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Perspective

The Emergency Use Authorization of Peramivir for Treatment of 2009 H1N1 Influenza

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On October 23, 2009, Food and Drug Administration (FDA) Commissioner Margaret Hamburg issued an Emergency Use Authorization (EUA) for peramivir for intravenous injection (BioCryst

Pharmaceuticals). Peramivir is an unapproved investigational neuraminidase inhibitor that may be effective in treating certain hospitalized adult and pediatric patients with suspected or confirmed cases of 2009 H1N1 influenza. The EUA allows health care providers to use peramivir, subject to specified conditions. This is the first EUA that has been issued for an unapproved drug.

The legal standard for the authorization of an EUA during a declared public health emergency requires a finding that it is “reasonable to believe” that the product “may be effective,” as well as a finding that its known and potential benefits outweigh its known and potential risks.¹ There

must also be no other adequate, approved, and available treatment alternatives for the specific indication. This is a lower evidentiary standard than that used for marketing approval, which requires a finding of “substantial evidence” of efficacy for the proposed use based on adequate and well-controlled trials, as well as a robust safety evaluation (see table).

The FDA’s authority to issue an EUA was granted by Congress in the Project Bioshield Act of 2004. An EUA can be issued only after the secretary of health and human services has declared a public health emergency. In the case of the 2009 H1N1 influenza pandemic, such a declaration was made on April 26, 2009. An EUA

for a medical product has a term of 1 year, but it can be renewed, depending on the circumstances of the emergency. It is important that product development continue to focus on the goal of approval (there are ongoing clinical trials evaluating the efficacy of intravenous peramivir in treating influenza), because the EUA is only a temporary means for making a product available during an emergency.

The FDA conducted an expedited review of the available data on peramivir, including data in preliminary or summary reports of clinical trials completed to date. Four efficacy trials evaluating the intravenous administration of peramivir have been completed; the details of these trials and information about the use of peramivir are summarized in the “Peramivir Fact Sheet for Health Care Providers” that was issued with the EUA.² A treatment bene-

fit — alleviation of symptoms approximately 1 day sooner than with placebo — was observed after the administration of single intravenous doses of 300 mg or 600 mg of peramivir in patients with acute, uncomplicated sea-

sonal influenza. This treatment effect is similar to that seen with currently approved oral neuraminidase inhibitors. Two other trials of peramivir were conducted using oral oseltamivir as an active control (with no placebo group). No conclusions about efficacy can be drawn from the results of these trials because they did not demonstrate that peramivir was superior to oseltamivir and a clinically meaningful noninferiority margin for such a comparison has not been established. A fourth small trial revealed no significant differences in efficacy between two different doses of peramivir or between single and multiple doses. There are very limited data available regarding the use of peramivir in seriously ill hospitalized patients. Because the 2009 H1N1 virus is a novel influenza virus, trials of peramivir have not been conducted in patients with this infection. Overall, our determination that intravenous peramivir may be effective in treating hospitalized patients with 2009 H1N1 influenza was based on the drug's demonstrated activity as a neuraminidase inhibitor and the treatment benefit observed in patients with acute, uncomplicated influenza.

. . . providers can request peramivir under the EUA (www.cdc.gov/h1n1flu/EUA/peramivir_recommendations.htm).

was selected on the basis of findings of a treatment benefit at doses of 300 mg or 600 mg in acute, uncomplicated influenza; the expected proportionally greater exposure at 600 mg than at lower doses; and the consideration that patients with more severe disease may need a higher dose. The treatment duration was selected on the basis of the expected need for a longer duration in hospitalized patients and is consistent with the design of ongoing phase 3 trials in hospitalized patients. The available safety data, including data from the limited number of patients who received 600 mg daily for 5 or more days, supported the selection of this dose and duration under the EUA.

Only 1891 clinical trial subjects have received peramivir at any dose, in any formulation (intravenous or intramuscular), or for any duration, including 478 who received a single dose of 600 mg intravenously and 33 who received 600 mg (or more) intravenously once daily for 5 or more days. No pediatric patients have received peramivir in clinical trials. The most commonly reported adverse effects in clinical trials were diarrhea, nausea, vomiting, and neutropenia. A limited number of pediatric and adult patients have also received peramivir under Emergency Investigational New Drug (EIND) procedures.

The FDA determined that despite the limited data on efficacy and safety, the criteria for an EUA for peramivir had been met for the treatment of certain patients hospitalized with known or sus-

pected 2009 H1N1 influenza. Specifically, it is reasonable to believe that peramivir may be effective in patients with the pandemic virus on the basis of the limited results available from trials in patients with seasonal influenza. Furthermore, the serious, and potentially fatal, nature of the disease observed to date in patients who have been hospitalized because of 2009 H1N1 influenza infection and the lack of alternative treatment options (i.e., an intravenous antiviral agent with activity against influenza) for many of these patients led to issuance of the EUA for peramivir.

The Centers for Disease Control and Prevention (CDC) is responsible for managing the drug's distribution and has established an electronic system through which health care providers can request peramivir under the EUA (www.cdc.gov/h1n1flu/EUA/peramivir_recommendations.htm). Currently, approximately 1200 treatment courses (if all given once daily for 5 days, or 600 treatment courses, if all given once daily for 10 days) of intravenous peramivir are available for distribution; more are expected to become available over time. The CDC will distribute peramivir directly to a hospital after verification of the request from a licensed clinician.

Health care providers and patients considering using peramivir under the EUA must carefully read the "Peramivir Fact Sheet for Health Care Providers" and the "Peramivir Fact Sheet for Patients and Parents/Caregivers" to assess the limited and preliminary nature of the available safety and efficacy data.^{2,3} Alternatives should be considered in making treatment decisions for individual patients who are hospitalized with 2009 H1N1 influenza.

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Criteria for Emergency Use Authorizations (EUAs), Investigational New Drug Applications (INDs), Emergency Investigational New Drug Applications (EINDS), and FDA-Approved Prescription Products.				
	EUA, in General (and for Peramivir)	EIND	IND	FDA-Approved Prescription Product
Access	Broad or restricted according to the letter of authorization (peramivir: seriously ill, hospitalized patients)	Single patient with serious illness or immediately life-threatening condition	Limited to clinical trials or expanded access	By prescription
Use	According to the conditions of authorization (peramivir: intravenous administration in a hospital)	Limited to single patient	Limited to clinical trials or expanded access	According to labeling and practice of medicine
Efficacy requirements	Reasonable to believe based on totality of scientific evidence, including adequate and well-controlled trials as available (peramivir: benefit observed in patients with acute, uncomplicated influenza)	Rationale for intended use, risk from treatment should be no greater than risk from disease or condition	No efficacy requirements, but safety data from animal studies are needed	Substantial evidence based on adequate and well-controlled clinical trials
Prescriber safety reporting	According to the conditions of authorization (peramivir: mandatory)	Required per IND regulations	Required per IND regulations	Voluntary MedWatch reporting
Informed consent	No	Yes	Yes	No
Approval by institutional review board	No	Exempted but must be reported to institutional review board within 5 days	Yes	No

Prescribing under the EUA is different from prescribing FDA-approved drugs (see table). Health care providers need to recognize that peramivir is an unapproved drug authorized for use only because of and during the 2009 H1N1 public health emergency. Although review by an institutional review board is not required, health care providers who prescribe the drug must fulfill certain requirements. These requirements are detailed in the "Peramivir Fact Sheet for Health Care Providers"² and include documentation in the medical record that the patient and caregivers have been given the "Peramivir Fact Sheet for Patients and Parents/Caregivers," informed of alternatives to receiving peramivir, and told that peramivir is an unapproved drug to be used only under the EUA. Providers must

also report all medication errors and selected adverse events to the FDA's MedWatch program (www.fda.gov/medwatch/report.htm), after which the FDA may contact the provider for additional information.

Because of the severity of illness in some patients hospitalized with 2009 H1N1 influenza, it is expected that some patients may not survive, whether or not they are treated with peramivir. Furthermore, it is expected that the evaluation of adverse events will be complicated by patients' underlying medical conditions, coexisting conditions, and use of concomitant medications. Interpretation of the safety data will be challenging and complex. The FDA will carefully assess all available data on an ongoing basis and will update clinicians and the public as we learn more about this drug's safety.

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1. Emergency Use Authorization of medical products: guidance — Emergency Use Authorization of medical products. Silver Spring, MD: Food and Drug Administration, 2009. (Accessed November 2, 2009, at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm>.)

2. Emergency Use Authorization of peramivir: fact sheet for health care providers. Silver Spring, MD: Food and Drug Administration, 2009. (Accessed November 2, 2009, at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187811.pdf>.)

3. Emergency Use Authorization of peramivir: fact sheet for patients and parents/caregivers. Silver Spring, MD: Food and Drug Administration, 2009. (Accessed November 2, 2009, at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187799.pdf>.)

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