

DPHHS HAN

From: DPHHS HAN
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Attachments: Peramivir Brief.pdf

State of Montana DPHHS HAN ADVISORY

Tuesday, October 27, 2009

Forwarding Instructions:

Please **FORWARD** this information on to your local Health Care Providers and Hospital HAN Contacts

DPHHS Information / Recommendations:

Important Information Regarding the Availability of a New Influenza Antiviral Medication

The FDA has issued an emergency use authorization (EUA) for an influenza antiviral medication that was previously only available as an investigational drug. This medication, Peramivir, is a neuraminidase inhibitor (like oseltamivir and zanamivir) that is administered intravenously (IV). The EUA is for use in hospitalized patients with confirmed or suspected 2009 H1N1 influenza A infection. Specifically, IV peramivir is authorized only for hospitalized adult and pediatric patients for whom therapy with an IV drug is clinically appropriate, based on one or more of the following reasons:

1. the patient is not responding to either oral or inhaled antiviral therapy, or
2. when drug delivery by a route other than an intravenous route -- e.g., enteral (absorbed by the intestines) or inhaled -- is not expected to be dependable or feasible;
3. for adults only, when the clinician judges IV therapy is appropriate due to other circumstances.

The drug is being held in the Strategic National Stockpile and distributed directly to a treating physician only by CDC. A brief excerpt from the fact sheet on the product is attached. More detailed information about Peramivir, indications for its use, and the steps physicians must follow to request this medication are detailed on the CDC web-site at:

<http://www.cdc.gov/h1n1flu/eua/peramivir.htm>

DPHHS Subject Matter Expert (SME) Contact:

For more information contact Dr. Steven Helgerson at (406) 444-7374

Distributed by the Department of Public Health and Human Services Health Alert Network (HAN) System

DPHHS Health Alert Hotline: 1-800-701-5769

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The goal of Montana's Health Alert Network is to transmit information to local public health authorities as quickly as possible, and assign a suitable priority to the message. For questions or comments about Montana's HAN system you may contact the DPHHS HAN Coordinator, Gerry Wheat at gwheat@mt.gov.

Categories of Health Alert Messages:

Health Alert: conveys the highest level of importance; warrants immediate action or attention.

Health Advisory: provides important information for a specific incident or situation; may not require immediate action.

Health Update: provides updated information regarding an incident or situation; unlikely to require immediate action.

EMERGENCY USE AUTHORIZATION OF PERAMIVIR IV FACT SHEET FOR HEALTH CARE PROVIDERS

**Peramivir Injection 200 mg/20mL (10 mg/mL) is an unapproved product
Peramivir must be administered intravenously**

The Secretary of the Department of Health and Human Services (HHS) has declared the rapid and extensive incidence of 2009 H1N1 infection a public health emergency that justifies the emergency use of certain drugs to treat 2009 H1N1 influenza. In response to this emergency, the Food and Drug Administration (FDA) has authorized the use of the unapproved drug, Peramivir IV, to treat certain adult and pediatric patients with suspected **or** laboratory confirmed 2009 H1N1 infection **or** infection due to nonsubtypable influenza A virus suspected to be 2009 H1N1 based on community epidemiology.

Do not use Peramivir IV for the treatment of seasonal influenza A or B virus infections, for outpatients with acute uncomplicated 2009 H1N1 virus infection or for pre- or post-exposure chemoprophylaxis (prevention) of influenza.

The prescribing health care provider and/or their designee is/are responsible for mandatory FDA MedWatch reporting of all medication errors and selected adverse events occurring during Peramivir IV treatment within 7 calendar days from the onset of the event. **See the Adverse Reactions and Medication Errors section below for details on the required FDA MedWatch reporting.**

To request Peramivir IV under Emergency Use Authorization (EUA) go to:
www.cdc.gov/h1n1flu/eua.

FDA has authorized the emergency use of Peramivir IV under EUA based upon its conclusion that the statutory criteria have been met. Even though there are a number of limitations to the safety and efficacy data available at this stage of Peramivir's development and the data reported are preliminary in nature, based upon the totality of scientific evidence available, it is reasonable to believe that Peramivir IV may be effective in certain patients as specified in this Fact Sheet.

The health care provider should communicate to the patient or parents/caregiver information consistent with this Fact Sheet and/or **the Fact Sheet for Patients and Parents/Caregivers** prior to the patient receiving Peramivir IV, including:

- (1) The Secretary of HHS has authorized the emergency use of Peramivir IV, which is not an FDA approved drug.
- (2) The patient has the option to accept or refuse Peramivir IV
- (3) The significant known and potential risks and benefits of Peramivir IV and the extent to which such risks and benefits are unknown;

(4) Information on available alternative treatments and the risks and benefits of those alternatives.

HIGHLIGHTS:

This section provides a brief introduction to selected information on use of Peramivir IV under EUA. Health care providers must read the full Fact Sheet for Health Care Providers that follows.

- Peramivir, a neuraminidase inhibitor, is an intravenous (IV) drug authorized for emergency use for the treatment of certain hospitalized patients with known or suspected 2009 H1N1 influenza.
- Peramivir IV is an unapproved drug and is still being evaluated in phase 3 clinical trials. Limited phase 2 and 3 safety and efficacy data for Peramivir IV are available, but not sufficient to constitute an adequate basis to establish safety and efficacy that is required for full marketing approval. The data are sufficient to allow approval for emergency use of Peramivir IV in certain patients as described herein.
- The standard adult dose of Peramivir is 600 mg once a day, administered intravenously for 5 to 10 days.
- Commonly reported adverse events in Peramivir IV clinical trials were diarrhea, nausea, vomiting, and neutropenia. Additional adverse events associated with the drug, some of which may be serious, may become apparent with more widespread use.
- Although not observed in clinical trial data available to date Peramivir IV may be associated with rare cases of anaphylaxis and serious skin reactions and a variety of neurologic and behavioral symptoms that have been reported with other neuraminidase inhibitors.

MANDATORY REQUIREMENTS FOR PERAMIVIR IV ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of this therapy the following steps are required. Use of unapproved Peramivir IV under this EUA is restricted to the following (all requirements **must** be met):

1. Treatment of certain patients with suspected or laboratory confirmed 2009 H1N1 virus infection or infection due to nonsubtypable influenza A virus suspected to be 2009 H1N1 based on community epidemiology. Specifically, Peramivir IV is authorized only for the following patients who are admitted to a hospital and under the care or consultation of a licensed clinician (skilled in the diagnosis and management of patients with potentially life-threatening illness and the ability to recognize and manage medication-related adverse events):

- a. Adult patients for whom therapy with an IV agent is clinically appropriate, based upon one or more of the following reasons:
 - i patient not responding to either oral or inhaled antiviral therapy, or
 - ii drug delivery by a route other than IV (e.g. enteral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible, or
 - iii the clinician judges IV therapy is appropriate due to other circumstances.
 - b. Pediatric patients for whom an IV agent is clinically appropriate because:
 - i patient not responding to either oral or inhaled antiviral therapy, or
 - ii drug delivery by a route other than IV (e.g. enteral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible
2. Health Care Providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been: (a) given the Fact Sheet for Patients and Parents/Caregivers, (b) informed of alternatives to receiving authorized Peramivir IV, and (c) informed that Peramivir IV is an unapproved drug that is authorized for use under Emergency Use Authorization.
 3. Patients with known or suspected renal insufficiency must have creatinine clearance determined prior to Peramivir IV dose calculation and first administration.
 4. Patients with history of severe allergic reaction to any other neuraminidase inhibitor (zanamivir or oseltamivir) or any ingredient of Peramivir IV must not receive Peramivir IV.
 5. The prescribing health care provider and/or their designee is/are responsible for mandatory responses to requests from FDA, CDC or their designee for information about adverse events and medication errors following receipt of Peramivir IV. For example, health care providers and/or their designee will be asked whether Peramivir IV was administered, if a selected adverse event or medication error occurred, and if the adverse event or medication error was reported to FDA MedWatch.
 6. The prescribing health care provider and/or their designee is/are responsible for mandatory FDA MedWatch reporting of all medication errors and selected adverse events occurring during Peramivir IV treatment within 7 calendar days from the onset of the event. Selected adverse events are death; neuropsychiatric events; renal adverse events; serious skin adverse events (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis); hypersensitivity reactions adverse events (e.g., anaphylaxis, urticaria, angioedema); severe IV site or IV administration adverse events (e.g. septic

phlebitis, infiltrated IV); or other serious adverse events. Serious Adverse Events are defined as: any life-threatening adverse drug experience that may prolong existing hospitalization, result in a persistent or significant disability/incapacity or a congenital anomaly or birth defect or an event that may jeopardize the patient to an extent that may require medical/surgical intervention to prevent one of the outcomes above including death [see Adverse Reactions and Medication Errors Reporting Requirements and Instructions section for details].

OTHER CONSIDERATIONS PRIOR TO PERAMIVIR IV USE

In addition to the information presented above FDA recommends (but does not require) considerations of the following information before use of Peramivir IV, some of which is provided in more detail in other parts of this document:

Data Available on Safety and Efficacy

- The efficacy and safety of Peramivir IV (or the other approved neuraminidase inhibitors) have not been established in hospitalized patients with any type of influenza A or B virus including 2009 H1N1 virus.
- Results from the phase 2 and 3 trials with IV and intramuscular (IM) administration include a statistically significant effect of a single 300 mg IV or 600 mg IV dose of Peramivir compared to placebo in adult patients with acute uncomplicated influenza. Additionally, three phase 2 trials and one phase 3 trial, including one trial in hospitalized patients, did not show statistically significant treatment differences between Peramivir and placebo or oseltamivir.
- Approximately 1,891 clinical trials subjects have received Peramivir given IV or IM, including 478 who received a single dose of 600 mg IV. Data on multi-dose administration are limited with 33 adult clinical trial subjects who received approximately 600 mg (or higher) intravenously once daily for five or more days.
- No pediatric patients (age < 18 years) have received Peramivir in clinical trials. No pharmacokinetic, safety or efficacy data are available in the pediatric population. However, limited use of Peramivir IV in children has been allowed for Peramivir IV 600 mg once daily for 5 to 10 days under emergency IND procedures.
- Limited safety data from adults are available on Peramivir IV use for 5 days or longer. However, limited use of Peramivir IV in adults has been allowed for Peramivir IV 600 mg once daily for 5 to 10 days under emergency IND procedures.
- Peramivir has not been administered to pregnant women or nursing mothers in clinical trials. No pharmacokinetic, safety or efficacy data are available in pregnant women or nursing mothers.

- Use of Peramivir has not been shown to reduce the risk of transmission of influenza to others.

Treatment Regimens and Timeliness

- Empiric antiviral treatment of hospitalized patients with suspected influenza should not be delayed pending laboratory confirmation of influenza because antiviral treatment is most effective when initiated as early as possible. In addition, a negative influenza antigen test (rapid influenza diagnostic test or immunofluorescence) does not rule out influenza virus infection.
- Initial treatment courses of 5 days or 10 days are permitted. Patients with critical illness (for example, those with respiratory failure or those requiring intensive care unit admission) might benefit from a longer treatment course, although there are no available data demonstrating that longer treatment courses are more effective. Limited data are available on the use of Peramivir IV for up to 10 days or longer.
- Peramivir IV can be used at any time after onset of symptoms in hospitalized patients; however, no data are available regarding initiation of Peramivir IV beyond 72 hours after symptom onset.

Drug Resistance

- 2009 H1N1 virus strains circulating worldwide are susceptible to the neuraminidase inhibitor class of antivirals (oseltamivir, zanamivir, Peramivir IV), and resistant to the adamantane class (amantadine, rimantadine). Rare, sporadic cases of oseltamivir-resistant virus infection associated with the H275Y mutation in the neuraminidase have been reported, including in the United States. To date, there is no evidence worldwide of on-going community-wide transmission of oseltamivir-resistant 2009 H1N1 virus. The latest antiviral resistance surveillance data for the United States can be found at: <http://www.cdc.gov/flu/weekly/>.
- Peramivir IV should not be used for treatment of 2009 H1N1 virus infection in patients with documented or highly suspected oseltamivir resistance.
- Peramivir IV should be used with caution in patients with documented (neuraminidase E119D or R292K) or highly suspected zanamivir resistance. The activity of Peramivir IV against zanamivir resistant virus is unknown.
- Limited data are available on the combination antiviral activity relationships of Peramivir with oseltamivir. No data are available on the combination antiviral drugs, although combination of Peramivir with oseltamivir in a mouse influenza A virus challenge study demonstrated additive antiviral activity compared to use of a single agent alone. The clinical significance of these data is unknown.