

Health Update:

CDC Considerations Related to Investigational Use of Intravenous Zanamivir for 2013-2014 Influenza Season

February 4, 2014

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Health Update
February 4, 2014

FROM: GAIL VASTERLING
DIRECTOR

SUBJECT: CDC Considerations Related to Investigational Use of Intravenous Zanamivir for 2013-2014 Influenza Season

The Centers for Disease Control and Prevention (CDC) has recently provided information, reproduced below, on intravenous (IV) zanamivir. There are, according to CDC, certain clinical situations where the use of IV zanamivir may be considered for patients with influenza. Because IV zanamivir is an investigational product, it is available only by enrollment in an ongoing clinical trial, or under an emergency investigational new drug (EIND) request to the manufacturer for use in hospitalized adult and pediatric patients with severe influenza. Included in the information below is how clinicians can make a request to determine a patient's eligibility for an ongoing clinical trial, or to use IV zanamivir under EIND if not able to enroll in an available clinical trial.

Intravenous Influenza Antiviral Medications and CDC Considerations Related to Investigational Use of Intravenous Zanamivir for 2013-2014 Influenza Season

Centers for Disease Control and Prevention January 30, 2014

<http://www.cdc.gov/flu/professionals/antivirals/intravenous-antivirals.htm>

Intravenous (IV) formulations have been developed for three neuraminidase inhibitor medications (oseltamivir, peramivir, zanamivir). However, IV peramivir and IV oseltamivir are currently not available via clinical trial, compassionate use, or Emergency Use Authorization.

IV Zanamivir: Background and Clinical Indications

Zanamivir is a neuraminidase inhibitor antiviral medication with the same mechanism of action as oseltamivir. The FDA-approved formulation of zanamivir is the inhaled dry powder (Relenza®) delivered via a diskhaler device, and its use is summarized elsewhere ([Influenza Antiviral Medications: A Summary for Clinicians](#)). IV zanamivir aqueous solution is an investigational product available only by enrollment in an ongoing clinical trial, or under an emergency investigational new drug (EIND) request to the manufacturer for use in hospitalized adult and pediatric patients with severe influenza.

- For the 2013-14 season (as of January 27, 2014) most tested influenza viruses have been susceptible to both oseltamivir and zanamivir; oseltamivir-resistant 2009 H1N1 viruses have been reported rarely to date.
- Enhanced surveillance for oseltamivir-resistant 2009 H1N1 viruses is ongoing.¹ While oseltamivir resistance among circulating U.S. influenza viruses is low to date, resistance can emerge during or after oseltamivir treatment in certain patients with prolonged influenza virus shedding (e.g., severely immunosuppressed patients, such as hematopoietic stem cell transplant recipients) [1-3]. Most oseltamivir-resistant H1N1 viruses have remained susceptible to zanamivir in laboratory testing thus far [4-6].

Office of the Director
912 Wildwood
P.O. Box 570
Jefferson City, MO 65102
Telephone: (800) 392-0272
Fax: (573) 751-6041
Web site: <http://www.health.mo.gov>

- Clinical trials of approved neuraminidase inhibitors, oral oseltamivir and inhaled dry powder zanamivir, have demonstrated some reduction in median time to symptom improvement when used for treatment of acute, uncomplicated influenza illness in otherwise healthy persons [7-16]. CDC has made recommendations below for other uses based on observational data [17-29] and on expert opinion.
- The efficacy and safety of IV zanamivir for treatment of patients hospitalized with severe influenza have not been established, but are currently being evaluated in clinical trials. In view of the limited alternatives, CDC recommends that investigational use of IV zanamivir may be considered for severely ill patients with oseltamivir-resistant 2009 H1N1 virus infection ([Antiviral Drug Resistance among Influenza Viruses](#)) [30-32].
- For hospitalized patients and patients with severe or complicated illness, CDC recommends treatment with oral oseltamivir. Limited data suggest that oseltamivir delivered by oral or nasogastric administration is generally well absorbed in critically ill influenza patients, including those in the intensive care unit, on continuous renal replacement therapy, and/or on extracorporeal membrane oxygenation [33-41]. There have been rare reports of patients with suspected decreased oral oseltamivir absorption because of decreased gastric motility or gastrointestinal bleeding [35, 40].
- For patients who cannot tolerate or absorb oral oseltamivir because of suspected or known gastric stasis, malabsorption, or gastrointestinal bleeding, the use of investigational IV zanamivir may be considered.
- Currently, phase III trials are evaluating the effectiveness of IV zanamivir compared to oral oseltamivir for treatment of patients hospitalized with severe influenza. At this time there is no evidence that an IV formulation of a neuraminidase inhibitor would be more effective than oral oseltamivir, especially if there are no concerns regarding absorption and oseltamivir resistance.
- Controlled clinical trials of oral oseltamivir and inhaled dry powder zanamivir generally enrolled patients with acute uncomplicated influenza illness within 2 days of illness onset. All neuraminidase inhibitor medications work best when administered early. While it is generally expected that treatment is most effective if initiated within 2 days of illness onset [7-22, 24, 27-29, 42-47], some studies suggest there may be benefit if initiated up to 4 or 5 days after illness onset [22, 23, 25, 26, 28, 48-55]. However, delay in treatment initiation may result in reduced effectiveness.
- Oseltamivir and zanamivir, either inhaled or IV, should not be administered together [56].
- Inhaled zanamivir (Relenza[®]) is not recommended for use in patients with severe influenza disease because of the lack of data. The inhaled dry powder formulation of zanamivir (Relenza inhalation powder) must not be made into an extemporaneous solution for administration by nebulization or mechanical ventilation [57, 58]. Relenza Inhalation Powder must only be administered using the device provided.

How to Evaluate Clinical Trial Eligibility or Submit a Request for an IV Zanamivir Emergency IND

Ongoing clinical trials can be located at www.ClinicalTrials.gov. A request to determine a patient's eligibility for an ongoing clinical trial, or use IV zanamivir under EIND if not able to enroll in an available clinical trial, may be made by contacting the GSK Clinical Support Help Desk via email (gskclinicalsupportHD@gsk.com) or by calling 1-877-626-8019 or 1-866-341-9160. Availability is 7 days a week, 24 hours/day, including holidays. The GSK Clinical Support Help Desk will assess eligibility for clinical trials, and will provide information and instructions on obtaining IV zanamivir (i.e.,

EIND process), and provide the Request for Patient Information Form that needs to be completed for FDA review if a patient is not eligible for enrollment in an ongoing clinical trial and the physician wishes to request an EIND.

The EIND paperwork does not need to be completed before contacting the FDA, so a requesting clinician should contact GSK first, and then quickly contact FDA. To contact FDA:

- During normal business hours (8:00 a.m. – 4:30 p.m. Eastern Time), please call DAVP at 301-796-1500 or email DAVPEINDREQUEST@fda.hhs.gov.
- After normal business hours (weekdays after 4:30 p.m. or before 8:00 a.m. Eastern Time; weekends or holidays), please call the FDA Emergency Coordinator at 1-866-300-4374 or 301-796-8240 or the CDER Emergency Coordinator at 301-796-9900.

¹ A subset of influenza viruses collected for national surveillance and additional specimens from public health and academic laboratories are tested for resistance to neuraminidase inhibitors, and results are shared with CDC. This information is presented in the antiviral resistance section of the [FluView](#) report. Testing for oseltamivir resistant viruses at CDC can be requested via state laboratories.

[In Missouri, influenza-related questions can be directed to the Missouri Department of Health and Senior Services' Bureau of Communicable Disease Control and Prevention at 573/751-6113. Access to comprehensive information and guidance for medical providers and public health professionals on seasonal influenza is available at <http://health.mo.gov/emergencies/ert/med/seasonal.php>.]

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