DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 14 2000

. TRANSMITTED VIA FACSIMILE

Joanna McNamara
Program Director
Hoffman-La Roche Inc.
Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

RE: NDA 21-087
TAMIFLU (oseltamivir phosphate)
MACMIS ID#8675

Dear Ms. McNamara:

This letter concerns Hoffman-La Roche Inc.'s (Roche) promotional materials for Tamiflu. We refer you to Roche's March 31, 2000, letter responding to the Division of Drug Marketing, Advertising, and Communications' (DDMAC) March 24, 2000, letter inquiring about the alleged dissemination of violative "homemade" pieces for Tamiflu.

In your letter, you described the circumstances in which violative "homemade" pieces were disseminated. Additionally, your letter commented on your policy for prohibiting dissemination of homemade materials by your sales representatives, and specified that corrective actions are being taken to ensure that this activity will discontinue and not recur.

We have reviewed your response about the "homemade" pieces, along with other promotional materials for Tamiflu as part of our routine monitoring and surveillance program. From our review, we have concluded that Roche has distributed materials that are false or misleading, in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. These materials include: three homemade promotional pieces entitled, "Tamiflu (oseltamivir) is here in time for the influenza season," "Master the A.R.T. of Influenza Management," and "The first anti-flu pill with A & B coverage (Tame-the-Flu)," a journal advertisement, telephone triage pad and a promotional piece containing a thermometer.

The promotional materials lack fair balance, contain misleading mechanism of action and *in vitro* claims, and contain misleading efficacy claims. In addition, you have failed to submit promotional materials to the FDA under Form FDA 2253 at the time of initial dissemination.

Lacking in Fair Balance
Information relating to risk information should be presented in a manner reasonably comparable to the presentation of information relating to the effectiveness of the drug. In the "homemade" pieces, Roche devotes an entire page of efficacy claims without presenting any risks associated with the recommended use of Tamiflu. Also, Roche presents safety claims, ***"Excellent safety and tolerability"*** and ***"Side effects were mild and moderate,"*** without disclosing risks that have been associated with Tamiflu. Further, the use of the term, ***"excellent,"*** misleadingly suggests that Tamiflu has less or fewer risks than has been demonstrated by substantial evidence. The approved product labeling states certain risks have been reported more frequently in patients taking Tamiflu compared with placebo. These risks include nausea, vomiting, bronchitis, insomnia, and vertigo. In fact, nausea occurred in 9.9% vs. 5.6% and vomiting occurred in 9.4% vs. 2.9% in Tamiflu treated patients versus placebo, respectively.

Similarly, both the Telephone Triage Pad and the promotional piece containing a thermometer are lacking in fair balance because these pieces present the product's indication without disclosing risks associated with Tamiflu. For example, in the Telephone Triage Pad, you have presented the product logo, ***"Tamiflu,"*** in conjunction with the statements,

"When a patient calls complaining of flu-like symptoms,"
"Patients are likely to have influenza if a fever is accompanied by 2 other symptoms and flu is in the community... they may be a candidate for antiviral treatment," and
"Dedicated to improving influenza management."

We note the statement, ***"Please see accompanying complete product information,"*** is included at the bottom of the telephone pad; however, it is not adequate for fair balance. Additionally, in the promotional piece containing a thermometer, you have presented a table listing flu and cold symptoms. However, you have not presented any risk information.

Misleading Mechanism of Action and *In Vitro* Claims
In the "homemade" pieces, Roche presents statements about the mechanism of action that are misleading because they are inconsistent with the approved product labeling and imply a known mechanism of action. For example, you state,

"This new class of influenza fighter acts by preventing the virus from escaping infected host cells, therefore preventing spread of viral infection," and
"Potent neuraminidase inhibition treats the cause of influenza infection."

However, according to the product labeling, "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" (underline added).

Further, Roche presents a statement in the "homemade" piece entitled, "The first anti-flu pill with A & B coverage," ***"Tamiflu maintains IC50 levels at all possible sites of infection over the dosing range (lung, trachea, sinusitis, and middle ear)."*** This statement is misleading because it implies clinical significance based on *in vitro* data when such has not been demonstrated by substantial evidence. According to the product labeling, the relationship between the *in vitro* antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established.

Misleading Efficacy Claims
In the homemade pieces, Roche has presented the following misleading efficacy claims:

"The pill with the power to stop the flu,"
"Tame-the-flu with Tamiflu,"
"Tamiflu will reduce duration of the flu by 31%,"
"Tamiflu will reduce the severity of influenza symptoms by 38%," and
"Tamiflu reduces incidence of secondary complications (i.e. bacterial infections) by 45%."

These claims are misleading because they suggest greater efficacy for Tamiflu than has been demonstrated by substantial evidence. For example, you have used the phrases ***"power to stop the flu"*** and ***"Tame-the-flu"*** and presented study results in percentages that overstate the 1.3-day difference in flu symptom improvement with Tamiflu compared with placebo. Further, you have claimed reductions in severity and incidence of secondary infections with Tamiflu that are misleading because they are not supported by substantial evidence.

Similarly, in your journal ad, you have presented the statement, ***"Reduces the duration of flu so you can help your patients feel better faster."*** This statement is misleading because, without providing efficacy data, it suggests greater efficacy for Tamiflu than the 1.3-day difference demonstrated in clinical trials.

In addition, you have presented multiple efficacy claims in your "homemade" pieces, as previously mentioned herein, but have not presented the limitations of these claims. These limitations include the following:

- there is no evidence for efficacy of Tamiflu in any illness caused by agents other than influenza Types A and B (data on Type B are limited),
- efficacy of Tamiflu in high risk patients has not been established, and there were no differences in the incidence of complications between treatment and placebo groups
- safety and efficacy of repeated treatment courses have not been established

Moreover, Roche broadens the indication for Tamiflu by failing to disclose that Tamiflu should be started in adults who have been symptomatic for no more than 2 days. According to the product labeling, efficacy of Tamiflu in patients who begin treatment after 40 hours of symptoms has not been established.

Failure to Submit
Promotional materials must be submitted to the FDA under Form FDA 2253 at the time of initial dissemination. However, our records indicate that the "homemade" pieces and the promotional piece containing a thermometer were not submitted at the time of initial use.

Requested Actions
Roche should immediately cease dissemination of promotional materials or activities that contain these or similar claims. In addition, Roche should respond in writing no later than April 28, 2000, describing its plan to comply. Roche should also include a list of all similarly violative materials being discontinued, as well as the date of discontinuation.

Regarding the violative "homemade" pieces, we note that you state, "We have taken corrective action with the representatives concerned to ensure that this incident is not repeated," in your letter dated March 31, 2000.

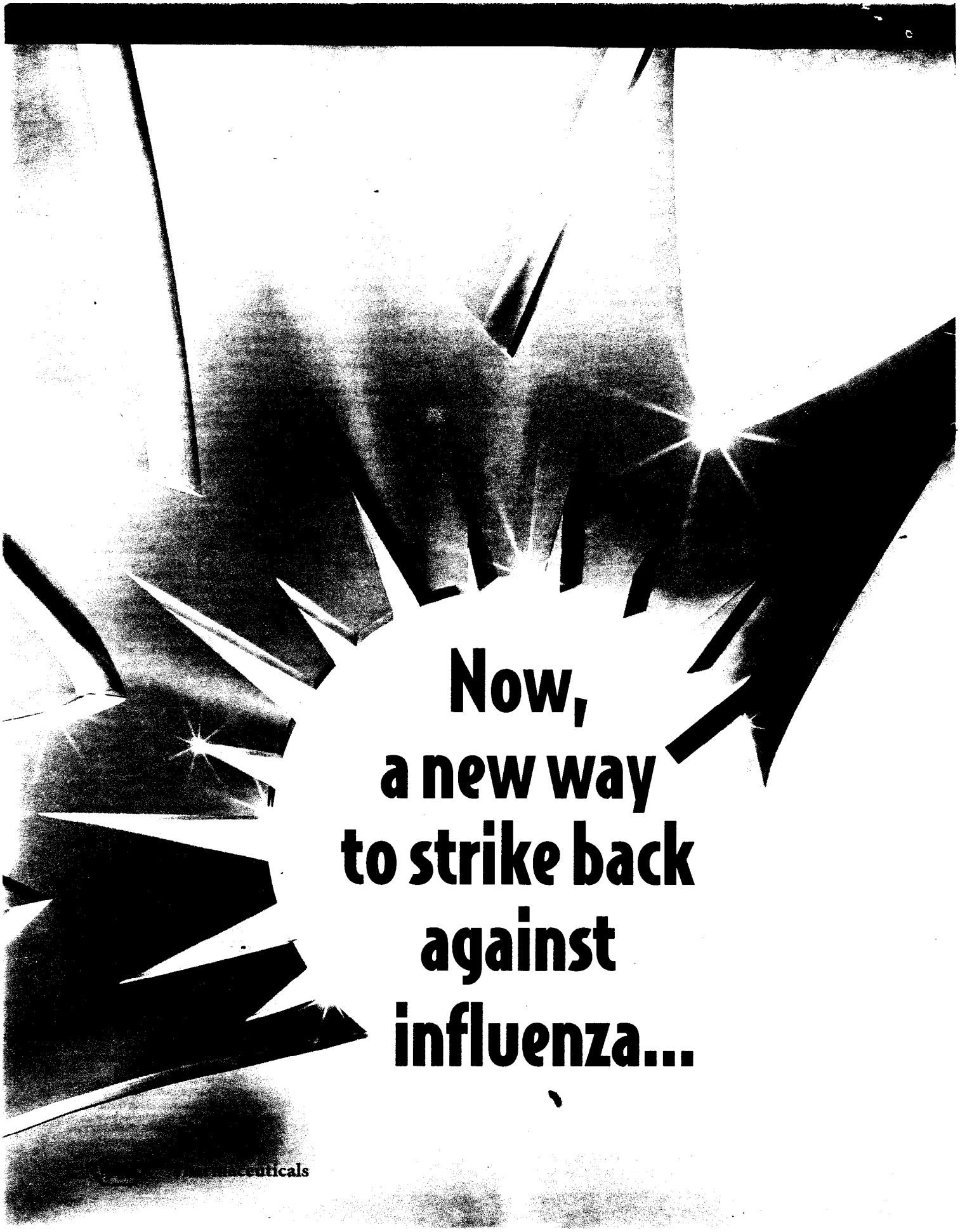
Your response should be directed to Ele Ibarra-Pratt by fax at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #8675 in addition to the NDA number.

Sincerely,

/S/

Ele Ibarra-Pratt, R.N., M.P.H.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications


Now,
a new way
to strike back
against
influenza...

NEW FROM ROCHE

Tamiflu™

oseltamivir phosphate ROCHE 75 mg

The first antiflu pill with type A and B coverage

Neuraminidase inhibition treats the cause of influenza infection

- Indicated for the treatment of uncomplicated acute illness due to influenza infection in adults

Reduces the duration of flu so you can help your patients feel better faster

Favorable safety and tolerability

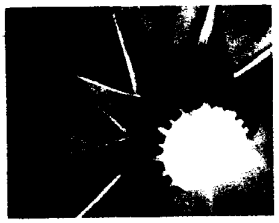
- The most frequently reported adverse events were mild-to-moderate, transient nausea or vomiting; other events reported more frequently than with placebo were bronchitis, insomnia and vertigo
- Less than 1% of patients discontinued TAMIFLU prematurely in clinical trials due to nausea or vomiting

Easy to prescribe, easy to take

- Convenient dosing: one 75 mg capsule twice daily for 5 days
- Treatment should **begin within 2 days** of symptom onset

There is no evidence for the efficacy of TAMIFLU in any illness other than influenza types A and B (data on type B are limited). Efficacy in high-risk patients has not been established and there were no differences in the incidence of complications between treatment and placebo groups in this population. The safety and efficacy of repeated treatment courses have not been established. As always, vaccination is considered the first line of defense against influenza.

Please see brief summary of complete product information on next page.



Identifying Influenza:
Telephone Triage Pad

When a patient calls complaining of *flu-like symptoms*, please complete this checklist:

Date: Time:

Patient's name:

Telephone number:

Notes/comments:

1. Have you experienced sudden onset of fever (≥101°F)?

☐ Yes ☐ No

2. Do you have (please check all that apply):

- ☐ Chills?
- ☐ Muscle aches and pains?
- ☐ A feeling of being tired and weak?
- ☐ A headache?
- ☐ A dry cough?
- ☐ A sore throat?
- ☐ A stuffy nose?

3. Have you had these symptoms for 2 days or less?

☐ Yes ☐ No

Patients are likely to have influenza if a fever is accompanied by 2 other symptoms and flu is in the community. If they answer YES to Question 3, they may be a candidate for antiviral treatment.[1]

Based on the information received, ask the doctor if the patient should be scheduled for an office visit.

Roche: Dedicated to Improving Influenza Management

Visit us at www.tamiflu.com

Reference: 1. Data on file (Ref. #155-018), Hoffmann-La Roche Inc., Nutley, NJ 07110.

Please see accompanying complete product information.

TAMIFLU is licensed by Roche Laboratories Inc. from Gilead Sciences, Inc., Foster City, CA.

18-082-155-031-0200
Plandex 155021
Printed in USA

Tamiflu™
oseltamivir phosphate

Roche Pharmaceuticals

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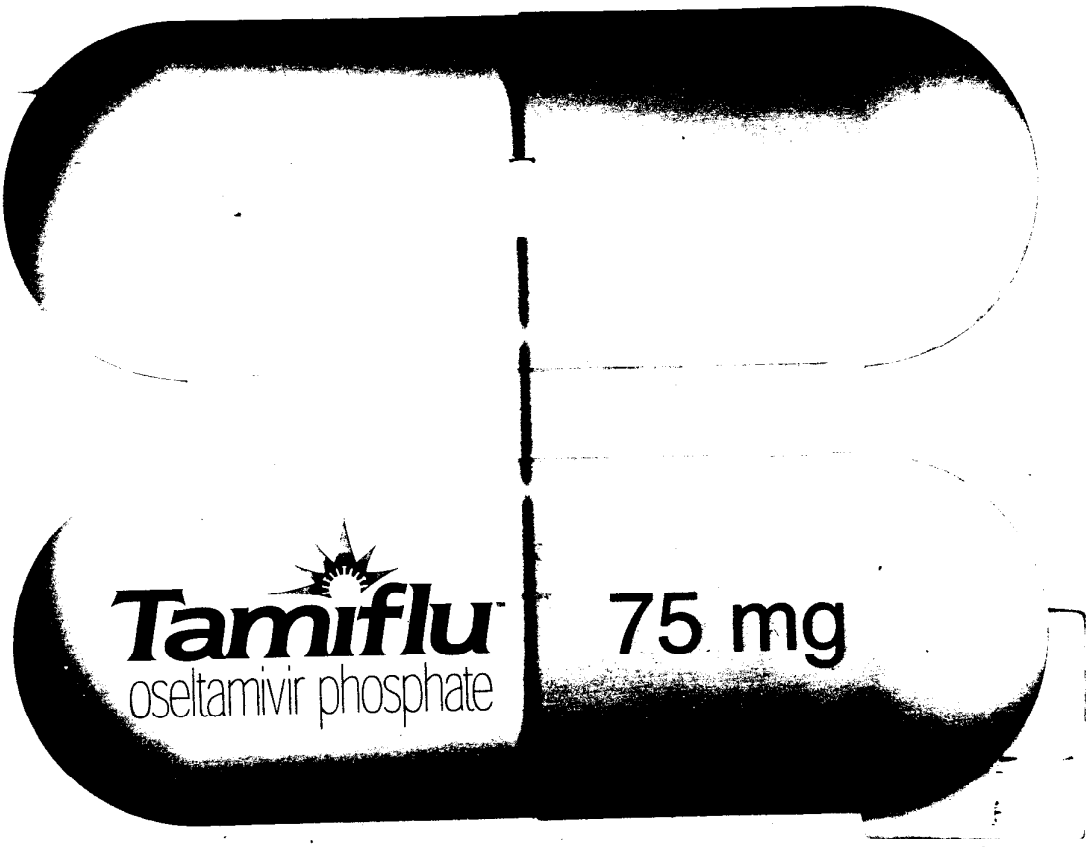
Tamiflu
oseltamivir phosphate
75 mg

Q: What's the *difference* between the flu and a cold?

A: Both the flu and a cold are viral infections that can cause coughing and sore throat. A cold is a minor viral infection of the nose and throat. But the flu is usually more severe, with higher fever and aches and pains.

Symptoms	Flu	Cold
Onset	Sudden	Gradual
Fever	Characteristic, high (over 101°F); lasting 3 to 4 days	Rare
Cough	Nonproductive; can become severe	Hacking
Headache	Prominent	Rare
Aches and Pains	Usual; often severe	Slight
Fatigue; weakness	Can last up to 2 to 3 weeks	Very mild
Extreme exhaustion	Early and prominent	Never
Chest discomfort	Common	Mild to moderate
Stuffy nose	Sometimes	Common
Sneezing	Sometimes	Usual
Sore throat	Sometimes	Common

- adapted from the National Institute of Allergy and Infectious Diseases

Roche **Pharmaceuticals**

Dedicated to Improving Influenza Management

TAMIFLU™ (oseltamivir phosphate) is licensed by Roche Laboratories Inc. from Gilead Sciences Inc., Foster City, CA.