CENTER FOR DRUG EVALUATION AND RESEARCH

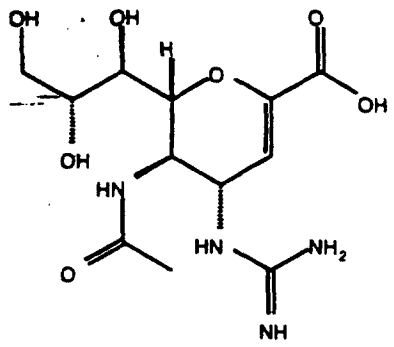
Application Number 21-036/S-001

PHARMACOLOGY REVIEW(S)

YOERG

MAR 10 2000

PHARMACOLOGIST'S REVIEW



Zanamivir

NDA 21-036 NDA Pediatric Supplements
Date Submitted: 10/29/99
Date Assigned: 10/30//99
Date Review Completed: 3/8/00
HFD-530

SPONSOR: GlaxoWellcome Inc.
5 Moore Drive, Research Triangle Park, NC

DRUG: Zanamivir, GG167; GR121167; 5-(Acetylamino)-4-[(aminoiminomethyl)amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid; $C_{12}H_{20}N_4O_7$; MW: 332.3

INFORMATION TO SPONSOR: Yes

FORMULATION: Oral Inhalation (solubility: 18 mg Zanamivir off-white powder/ml water); pK_a1 (guanidine group)=13; pK_a2 (carboxyl group)=2.4; administered to the respiratory tract by ROTADISK® which contains four regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of Zanamivir and 20 mg of lactose. The contents of each blister are inhaled through the mouthpiece of DISKHALER, a breath-activated plastic device.

INDICATION: Anti-Influenza

COMMENTS: Zanamivir is a competitive inhibitor of influenza A and B virus neuraminidase. The NDA was recently approved for treatment of influenza infection in the adult population. The current supplement provides new clinical data in children and is seeking a similar indication in the pediatric population. All preclinical information are cross-referenced to the original NDA and no additional pharm/tox information was included in the new submission.

t .. Detailed wording of the labeling changes as proposed by the Agency are provided in the APPENDIX. No other regulatory comments on pharm/tox will be provided to the sponsor.

/S/

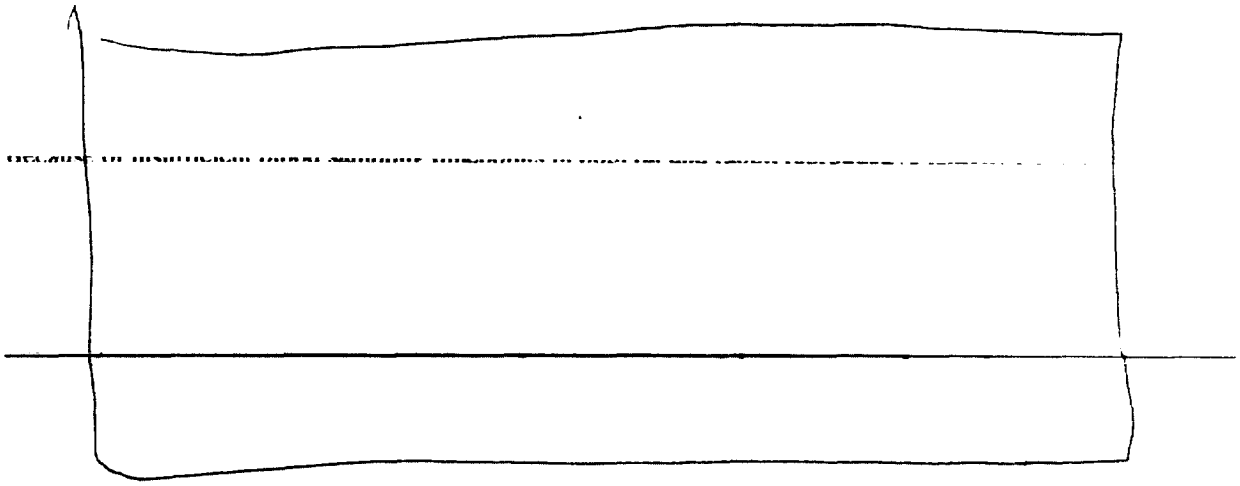
Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Concurrences:
HFD-530/DepDir/WDempsey NC 3/15/00
DAVDP/HFD-530/PTL/JFarrelly JF 3/10/00
Wu/Pharm/3/8/00 3-10-00

Disk: JFarrelly

HFD-530 NDA 21-036 (001)
HFD-530/Division File
HFN-340
HFD-530/CSO
HFD-530/MO
HFD-530/Chem
HFD-530/Micro
HFD-530/Pharm

APPENDIX (*new text underlined*)



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 23, 1999

To: Sherman N. Alfors

Address: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

From: Virginia L. Yoerg, Regulatory Project Manager, HFD-530 VLY 11/23/99

Through: Stanka Kukich, M.D., Medical Team Leader, HFD-530 SK 4/24 199
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, HFD-530 JDX 11/24/99
K.M.Wu, Ph.D., Pharmacology/Toxicology Reviewer, HFD-530 ESO 11/23/99 KMW 11/24/99

IND:

Subject: Pregnancy category change from B to C for Relenza®

The following comments are being conveyed on behalf of the Division of Antiviral Drug Products, and are directed toward your serial submission 082, dated October 13, 1999.

Because of the treatment-related embryofetal toxicities reported in submission 082, the Relenza® Pregnancy Category label should be changed from B to C. The recommended revised wording of the drug label in the Pregnancy Category paragraph is provided as follows:

Pregnancy:

Pregnancy Category C: Embryo/fetal development studies were conducted in rats (dosed from days 6 to 15 of pregnancy) and rabbits (dosed from days 7 to 19 of pregnancy) using 1, 9 and 90 mg/kg iv dosing once a day. A third embryo/fetal study was conducted in rats using subcutaneous doses of 1, 9 and 80 mg/kg three times a day during day 7-17 of pregnancy. In addition, pre- and post-natal developmental studies were also performed in rats (dosed from day 16 of pregnancy till litter day 21 to 23; 1, 9 and 90 mg/kg/day iv). In the subcutaneous embryo/fetal study conducted in rats, higher incidences of incomplete ossification of skull bones and sacral vertebral arches, kinked ribs, dilated ureter and elongated innominate artery were observed in the high dose group (80 mg/kg tid). The frequencies were not significantly higher than the historic controls but the toxicities were treatment-related. The AUC values of the no-effect dose (9 mg/kg tid) were 52 times the human exposure at the proposed clinical dose. Because of insufficient blood sampling, AUC values were not available in the iv reproductive toxicity studies.

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/

Virginia L. Yoerg
Regulatory Project Manager
Division of Antiviral Drug Products

concurrence:
HFD-530/MO/Styrt BAS 11/23/99

cc:
Orig
Division File
HFD-530/MTL/Kukich
HFD-530/MO/Baylor
HFD-530/MO/Styrt
HFD-530/PharmToxTL/Farrelly
HFD-530/PharmTox/Wu
HFD-530/RPM/Yoerg

IND 43,776

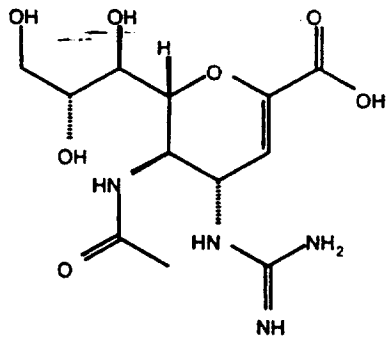
Facsimile

V:\

APPEARS THIS WAY
ON ORIGINAL

OCT 29 1999

PHARMACOLOGIST'S REVIEW



Amendment no. **082**
Date Submitted: 10/14/99
Date Assigned: 10/15/99
Date Review Completed: 10/17/99
Reviewed by: Kuei-Meng Wu
HFD-530

SPONSOR: GlaxoWellcome Inc.
5 Moore Drive, Research Triangle Park, NC

DRUG: Zanamivir, GG167; GR121167; 5-(Acetylamino)-4-[(aminoiminomethyl)amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid; $C_{12}H_{20}N_4O_7$; MW: 332.3

INFORMATION TO SPONSOR: Yes

FORMULATION: Inhalation administration (18 mg GR121167/ml and 8 mg NaCl/ml in 1 m• water); pK_a1 (guanidine group): 13; pK_a2 (carboxyl group): 2.4

INDICATION: Anti-Influenza

INTRODUCTION

This amendment contains a reprotoxicity report on subcutaneous zanamivir in rats. It is reviewed as follows (tables scanned from sponsor's file):

1. **GR121167X (Anti-influenza agent): Three Times Daily Subcutaneous Embryofetal Development Study In The Wistar Han Rat (Study No. R22558; 10 September 1999).**

Method:

GR121167X was administered subcutaneously 3 times daily, at 8 hour intervals, to give a total daily exposure of approximately 10-12 hours. The maximum drug free period between each dose was estimated to be approximately 4 hours. In view of the variations in rate of embryofetal development within and between dams, it was considered that this regimen would expose all stages of embryofetal development to high levels of GR 121167X. The high dosage (80mg/kg tid) was the maximum practicable dosage based on solubility (the maximum working concentration in aqueous solution was 16mg/mL, reduced from 18mg/mL in the earlier studies to avoid manufacturing difficulties due to the very slow rate of dissolution) and standard dose volumes for repeated subcutaneous administration (5ml/kg). The low and intermediate dosages (1mg/kg tid and 9mg/kg tid, respectively) were the same as those administered once daily in a previous rat embryofetal development study.

Results:

Following subcutaneous administration of GRI21167X both Cmax and AUC showed an approximately linear increase with increasing dose. GRI21167X was absorbed into the systemic circulation and mean Cmax values of 1.6, 15.2 and 141 ug/mL (for 1, 9 and 80 mg/kg doses, respectively) were obtained after approximately 15 minutes, post-dose. Systemic exposure at each dose level, for each of 3 daily doses were similar irrespective of the dosing interval, giving average AUCs of 2.3, 20.7 and 173 ug.hr/mL for 1, 9 and 80 mg/kg doses, respectively.

Fetal toxicitis recorded at 80mg/kg tid included high incidences of incomplete ossification of skull bones and sacral vertebral arches, kinked ribs, dilated ureter and elongated innominate artery. The sponsor indicated that none of the increases in the incidence recorded at this dosage achieved statistical significance. It should be noted that the incidence of incompletely ossified frontal skull bone(s) recorded at the 9mg/kg tid dosage was as high as the value recorded at the 80mg/kg tid dosage and may also be considered to be treatment-related.

The term incomplete ossification is applied by the sponsor to skull bones and vertebral arches when the margins of the bone are ill defined and/or sparsely ossified. Staining may be either pale and uniform or non-uniform across the bone. Unossified areas within the bone may be present, as well as notches in the bone margin.

Incidences of incomplete ossification of various skull bones and sacral vertebra/arches were noticeably higher than respective control group values at 80mg/kg tid. High incidences of incompletely ossified skull bones and sacral vertebra/arches indicate a delay in ossification. Although the incidences of some of these parameters recorded at this dosage remained within the respective background incidence data range, it is considered to be a definite trend towards increased incidence at 80mg/kg tid. An association between high incidences of incomplete ossification of skull bones and sacral vertebral arches to treatment cannot therefore be discounted.

Table xviii Incomplete ossification of skull bones

% fetuses affected	Dosage (mg/kg tid)				Background incidence
	0	1	9	80	mean (range)
Frontals, unilateral/bilateral	6.7	7.5	13.7	13.0	9.9 (
Interparietal	43.3	35.5	39.2	55.0	38.5 (
Jugal, unilateral/bilateral	7.7	7.5	5.9	15.0	6.3 (
Parietal, unilateral/bilateral	47.1	44.9	43.1	56.0	40.6
Squamosal process, unilateral/bilateral	8.7	9.3	7.8	14.0	7.3 (
Supraoccipital	22.1	18.7	22.5	32.0	20.6

excludes data from studies R21330 and R21702

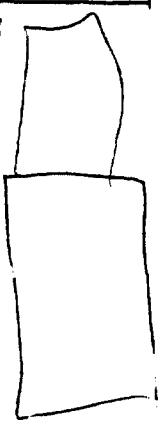


Table xix Incomplete ossification of sacral vertebral arches

% fetuses affected (unilateral/bilateral)	Dosage (mg/kg tid)				Background incidence
	0	1	9	80	mean (range)
1st	1.0	0.9	0	4.0	0.4 (
2nd	2.9	2.8	0	6.0	0.7 (
3rd	2.9	3.7	2.0	8.0	2.1
4th	6.7	5.6	4.9	9.0	4.3
Mean bodyweight of fetuses with one or more sacral arches incompletely ossified (g)	3.5	3.5	3.4	3.6	
Group mean bodyweight (g)	3.6	3.6	3.6	3.6	3.4 (

Kinking of ribs was recorded when an area of a rib shows a nodule of ossification, with or without an obvious change in direction of the rib. The sponsor indicated that background incidence data has shown that the spontaneous occurrence of kinked fibs in the Wistar Han strain of rat to be highly variable. The incidences recorded at the 80 mg/kg tid dosage were above the background data incidence mean and were, for this reason, considered to be related to treatment.

Table xx Kinked ribs

% fetuses affected	Dosage (mg/kg tid)				Background incidence
	0	1	9	80	mean (range)
4-6, slight, unilateral/bilateral	14.4	15.0	20.6	26.0	22.5
7-9, slight, unilateral/bilateral	13.5	16.8	21.6	29.0	23.3
10-13, slight, unilateral/bilateral	10.6	13.1	15.7	24.0	19.6

excludes data from studies R21330 and R21702

Slight dilation of the ureter describes a condition where the ureter shows some swelling, usually at the renal end only. The increase in incidence of this observation at 80 mg/kg tid was considered to be treatment-related.

Table xvii Dilated ureter

Parameter	Dosage (mg/kg tid)				Background incidence
	0	1	9	80	mean (range)
Unilateral/bilateral, slight					
% fetuses affected	1.0	1.5	1.0	3.1	0.5

When the innominate artery extends further than the right edge of the trachea it is described as elongated. The position of the innominate artery's origin on the aortic arch and the size, form and position of the vessels branching from it remain unchanged. The incidence recorded at 80mg/kg tid was higher than the top of the background data range and because of this an association with treatment could not be discounted.

Table xxi Elongated innominate artery

Parameter	Dosage (mg/kg tid)				Background incidence
	0	1	9	80	mean (range)
% fetuses affected	3.0	2.0	3.5	5.2	2.4

CONCLUSIONS:

Although the sponsor indicated that there is no statistical significance in toxicity findings of incomplete ossification of skull bones and sacral vertebral arches, kinked ribs, dilated ureter and elongated innominate artery, the sponsor did agree these toxicities are treatment related. The sponsor's conclusion that NOEL dose was 80 mg/kg is misleading and these treatment-related embryofetal toxicities should be reflected in the label and zanamivir's Pregnancy category should be changed from B to C.

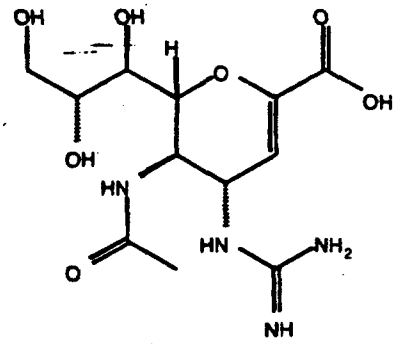
Regulatory Action:

Pregnancy:

s
of

MAR 2 2 2000

PHARMACOLOGIST'S REVIEW



IND Amendment no. **085 & 086**
Date Submitted: 2/23/00
Date Assigned: 2/29/00
Date Review Completed: 3/8/00
Reviewed by: Kuei-Meng Wu
HFD-530

SPONSOR: GlaxoWellcome Inc.
5 Moore Drive, Research Triangle Park, NC

DRUG: Zanamivir, GG167; GR121167; 5-(Acetylamino)-4-[(aminoiminomethyl)amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid; $C_{12}H_{20}N_4O_7$; MW: 332.3

INFORMATION TO SPONSOR: No

FORMULATION: Inhalation administration (18 mg GR121167/ml and 8 mg NaCl/ml in 1 m• water); *pK_a1* (guanidine group): 13; *pK_a2* (carboxyl group): 2.4

INDICATION: Anti-Influenza

INTRODUCTION

These two amendments are related to the sponsor's responses to the division's proposal for changes of Pregnancy Category labeling from B to C. The sponsor indicated that the increased incidences of incomplete ossification of skull bones and sacral vertebral arches, kinked ribs, dilated ureter and elongated innominate artery were within their historic controls. The sponsor pooled individual subcategory data under the skull bones category and showed a reduced difference between treatment group and controls. Similar manipulations were done for the ribs and sacral vertebral arches categories. The Reproductive Toxicity Committee, CDER, was consulted for this issue. The Committee concluded that the labeling should be changed as the original data showed. The sponsor accepted the final decision made by the division and the Committee. Detailed wordings of the labeling changes are as follows (underlined). No other regulatory comments on pharm/tox will be provided to the sponsor.

> **Pregnancy:** Pregnancy Category C. Embryo/fetal development studies were conducted in rats (dosed from days 6 to 15 of pregnancy) and rabbits (dosed from days 7 to 19 of pregnancy) using the same IV doses. Pre- and post-natal developmental studies were performed in rats (dosed from day 16 of pregnancy until litter day 21 to 23). In all studies, intravenous (1, 9, and 90 mg/kg per day) instead of the inhalational route of drug administration was used. No malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because of insufficient blood sampling timepoints in both rat and rabbit reproductive toxicity studies, AUC values were not available. However, in a subchronic study in rats at the 90-mg/kg-per-day IV dose, the AUC values were greater than 300 times the human exposure at the proposed clinical dose.
>
> <u>An additional embryo/fetal study, in a different strain of rat, was conducted using subcutaneous administration of zanamivir, 3 times daily, at doses of 1, 9, or 80 mg/kg during days 7 to 17 of pregnancy. There was an increase in the incidence rates of a variety of minor skeleton alterations and variants in the exposed offspring</u>

in this study. Based on AUC measurements, the high dose in the study produced an exposure greater than 1000 times the human exposure at the proposed clinical dose. However, the individual incidence rate of each skeletal alteration or variant, in most instances, remained within the background rates of the historical occurrence in the strain studied.

Zanamivir has been shown to cross the placenta in rats and rabbits. In these animals, fetal blood concentrations of zanamivir were significantly lower than zanamivir concentrations in the maternal blood.

There are no adequate and well-controlled studies of zanamivir in pregnant women. Zanamivir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

/S/

Kuej-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

cc:
86)
HFD-530/Division File
HFD-530/CSO/
HFD-530/MO/
HFD-530/Pharm/KWu

Concurrences:
HFD-530/Acting DepDir/WDempsey 3/22/00
HFD-530/PTL/JFarrelly 3/24/00
HFD-530/Wu/Pharm/3/8/00 3-22-00

Disk:
HFD-530/JFarrelly

APPEARS THIS WAY
ON ORIGINAL