CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-036/S-001

MICROBIOLOGY REVIEW(S)

Microbiology Review
Division of Antiviral Drug Products (HFD-530)

NDA: 21-036	**Serial No.** SE1-001 SE1-00BI	**Reviewer:**	N. Battula
Date submitted:	October 25, 1999	**Date received:**	October 26, 1999
Date assigned:	November 14, 1999	**Date reviewed:**	March 16, 2000

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

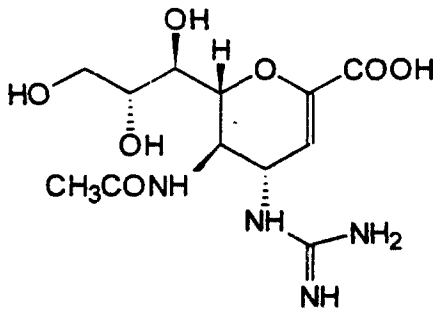
Product Names: Proprietary: Relenza®
Nonproprietary: Zanamivir
Code: GR121167X or GG167

Chemical name: 5-(acetylamino)-4-[(aminoiminomethyl)amino]- 2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enoic acid.

Empirical formula: $C_{12}H_{20}N_4O_7$

Molecular Weight: 332.3

Structural Formula:



Dosage form: Inhalation powder (Relenza Rotadisk)

Indication: Treatment of influenza A and B

Related documents:

BACKGROUND and SUMMARY: On July 26, 1999 Relenza® (NDA 21-036) was approved for the treatment of uncomplicated illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days. In this supplemental NDA, Glaxo Wellcome Inc. is requesting approval of Relenza® (inhalation powder) for the treatment of acute uncomplicated illness due to influenza virus in pediatric patients 5 to 12 years of age who have been symptomatic for no more than 2 days. The proposed indication is based on the results obtained from two (NA130009 and NA130010) Phase 3 placebo-controlled multicenter studies. Relenza® treatment effects were based on the assessment of the symptomatic course of influenza illness. The primary endpoint in these studies was the median time to alleviation of clinically significant signs and symptoms of influenza. Secondary endpoints involved multiple criteria including quantitative evaluation of influenza virus titers.

The virology portion of the supplemental NDA was provided in two parts. The first part (Volume 3, Virology Section) that was submitted with the original sNDA of October 25, 1999 contained a study report entitled "Report SR1999/00080/00: GR121167X (zanamivir) susceptibility monitoring of influenza clinical isolates from the NAI30009 clinical efficacy study of inhaled zanamivir for the treatment of influenza A and B infections in the children ages 5-12 (protocol NS130009)." The second part (SE1-00BI) was submitted on February 24, 2000 and contained a document "Response to FDA Request/Comment: Final Response to December 6, 1999 Comments (Sequencing Studies)."

Part 1 of the virology submission reported the evaluation of neuraminidase susceptibility profiles of influenza virus isolates from some of the pediatric subjects (5 to 12 years of age) enrolled in the clinical efficacy trial NAI30009. Table 1 shows methods of influenza diagnosis and profile of subjects (n=471) enrolled into the trial NAI30009. The diagnosis of influenza virus infection was confirmed by virus isolation from patient specimens that were collected at the local recruitment centers. Results from the local centers show that 226/471 (48%) of the trial enrollees were positive for influenza virus.

Table 1. Influenza virus diagnosis at local recruitment centers: Study NAI30009

Influenza diagnosis	Placebo	Zanamivir	Total
Total Subjects	247	224	471
Positive for influenza A	120	106	226
Positive for influenza B	62	58	120
Influenza type unknown	0	1	1
Positive by culture	116	110	226
Positive by PCR	162	144	306
Positive by Serology	129	118	247

Influenza virus neuraminidase activity was determined in virus isolates obtained from 9 zanamivir treated patients and 15 placebo treated patients from study NAI30009. The applicant was able to recover matched isolates from baseline, day 3 and day 6 from a single patient out of 9 zanamivir treated patients, and from 2 out of 15 placebo treated patients. Virus could not recovered from the 14-day specimens of zanamivir or placebo treated subjects.

The applicant stated that there were no significant shifts in the neuraminidase susceptibility of influenza virus isolates from any of the zanamivir or placebo treated pediatric patients. However, the number of virus isolates analyzed is too small a sample size to evaluate the potential for drug-induced changes in the susceptibility of influenza virus neuraminidase activity to zanamivir or genotypic changes in the viral hemagglutinin. Therefore, as stated above the sponsor is encouraged to improve the method of virus recovery in order to facilitate the generation of a sufficient number of serial samples from both placebo and zanamivir treated subjects such that the potential emergence of resistance to zanamivir may be properly defined. In addition this may facilitate addressing the subsequent question of zanamivir induced cross-resistance to other drugs of this class.

Part 2 of the virology submission contained sequencing data on the genotypic analysis of virus isolates from study NAI30009 that have been evaluated for changes in neuraminidase enzyme susceptibility. In this study, the influenza virus genes encoding

the hemagglutinin and the neuraminidase were sequenced to determine whether genotypic changes were occurring as a consequence of treatment with zanamivir. The applicant analyzed genetic sequences of matched (baseline, day 3 and day 6) influenza virus isolates from a single zanamivir treated patient and from 7 other zanamivir-treated patients with baseline virus isolate matched with day 3 isolate. Matched isolates at baseline, day 3, and day 6 were analyzed from two placebo treated patients for comparison. The sequencing data from the zanamivir treated patients were compared to the sequencing data of the 2 placebo treated patients.

Based on the neuraminidase and hemagglutinin sequencing results from these few samples the applicant stated that there were no changes in the NA gene. However, 3 substitutions in the hemagglutinin were observed in several isolates obtained from the zanamivir treated subjects. The applicant indicated that these substitutions were natural variations in the hemagglutinin and are unlikely to contribute to zanamivir resistance. The number and type of influenza virus samples collected and analyzed for phenotypic or genotypic changes in influenza virus are insufficient to support a broad conclusion on the potential for zanamivir induced phenotypic or genotypic resistance development in viral isolates.

Cross-resistance among neuraminidase inhibitors: In the class of neuraminidase inhibitors of influenza virus, zanamivir (Relenza®) was the first drug approved for treatment of influenza. Therefore, in the microbiology section of the (original) zanamivir label a cross-resistance section was not included. After zanamivir (Relenza®) approval, oseltamivir (Tamiflu®), another neuraminidase inhibitor of influenza virus was approved for the treatment of influenza. Resistance and cross-resistance data submitted by the sponsors of zanamivir and oseltamivir indicate the occurrence of phenotypic and genotypic cross-resistance between these two drugs in vitro. Therefore, in the revised version of the zanamivir (Relenza®) label a cross-resistance subsection was added to the microbiology section of the label (italicized) to reflect the cross-resistant between the two approved influenza virus neuraminidase inhibitors.

Cross-resistance: Cross-resistance has been observed between zanamivir-resistant and oseltamivir-resistant influenza virus mutants generated in vitro. No studies have been performed to assess the risk of emergence of cross-resistance during clinical use.

Draft microbiology label: Attached is the microbiology section of the label for zanamivir as of 3-20-2000. Revisions to the label are italicized.

MICROBIOLOGY:

Mechanism of Action: The proposed mechanism of action of zanamivir 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 zanamivir against laboratory and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of zanamivir required for inhibition of influenza virus were highly variable depending on the assay method used and virus isolate tested. The 50% and 90% inhibitory concentrations (IC_{50} and IC_{90}) of zanamivir were in the range of 0.005 to 16.0 μM and 0.05 to >100 μM, respectively (1 μM = 0.33 μg/ml). The relationship between the in vitro inhibition of influenza virus by zanamivir and the inhibition of influenza virus replication in humans has not been established.

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

In an immunocompromised patient infected with influenza B virus, a variant virus emerged after treatment with an investigational nebulized solution of zanamivir for 2 weeks. Analysis of this variant showed a hemagglutinin mutation (Thr 198 Ile) which resulted in a reduced affinity for human cell receptors, and a mutation in the neuraminidase active site (Arg 152 Lys) which reduced the enzyme's activity to zanamivir by 1000-fold.

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

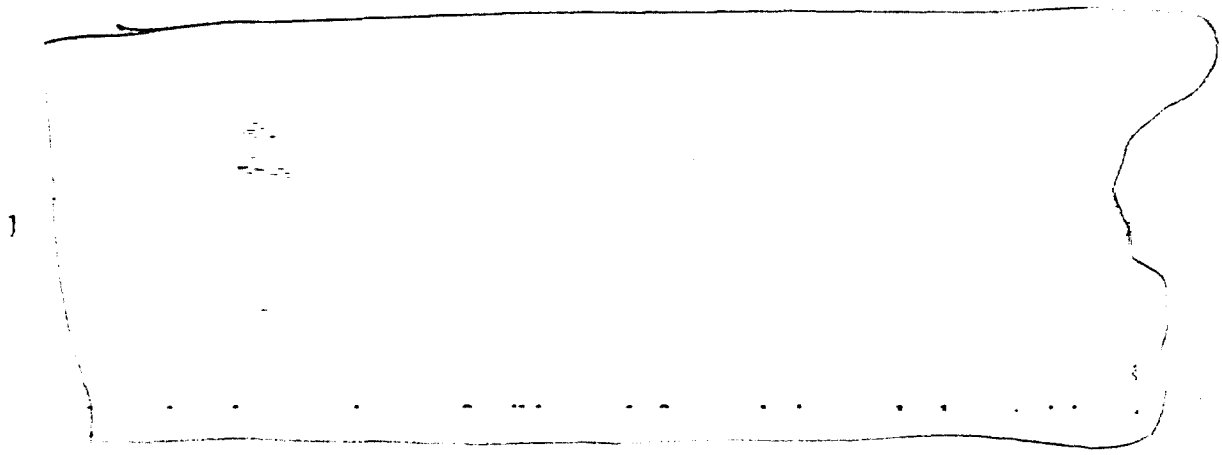
Cross-resistance: Cross-resistance has been observed between zanamivir-resistant and oseltamivir-resistant influenza virus mutants generated in vitro. No studies have been performed to assess the risk of emergence of cross-resistance during clinical use

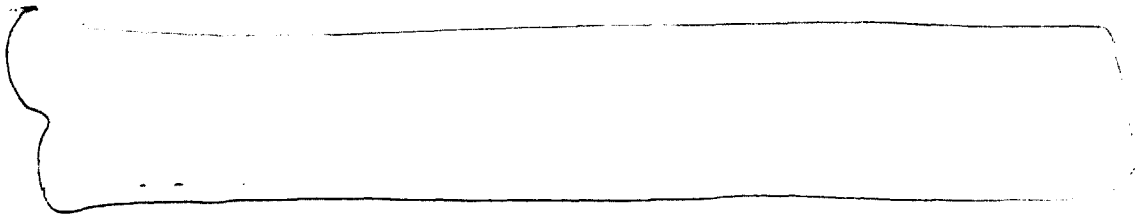
Influenza Vaccine Interaction Study: An interaction study (n = 138) was conducted to evaluate the effects of zanamivir (10 mg once daily) on the serological response to a single dose of trivalent inactivated influenza vaccine, as measured by hemagglutination inhibition titers. There was no clear difference in hemagglutination inhibition antibody titers at 2 weeks and 4 weeks after vaccine administration between zanamivir and placebo recipients.

Influenza Challenge Studies: Antiviral activity of zanamivir was supported for influenza A, and to a more limited extent for influenza B, by Phase I studies in volunteers who received intranasal inoculations of challenge strains of influenza virus, and received an intranasal formulation of zanamivir or placebo starting before or shortly after viral inoculation.

CONCLUSION: The microbiology data submitted in this sNDA supports the draft labeling claims in the microbiology section of the label.

RECOMMENDATIONS: **Phase 4 considerations;**





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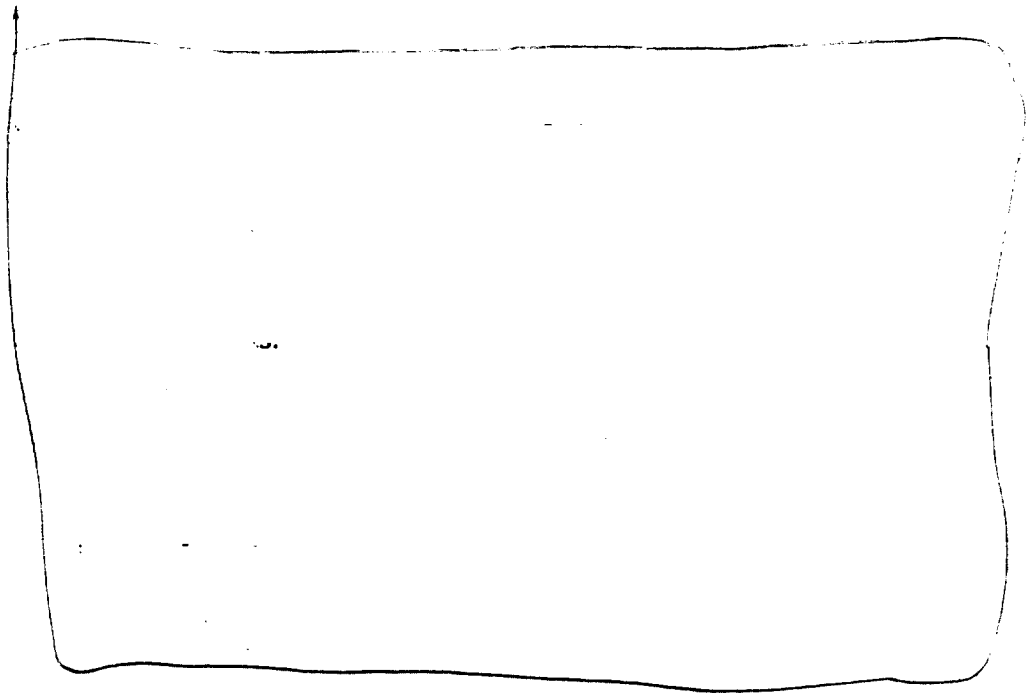

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ON ORIGINAL

/S/

Narayana Battula, Ph.D.

Concurrence:

HFD 530Assoc. Dir. 3/28/00

HFD 530/TLMicro 3/24/00

Distribution:

Original NDA

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HFD-530/MO

HFD-530/TLMicro

HFD-530/Reviewer Micro

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