

# Emergency Use Authorization for Intravenous Peramivir: Evaluation of Safety in the Treatment of Hospitalized Patients Infected With 2009 H1N1 Influenza A Virus

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(See the Major Article by Yu et al, on pages 8–15 and the Editorial Commentary by Pavia, on pages 16–8.)

**Background.** On 23 October 2009, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for intravenous peramivir, an unapproved antiviral, to treat suspected or confirmed 2009 H1N1 influenza A virus infection. Eligible hospitalized patients were unresponsive to or unable to tolerate available antivirals or lacked dependable oral or inhaled drug delivery routes. The EUA required healthcare providers to report medication errors, selected adverse events (AEs), serious AEs, and deaths to the FDA.

**Methods.** An FDA safety team analyzed reports submitted to the Adverse Event Reporting System (AERS) and sought follow-up in selected cases.

**Results.** The FDA received AERS reports for 344 patients (including 28 children and 3 pregnant women). Many patients were critically ill on mechanical ventilation (41%) and renal replacement therapies (19%); 38% had received oseltamivir. The most frequently reported serious AEs by MedDRA preferred term were death (15%), H1N1 influenza (8%), respiratory failure (8%), acute renal failure (7%), and acute respiratory distress syndrome (7%). Six medication errors were reported. Most deaths occurred among patients who were obese, immunosuppressed, aged >65 years, or received oseltamivir. Rash was the only treatment-emergent AE attributable to peramivir. Influenza severity, comorbidities, and concomitant medications confounded additional peramivir AE assessments. Missing clinical and laboratory data precluded evaluation of some reports.

**Conclusions.** Many peramivir recipients under the EUA were critically ill and at risk for influenza-related complications. The safety data were insufficient to assess whether peramivir affected outcome or caused adverse reactions other than rash. Clinical trials in hospitalized patients with serious influenza infections should provide additional information.

The 2009 H1N1 influenza A pandemic originated in Mexico in March 2009 and quickly spread to the

United States, prompting the Secretary of the US Department of Health and Human Services to declare a public health emergency on 26 April 2009 [1]. Oral oseltamivir and inhaled zanamivir, 2 commercially available neuraminidase inhibitors (NAIs) approved for acute uncomplicated influenza and influenza prophylaxis, were used for treatment. However, in view of reports of hospitalizations and deaths among pregnant women, children, and young adults [2, 3], it became apparent that those formulations may not have provided adequate drug delivery for critically ill patients with severe or life-threatening infections.

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Intravenous peramivir, an unapproved NAI [4], was initially accessible only through clinical trials or expanded access through the US Food and Drug Administration (FDA) during the early influenza activity peak in June 2009. However, as the pandemic activity expanded and at the request of the US Centers for Disease Control and Prevention (CDC), the FDA Commissioner issued an Emergency Use Authorization (EUA) on 23 October 2009 that enabled healthcare providers (HCPs) to access the drug for certain hospitalized adult and pediatric patients with suspected or confirmed 2009 H1N1 influenza [5]. This marked the first instance in which the FDA issued an EUA for an unapproved drug. Intravenous peramivir could be accessed through the CDC from 23 October 2009 to 23 June 2010, the termination date for the EUA. In place of labeling that would accompany an approved drug product, the FDA created a fact sheet [6] summarizing the conditions of use and the premarket safety and efficacy experience.

In this article, we provide a descriptive analysis of the safety data for intravenous peramivir accessed under the EUA. Although the EUA provided access to peramivir, use of a product under an EUA is not considered to be a clinical trial for safety assessment. Under the EUA, safety surveillance was limited to adverse event reporting to the FDA's Adverse Event Reporting System (AERS), which was established as the principal repository for drug safety information.

## METHODS

### FDA Adverse Event Reporting System

The EUA required that all medication errors, selected adverse events, serious adverse events, and deaths occurring during peramivir treatment be reported by HCPs to the FDA within 7 calendar days from the event onset. Neuropsychiatric, renal, serious skin, hypersensitivity, and severe intravenous administration-related events were selected adverse events subject to the reporting requirement, as they had been observed either in preclinical studies or in patients treated with other NAIs.

HCPs were instructed to report the adverse events to the FDA MedWatch Program by mail or online (<http://www.fda.gov/medwatch>). MedWatch is the FDA safety information and adverse event reporting program, which provides a gateway for HCPs and consumers to submit safety reports to the agency. Submitted MedWatch reports are subsequently incorporated into AERS, the FDA's computerized safety information database, permitting them to be accessed to support the agency's drug safety surveillance programs. The adverse event information in AERS is coded using the Medical Dictionary for Regulatory Affairs (MedDRA). MedDRA provides a standardized set of medical terms that allows more efficient information exchange and analysis by regulatory agencies and the pharmaceutical industry [7].

To conduct safety surveillance, the FDA assembled a multi-disciplinary safety team that monitored the adverse events reported to AERS. The following information was collected from each AERS report (if provided): age, sex, gravidity, FDA report received date, dose and duration of peramivir administration, concomitant antimicrobials, concurrent or preexisting medical conditions, laboratory tests for influenza A virus, treatment, reporter adverse event attribution, and outcome. We excluded duplicate AERS reports by comparing individual attributes contained in the reports involving patients of the same age, sex, and state of origin.

Death categorized as an outcome or an adverse event was inconsistently coded in the AERS reports. Therefore, for our mortality analysis, we included all patients with an outcome of death coded as an adverse event and all patients whose narrative summaries indicated that they had died during or following peramivir therapy regardless of the outcome designation or adverse event coding.

### Statistical Analysis

In this case series, we provided a descriptive safety analysis using tables and measures of central tendency. We were unable to provide an analysis based on a prespecified study hypothesis supported by tests of statistical significance owing to the lack of randomization to a parallel active control treatment group and substantial missing data in the AERS reports.

## RESULTS

### Peramivir Exposure

From 23 October 2009 to 23 June 2010, the CDC processed 1371 requests for releases of intravenous peramivir, each for the treatment of a specific individual. The CDC conducted 3 follow-up surveys to assess actual product use, which indicated that at least 1274 patients had received  $\geq 1$  dose of the drug. However, the total number of peramivir recipients could not be determined [8].

### FDA Safety Subgroup

The FDA received 369 AERS reports describing 900 adverse events, including medication errors and deaths, in 344 unique patients (which constitute the "FDA Safety Subgroup"). The FDA received most of the reports between late October and December 2009, corresponding with peak releases of peramivir by the CDC during the height of influenza activity in the fall of 2009. Additional information compiled by an FDA-hired contract research organization and by the CDC based on follow-up surveys of HCPs were also included in the 344-patient database. Sixteen duplicate reports and 9 reports of peramivir use not conducted under EUA auspices were excluded from the analysis. Because EUAs are not considered to be clinical investigations,

no safety or outcome information was collected for patients who received peramivir but for whom no AERS report had been submitted to the FDA. Thus, our safety database was limited to the subgroup of 344 patients for whom the FDA received at least 1 adverse event report.

Table 1 summarizes select demographic characteristics of patients in the FDA safety subgroup and indicates the magnitude of missing data. Overall, the median age was 45 years (range, <1–90 years), and females constituted 45% of the subgroup. The median duration of peramivir administration

**Table 1. Characteristics of Patients in the FDA Safety Subgroup (N = 344)**

Characteristic	No. (%)
<b>Age</b>	
Pediatric patients, aged <18 years	28 (8)
Adult patients, aged 18–65 years	290 (84)
Elderly patients, aged >65 years	21 (6)
Age not reported	5 (1)
<b>Comorbidities reported with frequency ≥5%</b>	
Immunosuppression <sup>a</sup>	57 (17)
Obesity (obesity and morbid obesity)	52 (15)
Hypertension	40 (12)
Chronic pulmonary disorders (asthma or COPD)	30 (9)
Diabetes mellitus	28 (8)
Cardiac conditions <sup>b</sup>	18 (5)
Comorbidities frequency <5% or not reported	85 (25)
<b>Indicators of illness severity reported with frequency ≥5%</b>	
Mechanical ventilation	141 (41)
Renal replacement therapies, including dialysis	64 (19)
Multiorgan failure	28 (8)
Extracorporeal membrane oxygenation	18 (5)
Indicators of illness severity frequency <5% or not reported	152 (44)
<b>Reported prior or concomitant antimicrobial agents<sup>c</sup></b>	
Oseltamivir	132 (38)
Zanamivir intravenous (investigational)	1 (<1)
Other nonneuraminidase inhibiting antivirals <sup>d</sup>	6 (2)
Antibacterial drugs	104 (30)
Prior or concomitant antimicrobial agents not reported	177 (51)
All-cause mortality (reported deaths) <sup>e</sup>	206 (60)

Abbreviations: COPD, chronic obstructive pulmonary disease; FDA, US Food and Drug Administration.

<sup>a</sup> Including malignancy, leukemia, lymphoma, multiple myeloma, bone or organ cancer, bone marrow or stem cell transplant, organ transplant, myelodysplasia or dysplastic syndrome, myelofibrosis, pancytopenia, human immunodeficiency virus, AIDS, aplastic anemia.

<sup>b</sup> Including coronary artery disease, myocardial infarction, congestive heart failure, atherosclerotic cardiovascular disease, heart failure, cardiomyopathy, atrial fibrillation.

<sup>c</sup> Not mutually exclusive.

<sup>d</sup> Amantadine (n = 2), acyclovir (n = 3), antiretroviral therapy (abacavir, lamivudine, efavirenz; n = 1).

<sup>e</sup> Includes 18 elderly (>65 years), 169 adults (18–65 years), 16 pediatric (age <18 years), and 3 others (age not reported).

was 5 days (range, 1–14 days) based on data reported for 260 patients. Eighteen patients received peramivir for >10 days, whereas 36 patients received only 1 dose. The most common comorbidities included immunosuppression, obesity, hypertension, chronic pulmonary diseases, diabetes mellitus, and cardiac disease. A large proportion of patients were substantially ill and received mechanical ventilation, renal replacement therapies, and extracorporeal membrane oxygenation. Eight percent of the patients also experienced multiorgan failure.

Oseltamivir was the most commonly administered antiviral agent; however, it was not possible to determine the proportion of patients who received prior oseltamivir therapy compared to coadministration with peramivir owing to missing data from the AERS reports. Sixteen peramivir recipients had negative laboratory tests for 2009 H1N1 influenza virus, and 3 patients had strains that exhibited in vitro resistance to peramivir.

Antibacterial drugs were prescribed to 30% of patients in the FDA Safety Subgroup primarily because of concerns about concomitant bacterial pneumonia or sepsis. Bacterial coinfections due to specific pathogens were reported in only 10 patients (3%), involving *Streptococcus* species (n = 1), *Staphylococcus* species (n = 1), *Acinetobacter* species (n = 2), *Escherichia coli* (n = 1), *Enterococcus* species (n = 2), *Pseudomonas* species (n = 1), or *Klebsiella* species (n = 2).

### Serious Adverse Events

The most frequent MedDRA-coded serious adverse event in the FDA Safety Subgroup was death (15%; 53 of 344 patients). As shown in Table 2, *H1N1 influenza, respiratory failure, acute respiratory distress syndrome* (ARDS), and *disease progression* were the predominant MedDRA-coded preferred terms, excluding death, and likely reflected in part the severity of the patients' influenza A infection. Additionally, *renal failure acute* and *renal failure* were other commonly reported MedDRA-coded preferred terms. Laboratory test abnormalities were infrequently reported as adverse events (Table 2). Of the laboratory test abnormalities, *blood creatinine increased, alanine aminotransferase increased, aspartate aminotransferase increased, and liver function test abnormal* were reported with ≥1% frequency.

### Serious Adverse Events With Frequency of <1% in the FDA Safety Subgroup

The serious adverse events that occurred at a rate of ≤1% included convulsion, hepatic failure, pancreatitis, ventricular fibrillation, aplastic anemia, pancytopenia, Stevens-Johnson syndrome, and torsades de pointes. Independent review by FDA Safety Team members could not establish causality with respect to any of those events owing to confounding by influenza severity, concomitant medications, or concurrent medical disorders.

**Table 2. Adverse Events<sup>a</sup> With Reporting Frequency  $\geq 2\%$  by MedDRA<sup>b</sup> Preferred Term (N = 344)**

Adverse Event by Preferred Term (No.) <sup>c</sup>	Reporting Frequency
Death (53) <sup>d</sup>	15%
H1N1 influenza (26), respiratory failure (26)	8%
Acute respiratory distress syndrome (25), renal failure acute (25)	7%
Disease progression (21)	6%
Renal failure (17), hypotension (16)	5%
Cardiac arrest (15), no therapeutic response (14), pneumothorax (14), renal disorder (14), blood creatinine increased (13), pneumonia (13)	4%
Condition aggravated (12), hemodialysis (12), delirium (11), multiorgan failure (11), cardiorespiratory arrest (9), electromechanical dissociation (9), hypoxia (9)	3%
Agitation (8), alanine aminotransferase increased (8), aspartate aminotransferase increased (8), liver function test abnormal (8), renal impairment (8), rash (7), rash erythematous (7), brain death (6), continuous hemofiltration (6), general physical health deterioration (6), pyrexia (6)	2%

<sup>a</sup> Not mutually exclusive.

<sup>b</sup> MedDRA (Medical Dictionary for Regulatory Affairs) is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

<sup>c</sup> No. = number of patients with the reported adverse event.

<sup>d</sup> Refers only to deaths in which the fatal outcome was MedDRA-coded as an adverse event in the AERS reports.

### Adverse Events in Pregnancy

Three women received peramivir during pregnancy or parturition. One asthmatic female experienced a miscarriage 6 days after discontinuation of peramivir. Another patient with renal failure and ARDS from presumed influenza virus infection delivered a healthy baby on the second day of peramivir administration. The third patient had severe pneumonia requiring mechanical ventilation and experienced delirium and extremity weakness, which resolved following extubation. None of the adverse events described above were attributed to peramivir by the reporting HCP.

### Adverse Drug Reactions

Following review of the AERS reports, we assessed rash as a drug-related adverse reaction. Urticarial, erythematous, and maculopapular rashes developed during peramivir exposure and later improved following withdrawal of the drug indicative of a positive dechallenge. Of the 21 patients with rash, HCPs attributed skin reactions to peramivir in 13 patients. One patient exhibited a positive rechallenge in which rash recurred following readministration of the drug. Rash onset latencies were estimated in 8 cases in which reporters characterized rash onset as occurring “shortly” after the first dose up to 8 days after the initial peramivir exposure.

**Table 3. Reporter-Attributed Adverse Events<sup>a</sup> (N = 344)**

Adverse Event Type (No.) <sup>b</sup>	Reporting Frequency
Nonserious skin (13) <sup>c</sup>	4%
Hepatic (6) <sup>d</sup>	2%
Hematuria (3), neuropsychiatric (3) <sup>e</sup> , other (3) <sup>f</sup>	1%
Angioedema (2), hematopoietic (2) <sup>g</sup> , pancreatitis (2), renal (2) <sup>h</sup> , cardiac (1) <sup>i</sup>	<1%

<sup>a</sup> Not mutually exclusive.

<sup>b</sup> No. = number of patients with the reported adverse event.

<sup>c</sup> Urticarial, erythematous, or maculopapular rash.

<sup>d</sup> Increased liver function tests, increased bilirubin, liver failure.

<sup>e</sup> Agitation, delirium, hallucination.

<sup>f</sup> Tinnitus, headache, diarrhea.

<sup>g</sup> Neutropenia, pancytopenia, aplastic anemia.

<sup>h</sup> Acute renal failure, serum creatinine increased.

<sup>i</sup> Sinus tachycardia and sinus bradycardia.

### Reporter Attribution in Adverse Event Reporting

Reporting HCPs infrequently attributed adverse events to peramivir. Thirty-five (10%) patients in the FDA Safety Subgroup experienced 37 adverse events in which HCPs could not exclude a contributory role for peramivir or considered peramivir as the primary suspect drug. The adverse events that were most frequently attributed to peramivir by reporting HCPs were nonserious and included rash, urticaria, tinnitus, headache, and diarrhea (Table 3). Other serious adverse events potentially attributed to peramivir included pancreatitis, delirium, neutropenia, renal failure, angioedema, hepatic failure, aplastic anemia, pancytopenia, sinus bradycardia, and sinus tachycardia. However, except for rash, FDA review revealed insufficient clinical details or confounding by influenza severity, concomitant medications, and concurrent medical disorders that precluded causality assessments.

### All-Cause Mortality

A total of 206 deaths were reported to AERS. Notwithstanding some uncertainty about the true number of peramivir-exposed patients (which was likely higher than reported) and the potential for unreported deaths, we estimated the overall proportion of reported deaths among all known peramivir recipients to be 16% (206 of 1274 patients).

In the 344-patient FDA Safety Subgroup, the 206 deaths included 53 patients with an outcome of death coded as an adverse event (Table 2) and 153 patients whose death was not coded as an adverse event but was evident upon review of the narrative summaries. None of the deaths were attributed to peramivir by the reporting HCPs.

Many fatalities had identifiable risk factors that could complicate their influenza course and increase the risk for death (Table 4). The most common risk factors for complications of

**Table 4. Risk Factors<sup>a</sup> for Complications of Influenza Identified in Fatal Cases (N = 206)**

Risk Factor	No. (%)
Immunosuppression <sup>b</sup>	43 (21)
Obesity	37 (18)
Hypertension	32 (16)
Diabetes mellitus	22 (11)
Chronic respiratory disorders (COPD and asthma)	20 (10)
Age >65 years	18 (9)
No risk factor	12 (6)
Cardiac disorders (CHF, MI, CAD)	13 (6)
Neurologic disorders <sup>c</sup>	7 (3)
Not reported	47 (23)

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

<sup>a</sup> Not mutually exclusive.

<sup>b</sup> Including malignancy, leukemia, lymphoma, multiple myeloma, human immunodeficiency virus/AIDS, aplastic anemia, bone or organ cancer, stem cell transplant, organ transplant, myelodysplasia, myelodysplastic syndrome, and myelofibrosis.

<sup>c</sup> Intracranial hemorrhage, subdural hematoma, Down syndrome, developmental delay, mental retardation.

influenza in the fatal cases included immunosuppression, obesity, and hypertension. Diabetes mellitus and chronic pulmonary disorders (chronic obstructive pulmonary disease and asthma) were other frequently reported risk factors.

Although the elderly constituted the smallest percentage of the FDA Safety Subgroup by age (Table 1), deaths were more common among patients aged >65 years (86%, 18 of 21) compared to younger adults and children. Among pediatric patients aged <18 years, 57% (16 of 28) died; fatalities occurred in 58% (169 of 290) of adults aged 18–65 years.

Of the reports that provided information on concomitant medications, patients who died were more likely to have received prior or concomitant oseltamivir compared to survivors. Among known oseltamivir recipients in the FDA Safety Subgroup, 37 patients survived whereas 95 died. However, data was not reported to assess whether the imbalance reflected lack of therapeutic effect due to resistance development or refractory clinical illness. Additionally, 21 patients received high doses of oseltamivir (150 mg twice daily) that were beyond the range recommended in the product label.

#### Medication Errors

Six peramivir-treated patients experienced medication errors that were reported to the FDA. The 6 cases included use of the wrong diluent to prepare the drug (n = 1), omission of the final dose as the drug was delivered frozen to the patient care unit (n = 1), dosing errors associated with impaired renal function (n = 3), and an uncharacterized medication error (n = 1). No adverse outcomes were attributed to the medication errors.

## DISCUSSION

The estimated mortality rate from 2009 H1N1 influenza among all known peramivir recipients was 16%, accounting for the limitations of our calculation discussed previously. This mortality estimate is within the 14.3%–46% range reported in published studies [9–12]. However, interpretation of published mortality data is problematic in view of inconsistent reporting time periods, varying from deaths occurring during hospitalization to deaths reported at 90 days after disease onset. Additionally, as with other reported adverse events, the mortality data for the FDA Safety Subgroup may underestimate the actual number of fatalities due to unreported deaths or deaths occurring outside of the peramivir treatment time period.

#### FDA Safety Subgroup

Most patients in the FDA Safety Subgroup were aged <65 years with moderate to severe influenza and progressive hypoxemia or multiorgan impairment requiring mechanical ventilation and renal replacement therapies. Immunosuppression and obesity enhanced the risk for complications and death. These findings paralleled trends described in published reports of critically ill patients with 2009 H1N1 influenza A infection [13]. However, in contrast to published studies, pregnant women constituted <1% of the FDA Safety Subgroup, and only 8% of the patients were reported as previously healthy.

In published reports on hospitalized patients with 2009 H1N1 influenza A virus infection, the highest fatality rates involved those who were obese, diabetic, immunosuppressed, and received mechanical ventilation, vasopressor medications, and renal rescue therapies [14]. Patients aged ≥65 years were at increased risk for influenza complications [13]. Similarly, patients who died in the FDA Safety Subgroup were frequently elderly and immunosuppressed, had end-organ dysfunction, and received prior or concurrent oseltamivir.

Peramivir has a high rate of renal excretion. In the FDA Safety Subgroup, 16% had renal adverse events described by preferred terms (not mutually exclusive) as *renal failure*, *renal failure acute*, and *blood creatinine increased*, and approximately 19% required renal replacement therapies (including dialysis). However, given baseline renal impairment due to concomitant medical disorders and critical clinical condition combined with the lack of clinical details in the AERS reports, we were unable to determine whether renal impairment reflected nephrotoxicity from peramivir or organ dysfunction due to infection severity, hypotension, or exposure to other potentially nephrotoxic medications.

#### Published Clinical Trials of Intravenous Peramivir

Kohno and colleagues published the results of 2 clinical trials assessing intravenous peramivir in the treatment of influenza

virus infections. In a randomized, double-blind, placebo-controlled trial of 300 previously healthy adults with seasonal influenza administered a single dose of peramivir (300 or 600 mg) or placebo, diarrhea, nausea, and changes in clinical laboratory test values were the most common adverse events across the drug and placebo groups [15]. In an uncontrolled, double-blind, randomized trial of intravenous peramivir (300 or 600 mg/day) for 1–5 days in 42 high-risk patients with influenza A or B infection, diarrhea, changes in clinical laboratory test values, pneumonia, and oral herpes were the most frequently reported adverse events [16].

Several features of the clinical trials above preclude comparison with the FDA Safety Subgroup. First, both clinical trials excluded critically ill patients with serious comorbid conditions, respiratory failure requiring mechanical ventilation, and hemodialysis, who could access peramivir under the EUA. Second, neither clinical trial limited enrollment to patients with suspected or proven 2009 H1N1 influenza A virus. Third, the single-dose peramivir trial restricted enrollment to patients aged 20–64 years, excluding pediatric and elderly patients who could receive the drug under the EUA. Fourth, the multiple-dose study in high-risk patients included only 42 individuals, which was smaller than the FDA Safety Subgroup and lacked statistical power to assess rare adverse events.

### Limitations

The EUA for peramivir was not considered a clinical investigation and was not primarily intended to provide data sufficient for safety assessments. Clinical and outcome information was not routinely collected on all peramivir recipients; the adverse event reports submitted to AERS served as the only source for safety data. Our analysis was subject to selection bias, as the FDA Safety Subgroup may not have been representative of all patients who received the drug under the EUA. Channeling bias, in which patients with more advanced disease may preferentially have been selected for treatment with peramivir, may be another potential confounding factor. Additionally, adverse event reporting to AERS was prone to underreporting and substantial missing data, which precluded causality assessments for many adverse events and deaths. In view of uncertainties related to safety information reporting and the number of peramivir-exposed patients, we were unable to estimate the incidence of adverse events.

### Conclusions

There are several important conclusions based on our review of this case series. First, the safety data compiled for intravenous peramivir under the EUA do not allow a determination of whether exposure to the drug adversely affected outcome in hospitalized patients with 2009 H1N1 influenza. Many patients were critically ill and had independent risk factors for

influenza-related complications. However, published toxicology and limited clinical trials data suggest that treatment with intravenous peramivir administered at the doses and duration used in the EUA would have been unlikely to adversely affect outcome. Second, in view of the high background rate of organ system dysfunction, severity of illness, comorbidities, and substantial missing data, we could not reliably determine whether serious adverse events other than rash occurred as drug-related toxicities. The peramivir safety data were inadequate to demonstrate causal associations, as confounding and lack of clinical and laboratory details hindered independent assessment of potential drug–adverse event associations.

Currently, peramivir is an unapproved, investigational NAI. Clinical trials in hospitalized patients with serious influenza infections should provide additional safety information.

### Notes

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