volunteers, who had baseline HAI antibody titer of $\leq 1:8$, experimentally inoculated with A/Texas/36/91 (H1N1) and B/Yamagata/16/88 virus, respectively.

Administration of oseltamivir was started 24 hours prior to intranasal inoculation of the virus. The treatment duration was 5 days. Thirty-seven subjects were randomized to three treatment arms in study GS 97-802: placebo, oseltamivir 100 mg qd, and oseltamivir 100 mg bid. Fifty-nine subjects were randomized to three treatment arms in study NP15757: placebo, oseltamivir 75 mg qd, and oseltamivir 75 mg bid. The treatment duration was 7 days.

In both studies, the primary efficacy parameter was the proportion of subjects with laboratory confirmed influenza infection. Secondary efficacy parameters were peak virus titer, the duration of virus shedding and the area under the curve (AUC) of virus titer.

In GS 97-082, the proportion of influenza A infected subjects was significantly lower in the group receiving oseltamivir 100 mg qd (18%, 2/11) compared to placebo (67%, 8/12) ($p=0.036$). Although the number of subjects with influenza A infection in the 100 mg bid group (40%, 4/10) was numerically lower than in the placebo group, there was no

statistical difference between the 100 mg bid group and the placebo group ($p=0.391$). No virus was cultured from nasal washings obtained from subjects receiving oseltamivir at either dose following virus inoculation. In contrast, 50% (6/12) subjects in the placebo group shed virus for a median duration of 142.9 hours yielding a median peak viral titer of $0.8 \log_{10} \text{TCID}_{50} / \text{ml}$.

In study NP15757, oseltamivir administration did not reduce the rate of infection with experimental influenza B. The active treatment groups had a lower percentage subjects shedding virus more than 24 hour after inoculation than did the placebo group; however, the difference was not found to be statistically significant ($p=0.256$).

Taken together, both experimental challenge prophylaxis studies did not consistently demonstrate the protective effect of oseltamivir in the rate of infection. A possible explanation could be that the strains employed in challenge study designs were attenuated; thus, symptoms associated with experimental infection were expected to be milder. However, analyses of the virologic efficacy parameters in both studies (AUC of virus titer, peak virus titer, duration of virus shedding) showed that the numbers were lower in the oseltamivir groups than in the placebo group, suggesting an antiviral effect of oseltamivir against influenza type A and B.

E. Integrated Summary of Efficacy (ISE)

Data from studies WV15673, WV15697, and WV15825 were pooled and analyzed by the applicant. This pooled dataset was used to test the robustness of the efficacy of oseltamivir and to perform additional exploratory analyses.

1. Robustness Analysis

The robustness of the primary efficacy parameter was examined by using the following approaches:

- Using a higher temperature definition:
Using a temperature threshold of $100^{\circ} \text{F}/37.8^{\circ} \text{C}$ for diagnosis of clinical influenza in studies WV15673/15697, and WV15799; a threshold of $99.5^{\circ} \text{F}/37.5^{\circ} \text{C}$ for diagnosis in study WV15825 elderly population, given that elderly subjects are less likely to mount a high febrile response to influenza infection.
- Enumerating the number of cases which met the definition of laboratory confirmed clinical influenza based only on positive virus culture.

In both analyses, results showed a statistically significant reduction in the primary efficacy parameter in the oseltamivir group compared to the placebo group.

2. Exploratory Analysis

- Effect of oseltamivir prophylaxis on the humoral antibody response to infection or vaccination

There has been no formal oseltamivir-vaccine interaction study conducted so far. The applicant employed the pooled dataset to explore the effect of oseltamivir prophylaxis on the humoral antibody response to infection and/or vaccination.

In the pooled treatment studies in which participants were uniformly not vaccinated, the geometric mean change from baseline was similar in both oseltamivir group and placebo for those who were diagnosed as infected with influenza. These results suggested that oseltamivir did not suppress the humoral antibody response to infection.

A similar analysis was performed for the pooled prophylaxis studies as well as individual studies in which both vaccinated and unvaccinated subjects were enrolled. For the purpose of illustrating the effect of oseltamivir prophylaxis on the humoral antibody response to infection and vaccination, the data of viral antibody titers from study WV15825, where 80% of subjects were vaccinated, were selected to be presented in the following table.

Table 17: Change from Baseline for Viral Antibody Titers
(WV15825, ITT)

Change (increase)from baseline for viral antibody titers*	Placebo N=272	Oseltamivir N=276
All	23 (100%)	15(100%)
0-fold	4(17.4%)	1(6.7%)
2-fold		1(6.7%)
4-fold	3(13%)	4(26.7%)
8-fold	6(26%)	
16-fold	3(13%)	2(13.3%)
32-fold	3(13%)	1(6.7%)
64-fold	2(8.7%)	4(26.7%)
128-fold	1(4.3%)	1(6.7%)
256-fold	1(4.3%)	1(6.7%)
Geometric mean (fold)	10.5	16.8

Source: Table 16, vol. 18, page 65.

*Maximum titer used for each subject

Data in Table 17 show that, in this predominantly vaccinated population, the geometric mean fold increase in titer was higher in the oseltamivir group than in the placebo group; 16.8 compared to 10.5.

In the prophylaxis studies in young adults and elderly nursing home residents, including both vaccinated and unvaccinated, the distribution of antibody titer increases in infected subjects was similar in the placebo and oseltamivir group. The geometric mean fold increase in titer in this pooled database was 12.9 in the placebo group compared to 14.3 in the oseltamivir group.

Data from both treatment and prophylaxis studies have consistently suggested that oseltamivir does not suppress the magnitude of the type-specific antibody response to influenza virus infection in both vaccinated and unvaccinated populations.

- Effect of oseltamivir on interruption of the transmission of influenza within households

The applicant considered that data from study WP15799 suggested a successful transmission interruption of influenza within households as a result of oseltamivir prophylaxis. Their assessment was based on the virus shedding data shown in Table 18.

Table 18: Number of Contacts Shedding Virus Days 2 to 8
(ITTINAB, WV15799)

Placebo	Oseltamivir	p-value	95% CI for the difference
22/200	4/205	0.00033	54% to 94%

Source: Table 15, vol 18, page 62

The applicant's data interpretation posed two limitations:

- Virus shedding was defined as a positive influenza virus culture from nose and/or throat swabs. This qualitative measurement was designed to provide a laboratory confirmation for the diagnosis of clinical influenza, therefore, it was not performed for all participants. As a result, infected subjects with no symptoms (asymptomatic infection) were not included in the virus shedding data.
- Prophylaxis in the household setting includes two components: prevention of transmission and prevention of disease in the contacts. To address the transmission prevention, the study should have included two groups of index cases, i.e. treated vs. not treated. Since all index cases did not receive any active treatment in this study, the effect of oseltamivir in prevention of transmission of influenza viruses cannot be teased out and separated from the prophylactic effect of oseltamivir.

In summary, because virus culture was not performed for all participants and all index cases were uniformly not treated, no conclusion can be made regarding the effectiveness of oseltamivir in preventing virus transmission in families.

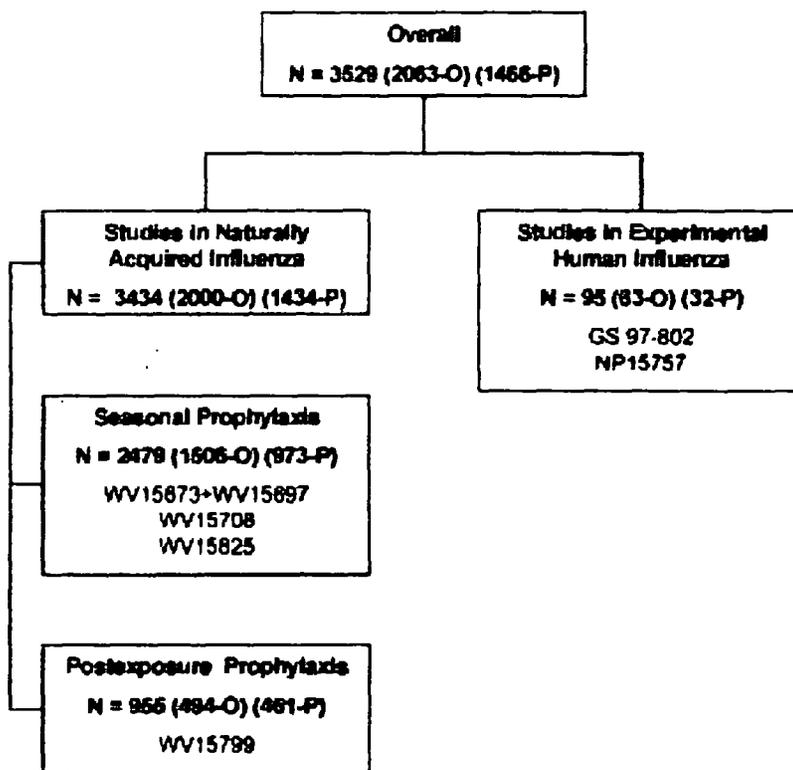
VII. Integrated Review of Safety

The clinical data cut-off date for the integrated summary of safety data was September 30, 1999. At that time, oseltamivir had not been launched in any market worldwide. To

supplement the applicant's safety information, adverse events for Tamiflu that had been reported to the Agency's Adverse Event Reporting System (AERS) since the approval of the drug up through April 2000 were also reviewed.

The safety database is summarized in Figure 4.

Figure 4: Pooled Safety Data Source



N = number of subjects in the safety population (oseltamivir) (placebo)

The safety database for oseltamivir in prophylaxis of influenza comprised 7 studies (both primary and secondary data source as listed in Table I.) A total of 3529 subjects took study medication. Of them, 73% of subjects were assigned to a study duration of 42 days, 26% of subjects were assigned to a study duration of 7 days, and 1.2% of subjects were assigned to a study duration of 5 days. Compliance with medication was good in all studies, 90% to 95% of the subjects took at least 80% of the prescribed medication.

The study populations spanned a wide age range (13 to 96 years). The great majority of the subjects were Caucasian, and women slightly outnumbered men (59% of the overall population was female.)

The data pooling strategy was to combine initially the safety dataset from all seasonal prophylaxis studies with a treatment duration of 42 days. Thereafter, data from ALL prophylaxis studies were combined including the post-exposure study (42-day and 7-day treatment duration).

A. Overview

The types of adverse events reported in the pooled seasonal prophylaxis studies and the post-exposure prophylaxis study were similar, although the overall frequency of adverse events reporting was lower in the post-exposure prophylaxis study. Thus, a summary of adverse events reported by subjects in all prophylaxis studies (i.e. combining the pooled seasonal prophylaxis studies and post-exposure prophylaxis) was selected to be presented in the following table.

Table 19: Summary of Most Frequent Adverse Events
(WV15763, WV15679, WV15708, WV15828, WV15799)

Adverse event	Placebo (n=1434)	Oseltamivir 75 mg qd (n=1480)
Nausea	62 (4.3%)	118 (8.0%)
Headache	251 (17.5%)	298 (20.1%)
Vomiting	15 (1%)	31 (2.1%)
Diarrhea	38 (2.6%)	48 (3.2%)
Pain	43 (3%)	53 (3.6%)
Fatigue	107 (7.5%)	117 (7.9%)
Abdominal pain	23 (1.6%)	30 (2%)
Insomnia	14 (1%)	18 (1.2%)
Dizziness	21 (1.5%)	24 (1.6%)
Upper respiratory infection	115 (8%)	120 (8.1%)
Dyspepsia	23 (1.6%)	25 (1.7%)

Source: Table 9, vol. 19

Nausea, headache, and vomiting are three events that showed the greatest increase in frequency in the oseltamivir group compared with placebo. The overall frequency of these events, with the exception of headache, was lower in the prophylaxis studies than in the treatment studies.

Headache was reported approximately 10-fold more frequently in the prophylaxis studies than in the treatment studies, for subjects in the placebo or oseltamivir groups. In the 42-day prophylaxis study, the incidence of headache seen in the oseltamivir group was 29%, whereas in the 7-day post-exposure prophylaxis study and the 5-day treatment studies, the incidence of headache was similar (2.4% and 1.8%, respectively.) Thus, when the frequency of reporting was inspected according to study duration, the data suggested that the overall increase in reports of headache was probably a result of longer study period

The intensity of nausea, headache, and vomiting was mild or moderate in the oseltamivir group and was similar to and sometimes milder than that reported for subjects in the placebo group.

The adverse event profile of oseltamivir was similar whether the drug was given once or twice daily. Nausea was slightly more frequent with twice daily than with once daily dosing. Headache was also more common with twice daily than with once daily oseltamivir. However, the incidence of vomiting was not increased with the higher dose of oseltamivir. Based on the results of the safety analysis in conjunction with the results of the efficacy analysis, once daily dosing was identified as the optimal regimen for influenza prophylaxis.

Of note, two low frequency events were not included in Table 19 but occurred slightly more often in the oseltamivir group, i.e. hyperglycemia and aggravated diabetes mellitus. These were reported for 7 subjects, all of them received oseltamivir and all had a history of diabetes mellitus. In addition, 1 placebo subject (also with baseline diabetes mellitus) had an adverse event of increased blood glucose.

There were no additional adverse events of significance observed in the two experimental challenge studies.

Overview of the reports of deaths and serious adverse events showed no notable differences between the study groups in the incidence and type of events. There were 4 deaths (2 placebo, 2 oseltamivir), all were elderly residents of nursing facilities. None of the deaths was considered by the investigator to be related to study medication. The incidence of serious adverse events was low in all study groups (0.8% to 2.4%). Most of the subjects who had serious adverse events were in study WV15825. The most frequent type of serious adverse event was infection, followed by respiratory disorders and cardiac disorders.

Overall, the proportion of subjects who withdrew prematurely from the prophylaxis studies in naturally acquired influenza was low: 4.7% for placebo; 5.5% for once daily oseltamivir and 3.1% for twice daily oseltamivir. The most common reason for withdrawal was the occurrence of adverse events.

Mean changes from baseline in values of key hematology (hemoglobin, WBC, platelets) and biochemistry (BUN, total bilirubin, SCOT, SGPT, creatinine, alk-phosphatase) parameters were examined. There were no clinically relevant changes from baseline for any of these parameters, including the subjects with severely impaired renal function. Shifts of laboratory results of ≥ 2 WHO grades (i.e. from Grade 0 to Grade 2 or 3 in value) were uncommon, and were seen equally in the placebo and oseltamivir group.

B. Adverse Event Reporting System

Adverse events for Tamiflu that were reported to the Agency's Adverse Event Reporting System (AERS) since the approval of the drug up through April 2000 have provided additional safety information. During the 1999-2000 winter season, a total of 5 patients with influenza-like symptoms, receiving Tamiflu treatment, were found to have developed septicemia (group A streptococcus, *Staphylococcus aureus*, *Streptococcus milleri*, *Streptococcus pneumoniae*, *Neisseria meningitidis*). Four of these patients died

of sepsis. The temporal sequence of these cases suggested that the original influenza-like symptoms could be the prodrome of a bacteremic illness in some and secondary bacterial infections in others. Because of these and similar cases reported for another approved neuraminidase inhibitor, Relenza, the Agency issued a Public Health Advisory on January 12, 2000 to alert the public to consider the possibility of bacterial infection in patients with influenza-like illnesses.

Also presented in the AERS, reports of arrhythmia, rash, angioedema, seizure, confusion and aggravation of diabetes were noted. Cases of arrhythmia, seizure and confusion from clinical trials of oseltamivir were reviewed. The applicant concluded that a relationship between oseltamivir and the above events could not be ascertained. In two AERS reports of allergic reactions involving rash and tongue swelling, a close temporal association between the events and oseltamivir treatment was suggested. Ventricular arrhythmias were reported in 3 patients and atrial fibrillation was reported in 1 patient. Except for the case of atrial fibrillation for which the reporter suspected the event to be possibly related to oseltamivir, all other cases were considered difficult to evaluate due to confounding factors. Seizures were reported in 3 cases and confusion was reported in 3 cases. In these patients, seizures or confusion could be related to the underlying viral illness and/or fever, although in 2 cases a positive temporal association with oseltamivir treatment was suggested. In summary, in the majority of reports there was insufficient information to allow an adequate assessment of causality. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Nevertheless, since these events reported through health professionals after marketing of the drug were potentially serious and could be potentially related to the drug, it is recommended that they be included in the package insert of oseltamivir.

C. Subgroup Analyses

I. Gender

In the pooled seasonal prophylaxis studies, the background incidence of nausea in the placebo group was generally higher for women than for men. The increase in reports of nausea by oseltamivir recipients compared with placebo recipients was also greater for female than for male subjects. There was a similar trend, but to a lesser degree, with regard to the incidence of headache. Because the number of subjects who vomited was low, it is difficult to see a difference between the sexes for this event. A similar gender difference was observed in the post-exposure prophylaxis study. In this review, only the gender analysis in the pooled seasonal prophylaxis studies was selected to be presented in Table 20.

Table 20: Incidence of Selected Adverse Events by Sex
(WV15673, WV15697, WV15708, WV15825)

	Female		Male	
	Placebo (n=620)	Oseltamivir (n=627)	Placebo (n=353)	Oseltamivir (n=359)
Nausea	41(6.6%)	76(12%)	9(2.5%)	15(4.2%)
Headache	185(29.8%)	205(32.7%)	58(16.4%)	81(22.6%)
Vomiting	7(1.1%)	22(3.5%)	2(0.6%)	5(1.4%)

Source: Table 27, Vol 19, page 52.

2. Age

Fifty-three percent of subjects in the pooled seasonal prophylaxis studies were aged 18-64 year and 47% were of ≥ 65 years of age. All elderly subjects (≥ 65 years of age) were from studies WV15708 and WV15825. In addition, a total of 207 adolescent subjects (13-17 years of age) were recruited in the post-exposure prophylaxis study. The following table summarizes the incidence of selected adverse events in elderly, adult and adolescent subjects.

Table 21: Summary of Selected Adverse Events According to Age
(WV15673, WV15697, WV15708, WV15825)

	≥ 65 yrs		18-64yrs		13-17yrs	
	Placebo (n=453)	Oseltamivir (n=467)	Placebo (n=520)	Oseltamivir (n=519)	Placebo (n=96)	Oseltamivir (n=111)
Nausea	13 (2.9%)	29(6.2%)	37(7.1%)	62(11.9%)	2(2.1%)	4(3.6%)
Headache	41(9.1%)	62(13.3%)	202(38.8%)	224(43.2%)	1(1.0%)	2 (1.8%)
Vomiting	5(1.1%)	13(3%)	4(0.8%)	13(2.5%)	2(2.1%)	1(0.9%)

Source: Table 33, vol.19, page 57; Appendix 32, vol. 20, page 74.

In general, the adverse event profile of osletamivir in the elderly subjects was similar to that in younger adults. However, the overall incidence of both nausea and headache was lower in the elderly group than in the younger adults. The reported intensity of the adverse events was also less severe in the elderly subjects than in younger adults. The pattern of adverse experience in the post-exposure prophylaxis was similar to that in the younger adults. However the number of subjects reporting any adverse event in the adolescent group was too small to draw any meaningful comparisons.

3. Race

Most study subjects were Caucasian. Because other racial groups were not represented in the studies in sufficient numbers, no analysis according to race was performed.

4. Renal Function

Oseltamivir is eliminated primarily by renal excretion of the active metabolite Ro64-0802, and reduced renal clearance causes increased exposure to the compound. In the pooled seasonal prophylaxis studies, 31 subjects were found to have an estimated creatinine clearance of less than 30 ml/min. The following table summarizes the incidence of the selected adverse events in subjects with varying degrees of renal dysfunction as measured by the estimated creatinine clearance.

Table 22: Summary of Adverse Events According to Renal Function
(WV15673, WV15697, WV15708, WV15825)

Estimated Creatinine Clearance	<30ml/min	30-60 ml/ml	60-90 ml/min	>90 ml/min
Placebo (n=973)	N=14	N=276	N=212	N=462
Nausea	0	9(3.3%)	15(7.1%)	26(5.6%)
Headache	4(28.6%)	28(10%)	42(19.8%)	169(36.6%)
Vomiting	0	3(1.1%)	3(1.4%)	3(0.6%)
Oseltamivir(N=986)	N=17	N=281	N=207	N=474
Nausea	2(11.8%)	18(6.4%)	13(6.3%)	58(12.2%)
Headache	2(11.8)	38(13.5%)	57(27.5%)	187(39.5%)
Vomiting	2(11.8%)	7(2.5%)	6(2.9%)	12(2.5%)

Source: Table 34, vol. 19, page 59.

In subjects with the most impaired renal function (<30 ml/min of creatinine clearance), there seems to be an increase in the incidence of nausea and vomiting. However, there is no clear exposure-response relationship with nausea. Subjects with the most impaired renal function had the highest incidence rate of vomiting (11.8%).

In addition, two open-label pharmacokinetic studies (WP 15648 and PP15974) in subjects with renal impairment were conducted. Both studies were reviewed in detail by Dr. Jenny H. Zheng, Pharmacokinetics Reviewer. In study WP15648, 20 subjects with various degrees of renal dysfunction received oseltamivir 100 mg bid for 5 days. In study PP15974, 24 dialysis patients with end stage renal disease (measured serum creatinine <10 ml/min) received a single 75 mg dose of oseltamivir. No placebo group was included in either study. The following Table summarizes the incidence of the 3 selected adverse events for these 2 studies.

Table 23: Summary of Adverse Events According to Renal Function
(WP15648)

Creatinine Clearance	<30ml/min	30-60 ml/ml	60-90 ml/min	>90 ml/min
WP15648 (n=20)	N=5	N=5	N=5	N=5
Nausea	2	0	0	2
Headache	1	1	1	1
Vomiting	0	1	0	0

Source: Appendix 35, vol. 20

Table 24: Summary of Adverse Events in Dialysis Patients
(creatinine clearance <10 ml/min) (PP15974)

Total # of patients n=24	On-treatment*	Off-treatment**	Total
Nausea	1	0	1(4.1%)
Headache	3	1	4(16%)
Vomiting	1	2	3(12%)

*On-treatment was defined as <2 days after study medication.

** Off-treatment was defined as >2 days after study medication.

Both studies were small and not placebo-controlled. The pattern of adverse events seen in study WP15648 was consistent with that seen in other studies with oseltamivir. However, the numbers of subjects in each category were too small to draw any conclusions. For study PP15974, the applicant recorded the occurrence of adverse events according to arbitrarily defined on- and off-treatment periods. On-treatment was defined as <2 days after study medication and off-treatment was defined as >2 days after study medication. This arbitrary distinction may not be warranted as the concentration-time profile of oseltamivir in subjects on dialysis predicted that, after a single dose of 75 mg of oseltamivir, patients could have a total drug exposure longer than 5 days. Given that all 'off-treatment' events were recorded on days 4-8, these events could have been considered as 'on-treatment' events as well. When the events from both 'periods' were combined, patients with end stage renal disease (serum creatinine clearance <10 ml/min) had the highest incidence of vomiting (12%), similar to that seen in pooled seasonal prophylaxis dataset (Table 22) for the group with estimated serum creatinine clearance of <30 ml/min.

Since the single 75 mg dose of oseltamivir provided a total exposure over a 92-96 hour period that was comparable to those at steady-state in patients with serum creatinine <30 ml/min receiving 75 mg q.d. for 5 days (which is the current labeling recommendation for this group of patients), the applicant proposed a single 75 mg dose of oseltamivir as the recommended dose in treatment of influenza in patients with end-stage renal disease.

The applicant's recommendation has raised the following safety concerns:

- In dialysis patients, peak concentrations of Ro64-0802 following a single 75 mg dose were approximately 5-fold higher than steady-state peak concentrations in patients with normal renal function. The AUC_{0-92h} of Ro 64-0802 in dialysis patients was also 5-fold higher than the corresponding value in subjects with normal renal function. Both parameters were deemed too high in subjects with serum creatinine of <10 ml/min.
- The safety data indicated that, under the recommended dosing regimens, the incidence rates of vomiting were high in subjects with serum creatinine clearance of <10 ml/min or 10-30 ml/min.

For the reasons discussed above, the applicant has agreed to revisit the dosing adjustment recommendations for subjects with impaired renal function. The applicant later responded in two facsimiles (11/6/00 and 11/9/00) stating that the currently labeled dosing recommendations for patients with <10 ml/min and 10-30 ml/min of serum creatinine clearance receiving oseltamivir for the treatment of influenza would remain unchanged. For subjects with creatinine clearance between 10 and 30 ml/min taking oseltamivir for prophylaxis the applicant proposed a dose of 75 mg alternate days. However, for patients on dialysis the applicant do not feel there are sufficient data to recommend a dose for prophylaxis.

5. Pediatric Population

The safety of oseltamivir administered to children aged 1 to 12 years is presented in _____ “Tamilfu oral suspension for treatment of influenza in pediatric patients” which is currently under review.

6. Drug-Drug Interactions

Three classes of drug were examined in subjects enrolled in studies WV15708 and WV15825 : angiotensin converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), and thiazides. For each, the three selected adverse events; nausea, headache and vomiting were compared between the subjects who were taking the drug on entry to the study and the subjects who were not. Furthermore, differences between the oseltamivir group and the placebo group were compared between the subjects who took the drug and those who did not in order to discern potential clinically relevant drug interactions.

At the start of the study dosing period, of the 1959 subjects in the database, 203 (10.3%) were on ACE inhibitor therapy, 396(20.2%) were taking an NSAID, and only 55 (%) were taking thiazide.

The results are summarized as the following:

- ACE Inhibitors

The three selected adverse events: nausea, headache, and vomiting, were reported with similar or lower frequency by subjects taking ACE inhibitors than by the subjects who were not, in both treatment groups.

- NSAID

Nausea was increased in the subjects taking NSAIDs, as compared with those who were not, and the difference between active drug and placebo was approximately 2-fold in both subsets of subjects. The incidence of vomiting was similar in subjects exposed to NSAIDs and subjects not exposed. Headach was reported more often in the NSAID subgroup. The difference between oseltamivir and placebo was similar to the subjects who took NSAIDs and the subjects who did not, suggesting a drug interaction between oseltatmivir and NSAIDs is unlikely. The NASID may have been taken for headache in most subjects, resulting in an increased number of reporting.

- Thiazides

Because the number of subjects who were taking thiazides was low, it is not possible to draw firm conclusions from these data. In general, the three

selected adverse events were not more frequent in subjects receiving thiazides, compared with subjects who did not.

7. Emergence of resistant virus to oseltamivir

The number of subjects shedding virus, while receiving oseltamivir, at sufficient levels to allow for phenotypic assay of the neuraminidase was small in all prophylaxis studies. There were 5, 2, and 2 such individuals in study WV15799, WV15673 + WV15697, and WV15825, respectively. All neuraminidase samples from these patients had IC₅₀ values for inhibition by Ro 64-0802 consistent with wild type N2 neuraminidase. Because the number of samples was small, no conclusion can be made on the emergence of resistant virus from the prophylaxis studies of oseltamivir.

VIII. Review of Package Insert

The applicant's originally proposed package insert of Tamiflu including the prophylaxis indication was discussed extensively with the division prior to completion of this review. The approved package insert resulted from substantial interaction between the applicant and the division, and adequately addresses the concerns from the review team.

IX. Conclusions

The protective efficacy of oseltamivir 75 mg qd in the prophylaxis of influenza in community and the household settings was demonstrated in 2 seasonal prophylaxis and 1 post-exposure prophylaxis study. All studies demonstrated that oseltamivir reduced the incidence of laboratory-confirmed clinical influenza type A and type B.

Overall, oseltamivir 75 mg qd for the prophylaxis of influenza A and B was well tolerated for up to 42 days and possesses a safety profile similar to that in seen in treatment studies. The safety of oseltamivir has been demonstrated in subjects aged 13 years and above and in the elderly (≥ 65 years).

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XII. Appendix I. Secondary Complications

	COA D	Diagnosis	Symptoms/ Signs	Auscultatory findings	Chest x-ray	Culture	Hospitalization	Antibiotic
Placebo								
Case1: 23632/ 4710	+	Pneumonia	Flu-like symptoms +chest pain, dyspnea, purulent sputum	Not recorded	Bilateral infiltrates	Not done	No	Levofloxac in
Case2: 23632/ 4719	-	Pneumonia	Tachycardia, dyspnea, purulent sputum, Cough	Right side rhonchi mid/lower +	Right infiltrate +	Not done	No	Levofloxac in
Case3: 23665/ 5706	+	Worsening of bronchitis, sinusitis	Nasal congestion , cough x10days, tearing,	Not recorded	Not done	Not done	No	No
Case4: 23665/ 5718	-	Bronchitis	Cough x3 days	Right upper/lower bronchial breath sounds +	Not done	Not done	No	No
Case5: 23675/ 4941	+	Acute bronchitis	Cough x14 days, non- purulent sputum	Bilateral involvement	No infiltrate seen	Not done	No	Azithromyc in
Case6: 23696/ 8415	-	Acute bronchitis	No cough, unclear how this case was discovered	Bilateral lungs bronchial breath sounds +	Not done	Not done	No	Amoxicilli n
Case7: 23696/ 8416	-	Pneumonia	Cough, headache, dyspnea, non- purulent sputum	Bilateral lungs bronchial breath sound +	Infiltrate+	Not done	No	amoxicillin
Oseltamivir 75 mg qd								
Case8: 23696/ 8405	+	Acute bronchitis	Cough x26 days	Bilateral lungs bronchial breath sound +	Not done	Not done	No	Cefuroxime

BACKGROUND and SUMMARY: On October 27, 1999, Hoffmann-La Roche Inc. received FDA approval of Tamiflu™ (NDA # 21-087) for the treatment of uncomplicated acute illness due to influenza infections in adults who have been symptomatic for no more than two days. Subsequently on May 22, 2000 Hoffmann-La Roche Inc. submitted this supplemental NDA #21-087 SE1-002, requesting approval of Tamiflu™ for the prophylaxis of influenza in adults and adolescents of 13 years and older.

In support of the prophylaxis indication for Tamiflu™, the applicant submitted data from several clinical studies. The studies include prophylaxis of naturally acquired influenza involving subjects in community settings, nursing home settings, and in settings of family transmission (Table 1). In addition, studies on the prophylactic effect of Tamiflu™ in human volunteers experimentally infected with attenuated strains of either influenza virus types A or B were also provided (Tables 2).

Drug nomenclature: Tamiflu™ is the formulated drug product for the treatment and prophylaxis of influenza. Oseltamivir phosphate is the ethyl ester prodrug that is in the formulated drug product. Oseltamivir carboxylate is the active pharmaceutical ingredient that is formed by ester hydrolysis of the prodrug. In nonclinical virology studies, the prodrug oseltamivir phosphate was used in the determination of antiviral activity, efficacy in animal models and the proof of prophylaxis studies involving experimental infection of human volunteers with attenuated influenza virus type A or B. In the neuraminidase (NA) enzyme susceptibility assays for the determination of resistance, the active pharmaceutical ingredient, oseltamivir carboxylate was used.

In the initial Tamiflu™ application for the treatment of adult influenza (NDA 21-087), Hoffman La Roche Inc. submitted detailed virology study reports. The submitted virology studies included: the mechanism of action of oseltamivir; anti-neuraminidase activity in vitro; anti-viral activity in vitro; efficacy of oseltamivir in influenza virus infected mice and ferrets; phenotypic resistance due to decrease in the sensitivity of the NA activity to oseltamivir; genotypic resistance due to mutations in the NA gene; resistance in human influenza virus challenge studies; resistance in naturally acquired infection; cross-resistance to other neuraminidase inhibitors; and the effect of Tamiflu™ on humoral immune responses. The microbiology submission of the adult treatment indication was reviewed in detail (please refer to the microbiology review of NDA21-087) and those studies are not repeated in this review.

In the clinical studies of this supplemental NDA for the prophylaxis of Tamiflu™, the applicant attempted to collect influenza virus samples from subjects on prophylactic Tamiflu™ and subsequently infected with influenza virus. Influenza virus samples collected either from nasal or throat swabs were expanded by propagation in MDCK cells

and the virus harvested from the cell supernatant was analyzed for the presence of resistant variants, i.e., influenza virus with a decrease in the susceptibility of its NA to the inhibitor oseltamivir carboxylate.

Based on the resistance data of the influenza virus samples collected from Tamiflu™ treated subjects, the applicant made additions to the microbiology section of their draft label. In this review, the applicant's data on the emergence of resistance in influenza virus was evaluated and appropriate revisions to the microbiology portion of the label were recommended. Prior to summarizing the resistance data, the assay for the determination of NA activity and measures for phenotypic and genotypic resistance are briefly summarized.

Assay for NA activity: Influenza virus neuraminidase is a glycohydrolase. The enzyme cleaves the terminal sialic acid residue found on the cell surface of an array of glycoproteins, glycolipids, and oligosaccharides. (The cell surface sialic acids are also the receptors to which the influenza virus hemagglutinin attaches and penetrates into the cell). In the determination of the NA enzyme assay, the applicant used a _____

Phenotypic resistance: Phenotypic resistance to oseltamivir was defined as a measurable decrease in the in vitro susceptibility of the NA activity. Resistance to the inhibitor is said to occur when the IC_{50} of the post treatment virus NA was greater than the mean + 2SD of the pre-treatment influenza virus NA. The incidence of resistance was calculated based on the number of phenotypically resistant virus cultures in the numerator and a denominator reflecting the total number of matched pre and post-treatment influenza virus cultures.

Genotypic resistance: To identify the genotype responsible for the reduced NA susceptibility to oseltamivir carboxylate, the nucleotide sequence of the NA gene of the matched isolates was determined. Viral RNA of the pre-treatment NA-sensitive virus isolates and the post-treatment NA-resistant virus isolates was converted into DNA by RT-PCR and the nucleotide sequence of the DNA encompassing the NA active site (amino acids 100-400) was determined. Change in the nucleotide sequence that result in amino acid substitution of the post-treatment resistant virus isolate as compared to the pre-treatment NA-sensitive control virus nucleotide sequence indicates the genotypic

changes and the amino acid(s) that contribute to the NA mutations and genotypic resistance to the NA.

The clinical studies of naturally acquired influenza infection conducted in support of the prophylaxis indication for Tamiflu™ are summarized in Table 1. The Table shows the age of the study subjects, duration of prophylaxis, the number of subjects taking prophylactic Tamiflu™ and the number of evaluable influenza virus samples from Tamiflu™ treated patients in different clinical studies involving community prophylaxis, nursing home prophylaxis, and family transmission prophylaxis. The applicant was able to collect post treatment virus samples from 9 individuals. Assay of NA susceptibility of these 9 virus samples showed that the IC₅₀ of oseltamivir carboxylate was within the range of the NA activity of wild type influenza virus isolates suggesting no detectable changes in the sensitivity of these isolates. One of the reasons for the low virus recovery may be because of the low overall incidence of influenza infection due to the prophylactic effect of Tamiflu™.

Table 1. Studies of prophylaxis of naturally acquired influenza

Study	Description	Age(yr.)	Duration	# receiving Tamiflu™ treatment	Evaluable samples from treated patients for NA resistance
WV15693 WV15697	Community prophylaxis	18-65	42 days	1040	2
WV15825 WV15708	Nursing home prophylaxis	≥ 65	42 days	466	2
WV 15799	Family transmission prophylaxis	≥ 13	7 days	494	5

In the microbiology portion of the label, the applicant included a statement that, "in clinical studies . . ."

In the clinical studies on the prophylaxis Tamiflu™ the number of evaluable influenza virus samples (n=9) obtained was too small a sample size to address the issue of emergence of resistance in prophylaxis. Therefore, the applicant was advised to modify their statement in the label to read as, "in clinical studies of post exposure and seasonal prophylaxis, determination of resistance was limited by the low overall incidence rate of influenza infection and prophylactic effect of TAMIFLU."

The experimental influenza virus infection studies of human volunteers conducted in support of the proof of concept for the prophylaxis indication of oseltamivir phosphate are summarized in Table 2. The table shows the age of the study volunteers, the duration

of prophylaxis, the number of volunteers taking prophylactic oseltamivir phosphate and the number of evaluable influenza virus samples from oseltamivir treated volunteers in the two experimental studies involving infection with attenuated strains of influenza virus type A or B.

Table 2. Studies of prophylaxis of experimentally induced influenza

Study	Description	Age(yr.)	Duration	# receiving Oseltamivir phosphate	Evaluable samples from treated patients for NA resistance
GS97-802	Influenza A/ Texas/ 36/91 (H1N1) [@]	18-40	5 days	24	0
NP15 757	Influenza B/ Yamagata/16/88 [*]	18-65	7 days	39	22

@ = Intranasally inoculated with 10⁶ tissue culture infectious dose (TCID)

* = Intranasally inoculated with 10⁷ TCID

In the experimental influenza infection studies, the prodrug, oseltamivir phosphate was orally administered approximately 24 hours prior to infection. In the test subjects infected with attenuated influenza virus A there was no virus recovery in the post treatment nasal wash samples and the NA assay could not be conducted to evaluate for the emergence of resistance. In the test subjects infected with attenuated influenza virus B, the virus was recovered from the nasal washes of 22 subjects. The sample size (n=22) analyzed for NA susceptibility is inadequate for a conclusive statement on the emergence of resistance in the healthy volunteers infected with an attenuated strain of influenza virus type B and treated with oseltamivir phosphate at 24 hours after infection.

Draft microbiology label:

MICROBIOLOGY: *Mechanism of Action:* Oseltamivir is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate. The proposed mechanism of action of oseltamivir is via inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

Antiviral Activity In Vitro: The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of oseltamivir carboxylate required for inhibition of influenza virus were highly variable depending on the assay method used and the virus tested. The 50% and 90% inhibitory concentrations (IC₅₀ and IC₉₀) were in the range of 0.0008 μM to >35 μM and 0.004 μM to >100 μM, respectively (1 μM=0.284 μg/mL). The relationship between the in vitro antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established.

Drug Resistance: Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have been recovered in vitro by passage of virus in the presence of increasing concentrations of oseltamivir carboxylate. Genetic analysis of these isolates showed that reduced susceptibility to oseltamivir carboxylate is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both.

In challenge studies in the treatment of human subjects infected with influenza virus, 3% (3/102) of the post-treatment isolates showed emergence of influenza variants with decreased neuraminidase susceptibility to oseltamivir carboxylate. Genotypic analysis of these variants showed a specific mutation in the active site of neuraminidase compared to challenge virus.

In clinical studies of post exposure and seasonal prophylaxis, determination of resistance was limited by the low overall rate of infection and prophylactic effect of TAMIFLU.

In clinical studies in the treatment of naturally acquired infection with influenza virus, 1.3% (4/301) of post-treatment isolates showed emergence of influenza variants with decreased neuraminidase susceptibility to oseltamivir carboxylate.

Genotypic analysis of these variants showed a specific mutation in the active site of neuraminidase compared to pretreatment isolates. The contribution of resistance due to alterations in the viral hemagglutinin has not been fully evaluated.

Cross-resistance: Cross-resistance between zanamivir-resistant influenza mutants and oseltamivir-resistant influenza mutants has been observed in vitro.

Due to limitations in the assays available to detect drug-induced shifts in virus susceptibility, an estimate of the incidence of oseltamivir resistance and possible cross-resistance to zanamivir in clinical isolates cannot be made. However, one of the three oseltamivir-induced mutations in the viral neuraminidase from clinical isolates is the same as one of the three mutations observed in zanamivir-resistant virus.

Insufficient information is available to fully characterize the risk of emergence of TAMIFLU resistance in clinical use.

Immune Response: No influenza vaccine interaction study has been conducted. In studies of naturally acquired and experimental influenza, treatment with TAMIFLU did not impair normal humoral antibody response to infection.

Influenza Challenge Studies: Antiviral activity of TAMIFLU was supported for influenza A and B by experimental challenge studies in volunteers who received intranasal inoculations of challenge strains of influenza virus. These subjects received TAMIFLU either 24 hours following or 24 hours before virus challenge.

CONCLUSIONS: To determine the efficacy of Tamiflu™ in preventing naturally occurring influenza illness, three seasonal prophylaxis studies and one post-exposure prophylaxis study in households (Table 1) were conducted. From these clinical studies, the applicant could collect post-treatment influenza virus samples from only 9 individuals. Assay of NA susceptibility of these 9 virus samples showed that the IC₅₀ of oseltamivir carboxylate was within the range of the NA activity of wild type influenza virus isolates suggesting no detectable changes in the sensitivity of these isolates.

One of the reasons for the low virus recovery may be because of the low overall incidence of influenza infection due to the prophylactic effect of Tamiflu™. Therefore, in the microbiology portion of the label we added a statement that reads, “in clinical studies of post exposure and seasonal prophylaxis, determination of resistance was limited by the low overall incidence rate of influenza infection and prophylactic effect of TAMIFLU.”

The combined prophylactic and therapeutic use and probable intermittent use of Tamiflu™ could result in long periods of exposure thereby increasing the chance for the emergence of Tamiflu™ resistant variants. In addition, combination of prolonged exposure and higher rates of replication in special populations such as the elderly, children, and the immunocompromised may further increase the emergence of drug-resistant influenza variants. In these situations not only Tamiflu™ resistant variants emerge, but also the potential exists for the emergence of antigenic variants because the NA inhibitors are facile inducers of mutations in the most antigenic molecule of the influenza virus, the HA.

In consideration of some of anticipated genetic variations and possible antigenic variants with unpredictable consequences, the applicant is requested to address some of the issues as a part of the phase 4 commitments.

The primary means of scoring for the emergence of resistance to Tamiflu™ was on the basis of a decrease in the in vitro susceptibility of influenza virus NA enzyme activity in the post-treatment virus isolates compared to the pre-treatment isolates of the same patient, i.e., enzyme resistance. It is well recognized that influenza virus escapes inhibition by NA inhibitors not only by mutations in the target NA but also by mutations in other genes such as the viral HA. Therefore, it is important to evaluate for the antiviral resistance by directly assaying for changes in the antiviral sensitivity of the whole virus

to the drug in cell culture i.e., antiviral resistance. The applicant should be requested to proactively develop a cell culture based assay (or other appropriate assays) that can support the replication of influenza virus to determine the antiviral resistance in addition to the current method that measures the NA enzyme resistance.

The initiation of influenza virus infection and the viral spread is mediated by the dynamic interactions between the receptor (sialic acid) binding activity of viral HA and the receptor destroying activity of the viral NA. Studies on the emergence of resistance to NA inhibitors showed that resistance occurs both in vitro and in vivo, and that the resistance was mediated by mutations in the viral NA or HA or both. Therefore, the measures for the phenotypic and the genotypic changes should include both the NA and HA, to reflect the incidence of resistance. The resistance surveillance studies should include the genotyping of the NA and the HA genes (both HA1 and HA2 portions of the HA molecule) of the resistant isolates.

The approval of prophylaxis indication for Tamiflu™ was on the basis that the drug provides protective effects for the duration over which the individual takes the drug and when influenza virus is circulating in the communities. The applicant conducted preventive therapy over a period of up to 42 days. The prophylactic and therapeutic use of Tamiflu™ results in exposure of the virus to the drug over a long period, thereby increasing the chances for emergence of influenza variants resistant to Tamiflu™. The incidence of resistance under prophylactic conditions could potentially be greater in some populations such as the elderly, children, and the immunocompromised. Indeed Tamiflu™ resistant influenza variants have been recovered from patients treated with Tamiflu™.

NA resistant variants of influenza virus could be either drug-dependent or drug-nondependent. The drug-nondependent viruses can grow with about the same efficiency in the presence or in the absence of the drug. These types of drug-nondependent influenza virus variants have been recovered both from in vitro as well as from patients treated with Tamiflu™. Additional studies on the emergence of resistance should be performed to characterize the resistant variants and the clinical implications of the drug-nondependent resistant influenza virus.

Drug-dependent viruses on the other hand primarily show their effects in the presence of the drug (i.e., enhanced replication and the effects of replication) and not in the absence of the drug. In vitro studies with NA inhibitors of influenza virus have demonstrated that NA inhibitor dependent influenza variants emerge in vitro [Ref: McKimm-Breschkin, J.L. et al., (1996) *Antimicrob. Agents Chemother.* 40, 40-46]. These drug-dependent influenza virus variants in addition to being drug-dependent have acquired altered growth

properties (i.e., increases in the rate of virus replication and virus yield), and altered cytotoxic properties (i.e., increase in both plaque number and plaque size).

In view of the observed emergence of drug-dependent variants that show altered biological properties and in consideration of the prolonged exposure in prophylaxis and treatment, it is important to investigate for the potential emergence of drug-dependent variants in Tamiflu™ exposed subjects. In addition, characterization of the molecular and biological properties of the drug-dependent variants should be determined.

In vitro studies on the NA-resistant influenza virus variants for the assessment of potential cross-resistance among the class of NA-inhibitors showed cross-resistance among them. The cross-resistance could be due to mutations either in the targeted NA gene or the non-targeted HA gene. Mutations that decrease the affinity of HA to its receptor sialic acid make the virus less dependent on NA activity and thus less sensitive to all NA inhibitors as a class. Resistance mutations of this type have been reported in influenza B virus that was derived from NA inhibitor treated patients. Therefore, it is important to carryout additional studies to assess class cross-resistance among the NA inhibitors, due to mutations in the targeted NA and the non-targeted HA genes.

RECOMMENDATION: With respect to microbiology, this application is supported. However, in consideration of the anticipated genetic variation due to prolonged exposure to Tamiflu™ and the potential for the emergence of antigenic variation, the applicant is reminded to address any outstanding Phase 4 commitments related to the development of resistance and previously agreed to on October 25,1999. In addition, the sponsor is requested to address the following Phase 4 commitment.

Phase 4 commitment: Please explore the isolation, characterization, and clinical implications of oseltamivir-dependent influenza virus variants.

(S)

Narayana Battula, Ph.D.
Microbiologist

Concurrence:

HFD 530/Assoc. Dir.

(S)

HFD 530/TLMicro

Distribution:

Original IND

HFD-530/MO

HFD-530/Division File

HFD-530/TLMicro

HFD-530/RMO: Carmouze, G.

HFD-530/Reviewer Micro

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 14, 2000

FROM: Antoine El-Hage, Ph.D./Karen M. Storms
Good Clinical Practice II, HFD-47
Division of Scientific Investigations

SUBJECT: **Clinical Inspection Summary - NDA 21-087/SE1-002**

TO: Grace Carmouze, Project Manager
Teresa Wu, M.D., Medical Reviewer
Division of Antiviral Drug Products (HFD-530)

APPLICANT: Hoffmann-LaRoche

DRUG: Tamiflu™ (oseltamivir phosphate) 75 mg

CHEMICAL CLASSIFICATION: 6

THERAPEUTIC CLASSIFICATION: P

INDICATION: Prophylaxis treatment of Influenza in adults

CONSULTATION DATE: June 23, 2000

DIVISION ACTION GOAL DATE: October 4, 2000

ACTION GOAL DATE: November 22, 2000

I. BACKGROUND

Oseltamivir phosphate, a neuraminidase inhibitor has shown specific inhibition activity of both Influenza A & B in tissue culture assays and human studies demonstrating the validity of neuraminidase inhibition as a clinically useful intervention to treat influenza infection. Clinical studies were conducted with oseltamivir phosphate and a marketing application was submitted to FDA for review.

These sites were essential for approval because this supplement provides for a prophylaxis indication. The primary efficacy parameter in all prophylaxis studies was the incidence of laboratory confirmed clinical influenza (influenza illness meeting the case definition). Laboratory confirmed clinical influenza was defined as: oral temperature ≥ 99.0 plus at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one constitutional

symptom (aches and pains, fatigue, headache, chills/sweats), all recorded within 24 hours plus laboratory confirmation of influenza infection.

II. RESULTS

	<u>City</u>	<u>State</u>	<u>IN</u>	<u>Assigned</u>	<u>Action</u>	<u>Reviewer</u>	<u>Class</u>
* Schwartz	Miami	FL	DA	10-JUL-00	13-NOV-00	AEH	VAI
Harper	Raleigh	NC	DA	10-JUL-00	18-AUG-00	AEH	VAI
Hayden	Charlottesville	VA	DA	10-JUL-00	12-OCT-00	AEH	VAI

* H. Schwartz, M.D. – WV15799

Review of this site's inspection is based solely on Form FDA-483. This site enrolled 73 subjects. The inspection revealed the following protocol violation: lack of source documentation for repeat laboratory tests due to elevated WBC, neutrophil and monocyte results for one subject. In addition, day 1, 2, and 3 temperatures for one subject were changed on the case report form without an explanation as to why these changes were made. Data appears acceptable.

Wayne Harper, M.D. – WV 15825

This site screened 58 subjects and enrolled 45. All subjects signed informed consents prior to study procedures. The inspection revealed that there were discrepancies between what was reported in the adverse event data listing and the corresponding subject diaries for seven subjects. In addition, there were changes made in two subjects' diaries without initials or dates to indicate the person(s) responsible for making the changes or the reasons for the changes. Data appear acceptable.

Frederick Hayden, M.D. – WV15673

This site enrolled 434 subjects, 26 of 434 subjects' records reviewed. There was adequate documentation to assure that all audited subjects did exist and available for the duration of their participation in the study. Informed consents were reviewed for 99 of the 434 subjects enrolled. The inspection revealed failure to perform required laboratory tests; failure to report serious adverse events to the sponsor as required by the protocol; and inadequate and inaccurate records. There was no underreporting or deaths at this site. Three serious adverse events were reported at this site, i.e., one subject was hospitalized due to basal skull fracture, one subject developed breast cancer, and one subject became pregnant. Data appear acceptable.

Limitation of the inspections – none

No follow-up actions are planned.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The three requested inspections have been completed. No objectionable conditions were found which would preclude use of the data submitted in support of the pending application.

- * Should the EIR for Dr. Schwartz' site contain additional information that would change our recommendation regarding study data, you will be informed.

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviation(s) from regulations. Data acceptable

VAIr = Deviation(s) from regulations, response requested. Data acceptable

OAI = Significant deviations for regulations. Data unreliable/unacceptable

Pending = Inspection not completed

/S/

Antoine El-Hage, Ph.D.

Branch Chief

Good Clinical Practice II, HFD-47

cc:

NDA #21-087/SE-002

HFD-45

HFD-47/KMS

HFD-47/AEH

HFD-47/rf/cf

HT 0-030/B. Jarmouze



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-087/S-002

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

JUN 1 2000

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

Dear Dr. Taylor:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: TAMIFLU™ (oseltamivir phosphate) Capsules

NDA Number: 21-087

Supplement Number: S-002

Date of Supplement: May 22, 2000

Date of Receipt: May 22, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on July 21, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Anthony W. DeCicco
Supervisory Consumer Safety Officer
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research



November 17, 2000

Food and Drug Administration
Division of Antiviral Drug Products (DAVDP), HFD-530
Center for Drug Evaluation and Research, ODE IV
First Floor Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850

Dear Reviewers:

**Re: NDA 21-087/S-002 - Tamiflu™ (oseltamivir phosphate) Capsules, Prophylaxis of Influenza
Estimated Timelines for Deferral of Pediatric Rule Requirement**

Please refer to the above sNDA and to our request of July 11, 2000 for a deferral of the Pediatric Rule requirements for this application. Per your request, the following is our estimated timeline for providing a final study report for a pediatric prophylaxis study:

- Discuss proposed plans/study design in 2Q01
- Trial to run in 02-03 winter
- Provide final study report by the end of 2004

These timelines are estimated based on the fact that we need to see the results of the FIT protocol before proceeding with anything (this protocol must enroll fully this flu season for the results to be available later in 2001 and these timelines to be possible). They also reflect some reservations that we have regarding study design and the ability to enroll a study, which is the reason for our planned discussions before beginning.

We trust that this provides the information that you need. Please do not hesitate to contact the undersigned if you have any questions.

Sincerely,

HOFFMANN-LA ROCHE INC.

Barbara S. Taylor, Ph.D.
Program Director
Drug Regulatory Affairs
(973) 562-3664 - Phone
(973) 562-3700 - Fax

BT/JS
HLR No. 2000-2865

Desk Copy: Grace Carmouze – via telefax

November 16, 2000

Food and Drug Administration
 Division of Antiviral Drug Products (DAVDP), HFD-530
 Center for Drug Evaluation and Research, ODE IV
 First Floor Document Room
 9201 Corporate Blvd.
 Rockville, Maryland 20850

Dear Reviewers:

**Re: NDA 21-087/S-002 - Tamiflu™ (oseltamivir phosphate) Capsules, Prophylaxis of Influenza
 Recommended Labeling Comments and Postmarketing Commitments**

Please refer to the above sNDA and to your two separate faxes of November 15, 2000 conveying your proposals for postmarketing commitments for the prophylaxis indication for TAMIFLU and your comments on the draft package insert and patient package insert submitted on November 14, 2000. This submission provides the Sponsor's responses to both of these communications.

Postmarketing Commitments

The Sponsor accepts your proposed commitments and with this submission we are providing rough estimates of timelines for addressing them.

<i>Commitment</i>	<i>Estimated Timeline</i>
1. Please investigate the effectiveness and safety of oseltamivir for the treatment and prevention of influenza infection in immunocompromised patients. In this population the emergence of resistant viruses should be closely monitored.	Discuss plans with Agency by end 2Q01; target completion by end 2003.
2. Please study the pharmacokinetics and safety of oseltamivir, given at the proposed dosing regimens based on simulations, in end-stage renal dialysis subjects.	Discuss plans with Agency by end 2Q01; target completion by end 2003.
3. Please submit a final study report for the completed study of oseltamivir in subjects with impaired hepatic function.	The study is ongoing; a report is expected by 2Q01.
4. Please submit a final study report for the completed long-term carcinogenicity studies in mice and rats.	Mice: July 31, 2002 Rats: December 19, 2001
5. Please explore the isolation, characterization and clinical implications of oseltamivir-dependent influenza virus variants.	Discuss plans with Agency by end 2Q01.

Labeling Comments

As discussed in our teleconference on November 15, we accept your comments in general and have made changes only to the table on oseltamivir carboxylate exposures in patients with renal impairment. We agree to your request to add the column for the 75 mg once daily dose and to delete the column for the 500 mg twice daily dose. Along with these requested changes we have also deleted the columns for exposures of patients with creatinine clearance of 30-60 ml/min as agreed. As discussed, given the fact that no dose reduction is recommended for this group, we believe that to include them in the table could confuse the medical community.

All other changes requested in your November 15 fax have been made in the attached copies of the package insert (Attachment 1: physician package insert in revision mode; Attachment 2: clean copy of physician package insert; Attachment 3: clean copy of patient package insert). We have also made a minor editorial change to the statement on immunocompromised patients (line 202) as requested by Dr Wu. In the Attachments, all changes from the currently approved package insert are indicated in revision mode and the most recent changes discussed in this submission are highlighted.

Division of Antiviral Drug Products (DAVDP), HFD-530
November 16, 2000
Page 2 of 2

We believe that these changes address all outstanding questions on this package insert and patient package insert. We appreciate and share your commitment to rapid turn-around of any questions, therefore should you have any questions please do not hesitate to contact the undersigned at the numbers provided below.

Sincerely,

HOFFMANN-LA ROCHE INC.

Barbara S. Taylor, Ph.D.
Program Director
Drug Regulatory Affairs
(973) 562-3664 - Phone
(973) 562-3700 - Fax

BT/JS
HLR No. 2000-2851
Attachments

Desk Copy: Ms. Grace Carmouze



Pm

Howard I. Schwartz, M.D.
Miami Research Associates
7500 87th Avenue, SW
Miami, Florida 33176

Food and Drug Administration
Rockville MD 20857

NOV 20 2000

Dear Dr. Schwartz:

Between July 26 and 28, 2000, Mr. Victor Spanioli, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #WV15799) of the investigational drug Tamiflu® (oseltamivir phosphate), performed for Hoffmann-LaRoche, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Spanioli presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. The discussion included protocol deviations and unexplained temperature changes for one subject. We note that you concurred with these observations and have initiated implementation of appropriate changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Spanioli during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

157

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN: 10-58876

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:

inadequate informed consent

inadequate drug accountability

failure to adhere to protocol

inadequate records

failure to report ADRS

other

cc:

HFA-224

HFD-530 Doc.Rm. NDA#21-087/SE1-002

HFD-530 Review Div.Dir.

HFD-530 MO

HFD-530 PM

HFD-45 Reading File

HFD-47 Chron File

HFD-47 GCP File #6036

HFD-47 El-Hage/Storms

HFR-SE250 DIB (Chappell)

HFR-SE2585 Bimo (Torres)

HFR-SE2575 Investigator (Spanioli)

r/d:(AEH)(11/16/00)

reviewed:AEH:(11/16/00)

f/t:mb:(11/17/00)

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Reviewer Note to Rev. Div. M.O.

In this study ("A double blind randomized placebo controlled study of RO64-0796) used for the prevention of clinical influenza post exposure in families). Seventy-two patients were recruited. Review noted violations in protocol (one patient recruited past the time defined in the eligibility criteria) and failure to record information in CRF's (abnormal laboratory findings. Consent was obtained from all subjects; approximately 40 consent forms were reviewed. The issues noted do not jeopardize the integrity of the data. Data appears to be acceptable.



NOV 6 2000

Frederick G. Hayden, M.D.
University of Virginia Health Sciences Center
Room 2153
Jefferson Park Avenue
Charlottesville, Virginia 22908

Dear Dr. Hayden:

Between September 7 and 13, 2000, Ms. Candice Cortes representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #WP 15673D) of the investigational drug Tamiflu™ (oseltamivir phosphate), performed for Hoffmann LaRoche. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

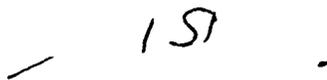
From our evaluation of the inspection report, the documents submitted with that report, and your written response dated October 6, 2000 to the items listed on the Form FDA 483, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Cortes presented and discussed with you her inspectional observations, which included: failure to perform required laboratory tests; failure to report serious adverse events as required by the protocol; and inadequate and inaccurate records.

In addition, we view the statement in the payment section of the consent form used in the study that subjects "...will receive \$300.00 for participating in and completing the study. No payment will be made to you, if you withdraw from the study for personal reasons...." to be an improper procedure. When subjects are to be paid for participating in a study, the payment should be prorated for the subject's actual participation in the study in order to avoid the possibility of coercion.

We trust, as you stated, that implementation of the corrective actions identified in your letter of October 6, 2000, should provide adequate measures to meet FDA regulatory requirements and ensure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Cortes during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Handwritten signature of Antoine El-Hage, consisting of a stylized 'A' followed by 'E-H'.

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 3 – Frederick G.Hayden, M.D.

FEI: 3003102686

Field Classification: Refer to Center

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:

inadequate informed consent

inadequate drug accountability

failure to adhere to protocol

inadequate records

failure to report ADRS as required by protocol

other

cc:

HFA-224

HFD-530 Doc.Rm. NDA# 21-087

HFD-530 Review Div.Dir.

HFD-530 MO (Wu)

HFD-530 PM (Carmouze)

HFD-45 Reading File

HFD-47 Chron File

HFD-47 CIB File #10213

HFD-47 El-Hage/Storms

HFR-CE250 DIB (Wagner)

HFR-CE2535 Bimo Monitor (Gion)

HFR-CE2545 Field Investigator (Cortes)

r/d:KMS:10/31/00

reviewed:AEH:(11/1/00)

f/t:mb:(11/1/00)

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Reviewer Note to Rev. Div. M.O.

- This site enrolled 434 subjects, 26 of 434 subjects' records reviewed. There was adequate documentation to assure that all audited subjects did exist and available for the duration of their participation in the study.
- Informed consents were reviewed for 99 of the 434 subjects enrolled.
- Three serious adverse events were reported at this site. i.e., one subject was hospitalized due to basal skull fracture, one subject developed breast cancer, and one subject became pregnant.



Food and Drug Administration
Rockville MD 20857

AUG 31 2000

Wayne Harper, M.D.
Wake Research Associates
3100 Blue Ridge Road, Suite 200
Raleigh, North Carolina 27612

Dear Dr. Harper:

Between July 24 and 27, 2000, Ms. Barbara Frazier representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # WV15825B) of the drug Tamiflu (oseltamivir phosphate), performed for Hoffmann LaRoche, Ltd. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, documents submitted with that report, and the data listings provided by the sponsor, we conclude that you did not adhere to all pertinent federal regulations and good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Frazier presented and discussed with you and your staff the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to maintain adequate and accurate records in that:
 - a. There were discrepancies between what was reported in the adverse event data listing and the corresponding subject diaries. Subjects 2612, 2614, 2618, 2628, 2646, 2652, and 2658, were reported as having influenza in the adverse event data listing, however, the diaries for subjects 2614, 2618, 2628, 2646, and 2652 document that these subjects did not have the required temperature of $\geq 99.5^{\circ}\text{F}$. In addition, subject 2612 did not have the required temperature and one of the constitutional symptoms and subject 2658 did not have one of the required constitutional symptoms to be diagnosed as having influenza.
 - b. When changes were made, the diaries for subjects 2612 and 2646 were not initialed or dated to indicate the person(s) responsible for making the changes or the reasons for the changes. All corrections made to original diaries should have been initialed and dated to attest for their accuracy.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

Page - 2 - Wanye Harper, M.D.

We appreciate the cooperation shown Investigator Frazier during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

151
Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003068433

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:

inadequate informed consent

inadequate drug accountability

failure to adhere to protocol

inadequate records

failure to report ADRS

other

cc:

HFA-224

HFD-530 Doc.Rm. NDA# 21-087/SE1001

HFD-530 Review Div.Dir.

HFD-530 MO (Wu)

HFD-530 PM (Carmouze)

HFD-45 Reading File

HFD-47 Chron File

HFD-47 CIB File #10171

HFD-47 Reviewer - Elhage

HFD-47 CSO - Storms

HFR-SE150 DIB (Kline)

HFR-SE150 Bimo Monitor (Todd)

HFR-SE150 Field Investigator (Frazier)

r/d:KMS:8/25/00

reviewed:AEH:(8/29/00)

f/t:mb:(8/31/00)

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Reviewer Note to Rev. Div. M.O.

- Fifty eight subjects were screened; 45 randomized; no underreporting or deaths at this site.
- All subjects signed informed consents prior to study procedures. Files reviewed include case report forms, drug accountability records, correspondence, and source documents for each subject including diaries and telephone contact log.
- Data appear acceptable.



MEMORANDUM OF FILING MEETING

Date of Meeting: June 30, 2000

NDA: NDA 21-087/SE1-002

Drug: Tamiflu (oseltamivir phosphate) Capsules

Sponsor/Applicant: Hoffmann-La Roche Inc.

Indication: Prophylaxis of Influenza

Participants: Heidi Jolson, M.D., M.P.H., Division Director
Debra Birnkrant, M.D., Deputy Director
Jeff Murray, M.D., M.P.H., Medical Team Leader
Teresa Wu, M.D., Medical Reviewer
Kellie Reynolds, Pharm.D., Biopharmaceutics Team Leader
Prabu Rajagopalan, Ph.D., Biopharmaceutics Reviewer
Ita Yuen, Ph.D., Pharm/Tox Reviewer
Nara Battula, Ph.D., Microbiology Reviewer
Tom Hammerstrom, Ph.D., Statistical Reviewer
Grace Carmouze, Regulatory Project Manager

Related Documents: IND 53,093, NDA 21-246

Background: Hoffmann-La Roche, Inc. submitted this supplemental NDA on May 22, 2000. This efficacy supplement provides for the prophylaxis of influenza using the approved 75mg capsule. The applicant has paid the user fee and has submitted the Financial Disclosure documentation. This application has been granted a priority review with an action date of November 22, 2000. This meeting was held to determine whether the application is fileable.

Discussion:

Chemistry

This supplement uses the approved 75 mg capsule, therefore there are no Chemistry issues.

Pharmacology/Toxicology

Dr. Yuen concluded that this NDA was fileable. The Division will wait for the applicant to

submit a draft carcinogenicity study report, in Tg.AC transgenic mice, in late October 2000. It was noted that the 2-year carcinogenicity studies would be submitted as part of the phase IV commitments.

Microbiology

Dr. Battula concluded that this NDA was fileable. However, there was concern that the resistance information stated in the proposed label is based on 14 subjects.

Biopharmaceutics/Clinical Pharmacokinetics

Dr. Rajagopalan concluded that this NDA was fileable. Dr. Rajagopalan stated that Dr. Jenny Zheng would finish the review of the supplement.

Statistics

Dr. Hammerstrom concluded that this NDA was fileable.

Clinical

Dr. Wu concluded that this NDA was fileable. An overview was given of the studies submitted. It was noted that the Medical Officer's review would give attention to on three proposed labeling claims, a vaccine-oseltamivir interaction, and updating safety information in the label (i.e. comparable to that of zanamivir).

Division of Scientific Investigations

DAVDP has requested that Dr. Antoine El-Hage inspect three domestic clinical sites.

Miscellaneous

The applicant will submit a deferral for a pediatric assessment of this indication.



Carmouze-530

Record of Teleconference

IND: 53,093

Date: January 7, 2000

Drug: Oseltamivir phosphate (neuraminidase inhibitor (Ro-64-0796) Oral Capsules)

Sponsor: Hoffmann-La Roche Pharmaceuticals

BETWEEN: Representatives of Hoffmann-La Roche Pharmaceuticals

Lutz Wevelsiep, Regulatory Program Manager
Tony Kennedy, Ph.D., Global Project Leader
Penny Ward, M.D., Clinical Scientific Leader
Robert Jeeter, Ph.D., Pharmacologist
Michael McClain, Ph.D. Pharmacology Consultant
Joanna Barret, Clinical Pharmacology
Stephen Pawsey, Ph.D., Clinical Science
Noel Roberts, Ph.D., Virology
Hugh Wiltshire, Discovery
Robert Tudor, Ph.D., Virology

Representative of Gilead Sciences, Inc.

Roger Mills, M.D., Director, Clinical Research
Alan Taylor, Ph.D., Pharmacologist

AND: Representatives of DAVDP

Jim Farrelly, Ph.D., Pharmacology and Toxicology Team Leader
Ita Yuen, Ph.D., Pharmacology and Toxicology Reviewer
Teresa Wu, M.D., Ph.D., Medical Reviewer
Grace Carmouze, Regulatory Project Manager

SUBJECT: CAC Studies/Prophylaxis PreNDA

Background:

The purpose of this teleconference was to discuss the required carcinogenicity studies and the preNDA questions outlined in the sponsor's briefing package (serial no. 184), dated December 1, 1999

Discussion:

Carcinogenicity Studies

Based on a review of the timeline for the two-year carcinogenicity studies submission, the Division did not believe there would be adequate time to review before the action date. The Division recommended that a Syrian hamster embryo (SHE) cell transformation assay and a Tg.AC recombinant mouse assay will expedite approval of the prophylaxis indication. The sponsor will consider carrying them out. In order for the Tg.AC recombinant mouse assay to be completed during the review period, the sponsor will forego the dose range-finding study and carry out the assay at doses that approach the maximum feasible dose. The sponsor indicated that such a study would not be submitted for review by the Executive CAC Committee. This recommendation is contingent on the sponsor concluding the two-year carcinogenicity studies in rats and mice.

Pre-NDA Meeting for a Prophylaxis Indication

Based on a review of the issues outlined in the Pre-NDA meeting briefing package for a prophylaxis indication (serial no. 184), dated December 1, 1999, the Division informed the sponsor that a face-to-face meeting was unnecessary. Below are the Division's responses to the issues outlined in the cover letter of the serial 184).

- 1. The sponsor proposes that the data package presented in the background package is sufficient to support a broad claim for the "prevention of influenza A and B in adults and adolescents." This claim is supplemental to the existing treatment indication for oseltamivir in adults. The sponsor also proposes that the data supports a duration of dosing which can be tailored to the time that an individual is likely to be exposed to the risk of developing influenza. Does the agency concur with this proposal?**

Yes. However, duration of dosing is a review issue and cannot be commented on at this time.

- 2. The sponsor proposes that the dose recommendation for all subjects, including those with impaired renal function, should be 75mg once daily. Does the agency concur with this proposal?**

This proposal is a review issue and cannot be commented on at that this time.

We believe that this represents important prescribing information. We would like to initiate preliminary discussions with the agency regarding the most appropriate way of potentially communicating this information in the product label.

This proposal is a review issue and cannot be commented on at that this time.

- 4. The safety profile of oseltamivir is qualitatively very similar to the safety profile in adults in the treatment of influenza, and no new safety concerns have been identified in the prophylaxis program. Indeed, the safety profile is better in this indication than in treatment and so the information presented in the existing table represents the "worst**

The issue will be addressed during the review of the safety database.

- 5. The sponsor proposes to incorporate information the outcomes in all relevant populations in study WV15799, including ITTINAB and ITT group, in the product label. We would like to initiate preliminary discussions concerning the most appropriate way of communicating this information in the product label.**

The Division stated that this issue will be further discussed during labeling discussions.



Record of Industry Meeting

Meeting Date: May 14, 1998 **Time:** 1-2:30 PM **Location:** 9201 Corp. Blvd., S400

IND Number: IND 53,093

Drug: Ro64-0796 Oral Capsules

Sponsor: Hoffman-La-Roche

Type of Meeting: Clinical Development Meeting

Meeting Chair: Sam Maldonado, M.D., M.P.H. **Sponsor Chair:** Linda Robertson, Ph.D.

Regulatory Management Officer: Debra Gump, R.Ph.

FDA Attendees, Titles, and Offices:

Heidi Jolson, M.D., M.P.H., Director, Division of Antiviral Drug Products
Debra Birnkrant, M.D., Deputy Director, Division of Antiviral Drug Products
Walla Dempsey, Ph.D., Deputy Director, Division of Antiviral Drug Products
Steve Gitterman, M.D., Ph.D., Team Leader
Sam Maldonado, M.D., M.P.H., Medical Officer
Jim Farrelly, Ph.D., Pharmacology, Team Leader
Ita Yuen, Ph.D., Pharmacology Reviewer
Janice Jenkins, Ph.D., Biopharmaceutics, Team Leader
Prabhu Rajagopalan, Ph.D., Biopharmaceutics Reviewer
Dan Boring, Ph.D., Chemistry Reviewer
Jim Ramsey, Ph.D., Microbiology Team Leader
Narayana Battula, Ph.D., Microbiology Reviewer
Paul Flyer, Ph.D., Biostatistics Team Leader
Michael Elashoff, Ph.D., Biostatistics Reviewer
Barbara Styr, M.D., M.P.H., Medical Officer
Debra Gump, R.Ph., Regulatory Management Officer

External Constituent and Titles:

Gilead Sciences, Inc.

Roger Mills, M.D., Director, Clinical Research

Hoffman-La-Roche

Tony Kennedy, Ph.D., Global Project Leader

Joanna McNamara, B.Sc., Regulatory Affairs
Leslie Struthers, Ph.D., Biostatistics
Penny Ward, M.D., Clinical Science Leader
Joe Masserella, B.Sc., Global Regulatory Leader
Linda Robertson, Ph.D., U.S. Regulatory Program Manager

Background:

On August 20, 1997, the sponsor(s), Gilead Sciences, Inc., and Hoffman-La Roche, met with the DAVDP to discuss the clinical development plan for Ro 64-0796 (GS4104) oral capsules. At this meeting, the sponsor(s) presented their plan for their phase 3 clinical program which consisted of four large pivotal trials in the Northern Hemisphere: two treatment studies WV15671 (US) and WV15670 (Europe) and two prophylaxis studies WV15673 (US) and WV15697 (US).

Due to the decreased incidence of influenza infection in the Northern Hemisphere this past year the sponsor requested a meeting with the Division to discuss their revised plans for their phase 3 studies.

Discussion:

1. **In the event of neither treatment study reaching the desired recruitment objective influenza infected subjects this season, is the plan for combining the data for the analysis to support approval acceptable to the agency?**
 - ◆ The Division found this proposal to be acceptable as stated previously in the teleconference dated April 21, 1998. In this teleconference it was clarified that the sponsor would supplement this study with an additional study in the Southern Hemisphere, WV15730. At that time, the Division emphasized to the sponsor that if their plan was to combine the studies, they would need to prepare a detailed analysis plan prior to unblinding the data and would need to additionally analyze each study individually. The sponsor concurred.
2. **In the event of the symptomatic influenza infection rate not reaching the desired frequency in either of the two seasonal prophylaxis protocols, is the plan for combining the data for analysis acceptable to the agency?**
3. **The company proposes that data from seasonal prophylaxis studies will be sufficient to support a general claim for efficacy in prophylaxis of influenza. Does the agency concur with this view?**
4. **Are the study protocols for the investigation of the utility of this agent for the treatment and prophylaxis of influenza in the elderly population acceptable? Can these additional data be used to support an application for marketing this product for the treatment and prophylaxis of influenza in the adult population?**

(The discussion for the above three questions were addressed concurrently.)

- ◆ Dr. Maldonado stated that an important concern for the proposed prophylaxis indication

is that its risk-benefit assessment will be different that the risk-benefit assessment for a treatment indication. It is expected that many individuals will be exposed to the drug in order to protect a minority from becoming infected. Therefore, the safety profile of this drug for a prophylaxis indication will be evaluated against the background of a significant number healthy individuals exposed to the drug.

- ◆ Dr. Jolson suggested that the sponsor consider conducting an open label safety study in the elderly or another population to capture an adequate safety data base in higher risk patients. She also stated that the data for the prophylaxis study needed to be compelling such that the benefit outweighs the risk. And lastly, she emphasized the need for the study to be adequately powered.
- ◆ It was clarified that the sponsor intends to file for an NDA in March 1999, for both a treatment and prophylaxis indication.

5. The company proposes to include data from the Phase 1b study in the pediatric population in the initial filing. This information will be provided within the pharmacology section of the product data sheet to indicate adjustment of dosing (if appropriate) in a pediatric population. Is this proposal acceptable to the agency?

- ◆ The sponsor explained that they would not be looking for pediatric labeling at the time of NDA filing but would propose to include the data from their phase 1b pediatric study in the Pharmacokinetics Section of the label. The sponsor indicated that they currently have an oral formulation ready but have very limited stability data. They also indicated that they intend to submit a pediatric formulation supplement in September 1999. Dr. Jenkins inquired about a bioequivalence study for the comparison of the two formulations. The sponsor stated that there will only be a bioequivalence study in adults at the time of NDA filing. Dr. Jenkins emphasized the need for a link of the oral solution to the capsule formulation in the label. It was suggested that the proposal of including information from the phase 1b pediatric study in the label was unnecessary and potentially misleading if the formulation used during this study was not in the label as well. The sponsor stated that they will take this information under consideration.
- ◆ It was clarified that all age groups in the phase 1b study will be receiving the oral solution.
- ◆ It was suggested that the sponsor considers the drug concentration in the oral solution for other patient populations (i.e., elderly) that might need to take this formulation.

6. It is proposed that children over 12 years of age be included in the adult population studies as soon as the safety data support this scenario. Children over 12 may be assumed to be pharmacologically identical to healthy adults and there is, therefore, no necessity to carry out a study specifically in children aged > 12 years. Does the agency concur with this view?

- ◆ This was acceptable to the Division. Dr. Maldonado suggested that the sponsor

monitor the pharmacokinetic parameters in this population to ensure that they experience similar exposures to that of the adults. The sponsor concurred.

7. Is the proposed further clinical development in the pediatric population sufficient to support a change of label to include an indication for the treatment of influenza in children > 1 year of age?

- ◆ Dr. Maldonado stated that the indication for this product would be a statement such as "for the treatment and prophylaxis of influenza A and B", however information for pediatric dosing would be included in the Dosage and Administration Section of the label.

The conversation was cordial throughout.

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 15, 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
Teresa Wu, M.D., Ph.D., Medical Officer

NDA: 21-087/S-002

Subject: Recommended Postmarketing Commitments

Below are the division's recommended postmarketing commitments for your review.

1. Please investigate the effectiveness and safety of oseltamivir for the treatment and prevention of influenza infection in immunocompromised patients. In this population the emergence of resistant viruses should be closely monitored.
2. Please study the pharmacokinetics and safety of oseltamivir, given at the proposed dosing regimens based on simulations, in end-stage renal dialysis subjects.
3. Please submit a final study report for the completed study of oseltamivir in subjects with impaired hepatic function.
4. Please submit a final study report for the completed long-term carcinogenicity studies in mice and rats.
5. Please explore the isolation, characterization and clinical implications of oseltamivir-dependent influenza virus variants.

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

11/15/00 11:33:48 AM

CSO

Recommended Postmarketing commitments

Jeffrey Murray

11/15/00 02:42:48 PM

MEDICAL OFFICER

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 15, 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
Teresa Wu, M.D., Ph.D., Medical Officer, HFD-530

NDA: 21-087/S-002

Subject: Labeling Comments

These comments are being conveyed on behalf of Dr. Teresa Wu, Medical Officer, and are directed towards your November 14, 2000 submission.

1. We suggest that 75 mg once daily pharmacokinetics parameters be added to the table and the _____ be deleted.

Osetamivir Carboxylate Exposures in Patients with Normal and Reduced Serum Creatinine Clearance

3. Line 305, Table 3: Please refer back to the label version dated November 6, 2000, for the display of the title and footnote.
4. Line 360, insert: "For plasma concentrations of oseltamivir carboxylate predicted to occur following various dosing schedules in patients with renal impairment, see CLINICAL PHARMACOLOGY: *PHARMACOKINETICS: Special Populations*"
5. Delete 369-372, 376-380, insert: "No recommended dosing regimens are available for patients undergoing routine hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease."

Comments to Patient Package Insert

6. _____

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

/s/

Grace Carmouze

11/15/00 04:27:42 PM

CSO

Labeling Comments to 11/14/00 submission

Jeffrey Murray

11/15/00 04:36:12 PM

MEDICAL OFFICER

6 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 8, 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: Jim Farrelly, Ph.D., Pharmacology/Toxicology Team Leader HFD-530

NDA: 21-087/S-002

Subject: Pharmacology/Toxicology Labeling Comments

The following comments are being conveyed on behalf of Dr. James Farrelly, Pharmacology/Toxicology Team Leader and directed toward your revised package insert (PI) [strikethrough] dated November 6, 2000.

1. Lines 228-238: Please insert the following:

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Long-term carcinogenicity tests with oseltamivir are underway but have not been completed. However, c _____ :

Oseltamivir was found to be nonmutagenic in the Ames test and the human lymphocyte chromosome assay with and without enzymatic activation and negative in the mouse micronucleus test. It was found to be positive in a Syrian Hamster Embryo (SHE) cell transformation test. Oseltamivir carboxylate was non-mutagenic in the Ames test and the L5178Y mouse lymphoma assay with and without enzymatic activation and negative in the SHE cell transformation test.

In a fertility and early embryonic development study in rats, ...

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



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 23, 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: Jeffery Murray, M.D., M.P.H., Medical Team Leader, HFD-530
Teresa Wu, M.D., Ph.D., Medical Officer, HFD-530

NDA: 21-087/S-002

Subject: Labeling comment

SI 10/23/00
10/23/00

These comment is being conveyed on behalf of Dr. Teresa Wu, and is directed towards your revised package insert (PI) dated October 19, 2000.

Comments to PI:

1. Please delete the sentence regarding _____ under 'Prophylaxis of Influenza'.

Reasons:

- *The minimally required diagnostic criteria for sinusitis, bronchitis, and pneumonia were not predefined. The lack of microbiologic evaluation in all 8 cases and insufficient radiographic evaluation in most cases have made a clinical review of the investigator's assessment problematic.*
- *It is questionable to consider acute bronchitis as a complication of influenza, given that increased bronchial reactivity and decreased tracheobronchial clearance are both within the spectrum of uncomplicated influenza. In addition, no information on smoking status was provided.*
- *Subject 23632/4710 presented a clinical diagnosis of 'pneumonia' on the same day of the onset of influenza. In the absence of any microbiologic evaluations, it is impossible to differentiate a non-viral pneumonia from a primary viral pneumonia due to influenza virus.*

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.

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

**MEMORANDUM**

Date: June 23, 2000

To: Antoine N. El-Hage, Ph.D., M.S.,
Branch Chief
Clinical Investigations II
Good Clinical Practices Branch
Division of Scientific Investigations HFD-47

Through: David A. Lepay, M.D., Ph.D., Director
Division of Scientific Investigations HFD-45

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

Subject: Request for Clinical Inspections
NDA 21-087/Supplement No: SE1-002
Sponsor: Hoffmann-La Roche
Drug: TAMIFLU (oseltamivir phosphate) 75mg
Therapeutic Class: 7030120

Protocol/Site Identification

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority. This supplement provides for a prophylaxis indication.

Indication	Protocol #	Site (Name and Address)
Prophylaxis	WV15799	Dr. H. Schwartz* Miami Research Associates 7500 SW 87 th Ave, Ste. 202 Miami, FL 33173
		Dr. M. Vichare California State Univ. – Chico Student Health Services Chico, CA 95929-0777
Prophylaxis	WV15673	Dr. F. Hayden*



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 4, 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
Teresa Wu, M.D., Ph.D., Medical Officer, HFD-53 *(S)*

NDA: 21-087/S-002

Subject: Comments for Proposed Labeling

These comments are being conveyed on behalf of Dr. Teresa Wu, Medical Officer and are directed toward your submission dated May 22, 2000.

1. Under 'MICROBIOLOGY: Drug Resistance', please delete the paragraph beginning _____

2. Under 'MICROBIOLOGY: Influenza Challenge Studies', _____

3. Under 'Description of Clinical Studies: Prophylaxis of Influenza', we suggest the following wording.

The efficacy of Tamiflu in preventing naturally occurring influenza illness has been demonstrated in three seasonal prophylaxis studies and a post-exposure prophylaxis study in households. The primary efficacy parameter for all these studies was the incidence of laboratory confirmed clinical influenza. Laboratory confirmed clinical influenza was defined as oral temperature ≥ 99.0 F/37.2 C plus at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one constitutional

symptom (aches and pain, fatigue, headache, chills/sweats), all recorded within 24 hours, plus either a positive virus isolation or a 4-fold increase in virus antibody titers from baseline.

In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults (aged 13 to 65 years), Tamiflu 75 mg once daily taken for 42 days during a community outbreak reduced the incidence of laboratory confirmed clinical influenza from 4.8% for the placebo group to 1.2% for the Tamiflu group.

In a seasonal prophylaxis study in elderly residents of skilled nursing homes, Tamiflu 75 mg once daily taken for 42 days reduced the incidence of laboratory confirmed clinical influenza from 4.4% for the placebo group to 0.4% for the Tamiflu group. About 80% of this elderly population were vaccinated, 14% of subjects had chronic airway obstructive disorders and 43% had cardiac disorders.

In a study of post-exposure prophylaxis in household contacts (aged— 13 years) of an index case, Tamiflu 75 mg qd administered within 2 days of onset of symptoms in the index case and continued for 7 days, reduced the incidence of laboratory confirmed clinical influenza from 12% for the placebo group to 1% for the Tamiflu group. Index cases did not receive Tamiflu in the study.

4. Under 'PRECAUTIONS', please add the statement "

6. Under 'ADVERSE REACTIONS', before the prophylaxis studies section, please add the following paragraph:

7. _____

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Please feel free to contact me if you have any questions regarding the contents of this transmission.

(S)

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



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 24, 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
Teresa Wu, M.D., Ph.D., Medical Officer, HFD-530

NDA: 21-087/S-002

Subject: Request of Information

(S) 1 S

These comments are being conveyed on behalf of Dr. Teresa Wu, Medical Officer, and are in response to your facsimile transmission dated August 22, 2000.

1. In study WV15799, placebo contact subject 22981/6700 had a different virus type from that of the corresponding index case (this was consistent with Appendix 57, vol. 28). Please clarify why this case was included in the primary efficacy analysis.
2. Please provide ID numbers for the 12 baseline virus shedders and their corresponding index cases for study WV15799.
3. For study WV15799, please perform a primary efficacy analysis in ITTINAB population to compare the effectiveness of prophylaxis according to virus type (A or B). Please use the number of index cases of matching virus type as the denominator.

Please see refer to the table below for an example.

	Contact			
	placebo		oseltamivir	
Index case infected with influenza A (n =)	no. of lab-confirmed clinical flu		n =	
Index case infected with influenza B (n =)	n =		n =	
placebo vs. oseltamivir	p-value	95% CI	p-value	95% CI

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



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: July 14, 2000

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

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

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

Through: Girish Aras, Ph.D., Statistical Team Leader
Thomas Hammerstrom, Ph.D., Statistical Reviewer
Jeffrey Murray, M.D., M.P.H., Medical Team Leader. HFD-530
18 7/17/00 7-17-00

NDA: 21-087/S-002

Subject: Statistical Comments

The following comments are being conveyed on behalf of Dr. Tom Hammerstrom, Statistical Reviewer, and are directed towards the CD-ROM desk copy, provided by the applicant, containing requested datasets.

1. Please identify the relationship between EVDT and DAY on the EFFICVA and EFFICV_1 datasets
2. Please explain why the events "within subject" come out sorted differently depending upon whether one sorts with DAY or with EVDT within SUBJECT?
3. Please clarify why there are considerably fewer symptom and temperature data for trial WV15825 on the CD-ROM desk copy than there are in electronic data officially submitted to the NDA

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

/S/

Grace N. Carmouze
Regulatory Project Manager



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 28, 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-530 127 28-00

Through: Girish Aras, Ph.D., Statistical Team Leader, HFD-530
Thomas Hammerstrom, Ph.D., Statistical Reviewer, HFD-530 151 3-28-00
Jeffrey Murray, M.D., M.P.H., Medical Team Leader, HFD-530 151 3/29/00

IND: 53,093, serial no. 205

Subject: Comments to Electronic Submission for Supplemental NDAs for Prophylaxis and Pediatric Indications

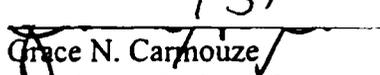
These comments are being conveyed on behalf of Dr. Tom Hammerstrom, Statistical Reviewer, and are directed towards submission number 205 (with CD-ROM).

Please provide the four datasets (i.e., DIED, DEMOGRAPH, RESULTS, and DISCONTINUE) for the study in elderly patients (WV15825). Below is a detailed description of what each dataset should include.

- 1) DIED should have exactly the same fields as the sample dataset DIED that as included on the CD-ROM.
- 2) DEMOGRAPH should have one record for each patient enrolled the study with the following fields:
 - a) Patient ID, a numeric variable
 - b) A categorical variable with the following values:
 - i) Enrolled but not randomized
 - ii) Randomized but received no treatment
 - iii) Randomized & treated but not infected

- iv) Randomized & treated & infected
 - c) A treatment assignment identifier
 - d) Center at which enrolled
 - e) Date and time of treatment start in SAS DATETIME format
 - f1-f7) Baseline values of each of the symptoms
 - g) Baseline temperature
 - h)-z) One variable for each of the baseline factors used in stratifying the original randomization
- 3) RESULTS should be a much smaller subset of the EFFIC datasets submitted on the CD-ROM. There should be one record for each diary card entry and each clinic visit by each subject. There should be no records corresponding to extrapolated or interpolated data. The fields should be the following:
- a) Patient ID, the same numeric variable as in DEMOGRAPH
 - b) Indicator of whether the record is a diary card entry or a clinic visit
 - c) Date and time of entry/visit in SAS DATETIME format
 - d1-d7) Values of each of the seven symptoms
 - e) Temperature
- 4) DISCONTINUE should have one record for each subject enrolled. The fields should be the following:
- a) Patient ID, the same numeric variable as in DEMOGRAPH
 - b) A categorical variable with the following values:
 - i) Enrolled but not randomized
 - ii) Randomized but received no treatment
 - iii) Randomized & treated but not infected
 - iv) Randomized & treated & infected
 - c) A treatment assignment identifier
 - d) Date and time of last diary card entry or clinic visit in SAS DATETIME format
 - e1-e7) Maximum value of each of the seven symptoms in the 24 hours preceding last entry/visit
 - f) Reason data collection discontinued, a character variable with maximum length 20

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.

151

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

**Record of Teleconference**

IND: 53,093

Date: March 22, 2000

Drug: Oseltamivir phosphate oral capsules

Sponsor: Hoffmann-La Roche Pharmaceuticals

BETWEEN: Representatives of Hoffmann-La Roche Pharmaceuticals

Joanna McNamara, Regulatory Affairs Leader
Barbara Taylor, Ph.D., Program Director, Drug Regulatory Affairs
Penelope Ward, M.D., Clinical Scientific Leader
Joanne Barrette, Ph.D., Clinical Pharmacology
Daniel O'Day, Program Leader
Robert Jeeter, Ph.D., Pharmacologist
Stephen Pawsey, Ph.D., Clinical Science
David Eickler, Ph.D., Toxicologist

Representatives of Gilead Sciences, Inc.

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SUBJECT: Timeline for CAC studies/Filing Strategy for Prophylaxis Indication (sn 209)

Background: The sponsor has indicated that they propose to submit a supplemental NDA (sNDA) for a prophylaxis indication on March 30, 2000. In a facsimile dated March 13, 2000, the sponsor outlined the proposed submission dates for carcinogenicity reports. The purpose of this teleconference was to discuss DAVDP's concerns with the timing of the carcinogenicity studies relative to the action date, if a priority review (i.e., six-month review clock) is granted. To facilitate the teleconference, the sponsor sent a facsimile, dated March 20, 2000 with the transgenic mouse protocol.

Discussion:

CAC Studies

The Division inquired why a dose-selection study was conducted given that the maximum feasible dose was a criterion for selecting the high dose in the final protocol for the transgenic mouse carcinogenicity study using the Tg.AC mouse. The sponsor replied that they wanted to ensure that the high dose would not cause unacceptable dermal irritation or increase the chances of a false-positive tumor response. Additionally, it was noted that because skin does not possess the necessary enzyme to convert oseltamivir phosphate to its active form, it was necessary that the active drug be manufactured. As a consequence, the start date of the study was delayed due to insufficient amounts of active drug.

The sponsor was requested to submit a justification for selecting the high dose of 780 mg/kg/day as the maximum feasible dose with the submission of the study reports. The sponsor agreed.

The sponsor informed the Division that the audited study reports of the transgenic mouse study would be available after the action date, based on a March 30, 2000 submission date. The Division reminded the sponsor that carcinogenicity study reports would be required for review prior to the action date and that the review clock for supplements cannot be extended by the submission of a major amendment. The Division stated that submission of unaudited draft reports for the transgenic mouse study and Syrian Hamster Embryo (SHE) cell assay would be acceptable. The sponsor indicated that the unaudited draft reports would be available on October 28, 2000. The sponsor also requested to submit monthly interim report for the in-life assay of the transgenic mouse study beginning July 2000.

sNDA Filing Strategy Recommendations

The sponsor indicated that they planned to submit the sNDA at the end of March 2000 with an anticipated action date at the end of September 2000, if a priority review was granted. Because the availability of the carcinogenicity studies was a concern, the Division recommended that the sponsor reconsider the sNDA filing strategy. The recommendations are as follows:

- Change the review to a standard review (ten-month clock) to allow time for the sponsor to submit the study reports and the Division to review the application within the review clock. The Division stated that the review of these study reports would be done in an expedited manner; or
- Delay submitting the sNDA to allow one month for the pharmacology toxicology reviewer to review the reports prior to the action date; or
- Risk a non-marketable action letter (e.g., approvable letter) pending the submission of the unaudited carcinogenicity reports.

The sponsor will discuss internally the above-mentioned recommendations and will communicate their decision to the Division shortly.