

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.**

Updated information in this Fact Sheet is highlighted in yellow.

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 and comply with the terms and conditions of the EUA.

- 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 reporting of all medication errors and selected adverse events occurring during Peramivir IV treatment within 7 calendar days from the onset of the event to FDA via MedWatch Form 3500. 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 pediatric use of Peramivir IV for 5 to 10 days has been allowed 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.

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1. AUTHORIZED USE:

Peramivir injection is authorized for use under an EUA for treatment of certain 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. Specifically, Peramivir IV is authorized only for the following patients who are admitted to a hospital:

- 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. DOSAGE AND ADMINISTRATION

All patients with known or suspected renal insufficiency must have creatinine clearance determined and dosing of Peramivir IV adjusted accordingly [see Impaired Renal Function].

Initial treatment courses are for 5 to 10 days duration. Treatment beyond 10 days is permitted depending on clinical presentation such as critical illness (e.g., respiratory failure or intensive care unit admission), continued viral shedding or unresolved clinical influenza illness.

The compatibility of Peramivir injection with IV solutions and medications other than Sodium Chloride Injection, USP is not known. The clinician should use clinical judgment regarding administration of concomitant medications during infusion based on the individual patient's medical situation. To the extent possible, Peramivir IV should not be administered simultaneously with another intravenous medication.

Heparin Lock

Before infusion of Peramivir IV via a heparin lock, the port should be flushed with 3-5 mLs of sterile saline. After the infusion of Peramivir IV is complete, the port

should be flushed again with sterile saline and then heparin can be added to maintain patency of this catheter.

Single or Multilumen Catheter

If other medications are also administered via a single lumen catheter or a single lumen of a multilumen catheter, at least 10 mLs of sterile saline should be administered between the infusion of any other medication and the administration of Peramivir IV to assure that all medication is flushed from the catheter tubing before Peramivir IV is administered.

Peramivir IV may be piggybacked into an existing saline infusion line. Where possible, the saline infusion rate should be reduced to assure that Peramivir IV is infused over 30 minutes for adults and over 60 minutes for pediatric patients.

Do not administer as an intramuscular (IM) injection.

There is no information available specific to patients receiving extracorporeal membrane oxygenation (ECMO) on Peramivir exposure or pharmacokinetics.

There is no information available specific to the administration of Peramivir IV in patients receiving peritoneal dialysis.

2.1 Adult Patients (≥ 18 years):

The recommended adult dose is 600 mg given intravenously over 30 minutes once daily for 5 to 10 days. Adult patients with known or suspected renal insufficiency must have creatinine clearance determined and the dose adjusted according to Table 1.

Infusion rates should not exceed 40 mg per minute. Peramivir IV must be diluted in 0.9% or 0.45% Sodium Chloride Injection, USP that does not contain dextrose or other electrolytes [see *DIRECTIONS FOR USE OF PERAMIVIR INJECTION*]. There are no data to support dilution of Peramivir IV with dextrose containing solutions or solutions containing electrolytes other than sodium chloride. To the extent possible, a separate IV line or separate IV lumen in a multilumen catheter is recommended for infusion of Peramivir IV [see *Dosage and Administration*].

2.2 Adults with Impaired Renal Function:

The dose of Peramivir IV should be adjusted in **adult** patients with renal impairment as outlined in Table 1. Please also refer to *Special Populations, Renal Impairment* section for rationale on dose adjustments.

NOTE: There are no data that would indicate a loading dose is necessary for patients with mild, moderate or severe renal impairment receiving the doses outlined in Table 1. Simulations of the proposed dosing regimens suggest minimal accumulation of peramivir after repeat dosing. Therefore, the use of a loading dose will not provide additional benefit in terms of reaching steady-state exposure faster. There are insufficient safety data available for the higher systemic exposures that are expected to result following administration of a loading dose to patients with mild, moderate or severe renal impairment.

Table 1: Adult Impaired Renal Function Dosage Recommendations

Creatinine Clearance (CrCl¹) or Estimated Clearance (CL_{CRRT}² + Residual Renal CL)	Dose (IV)
Mild Renal Impairment 50-80 mL/min	600 mg QD
Moderate Renal Impairment 31-49 mL/min	150 mg QD
Severe Renal Impairment 10-30 mL/min	100 mg QD
End-Stage Renal Disease (ESRD) on Intermittent Hemodialysis (HD)	100 mg on Day 1, then 100 mg given 2 hrs after each HD session on dialysis days only

¹ Calculated using Cockcroft and Gault equation, when serum creatinine represents a steady state of renal function.

² Calculated using equation applicable to type of CRRT. See equations under Calculation of CRRT Clearance for Various Types of CRRT.

Note: In patients with renal failure with CrCl <10 mL/min who are **not on dialysis or renal replacement therapy**, the recommended dose of Peramivir IV is 100 mg on Day 1 of dosing, followed by 15 mg QD thereafter [see *Special Populations, Renal Impairment*].

When only a serum creatinine determination is available, the following formula (Cockcroft and Gault equation)¹ may be used to estimate creatinine clearance in adults. The serum creatinine should represent a steady state of renal function.

$$\text{Males: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 x above value

Patients undergoing continuous veno-venous hemofiltration (CVVH) or other continuous renal replacement therapy (CRRT)

Very limited data available for Peramivir IV in the setting of CVVH and CVVHD indicate peramivir is efficiently cleared by continuous renal replacement therapy (CRRT). Ultrafiltrate concentrations from a single adult patient on CVVH revealed a high sieving coefficient (~80%), consistent with peramivir's low protein binding (<30%).

For renally impaired patients receiving CRRT, the peramivir dose should be selected according to Table 1, but using the CRRT clearance (CL_{CRRT} , as outlined below) instead of calculated CrCl determined with the Cockcroft and Gault equation. If the patient has any residual renal function while on CRRT, an estimate of the patient's renal clearance should be added to CL_{CRRT} in order to estimate total clearance before using Table 1.

Consultation with the health care provider managing the CRRT is recommended to most accurately estimate the patient's total clearance, including CRRT clearance, on a case-by-case basis.

The following equations were derived from previously published recommendations for drug dosing in the setting of CRRT,² and are based on several assumptions about peramivir, including low or negligible protein binding ($f_u = 1$) and a high sieving coefficient ($SC = 100\%$). These assumptions may result in over-estimation of clearance depending on actual protein binding or sieving coefficient. For CRRT methods with a diffusive component (CVVHD and CAVHD), the equation below does not account for dialysate saturation, which may result in a higher CL_{CRRT} estimate than is actually observed.

Calculation of CRRT Clearance for Various Types of CRRT

For slow continuous ultrafiltration (SCUF) or continuous arterio-venous hemofiltration (CAVH) or continuous veno-venous hemofiltration (CVVH):

$$CL_{CRRT} = Q_f$$

For continuous arterio-venous hemodialysis (CAVHD) or continuous veno-venous hemodialysis (CVVHD):

$$CL_{CRRT} = Q_d$$

For continuous arterio-venous hemodiafiltration (CAVHDF) and continuous veno-venous hemodiafiltration (CVVHDF):

$$CL_{CRRT} = Q_f + Q_d$$

Where Q_f = ultrafiltration rate (mL/min) and Q_d = dialysate flow rate (mL/min)

Dose modifications should be made, as appropriate, for changes in patient renal function, changes to ultrafiltrate or dialysate flow rate, or initiation, discontinuation or changes to CRRT.

2.3 Pediatric Patients from birth through 17 years of age:

Dosing in pediatric patients is based upon modeling. No pediatric patients have received Peramivir in clinical trials [see Dose Rationale]. However, limited pediatric use of Peramivir IV for 5 to 10 days has been allowed under emergency IND procedures.

The recommended pediatric dose should be calculated using the mg/kg dose according to the patient's age (See Table 2). Pediatric patients with known or suspected renal insufficiency must have creatinine clearance determined and the dose adjusted according to Table 3.

The calculated dose should be infused intravenously over 60 minutes once daily. Initial treatment courses of 5 days or 10 days are permitted. To the extent possible, a separate IV line or separate IV lumen in a multilumen catheter is recommended for infusion of Peramivir IV [see Dosage and Administration.

The maximum daily dose should not exceed 600 mg IV of Peramivir injection. Infusion rates should not exceed 40 mg per minute. Peramivir injection must be diluted in 0.9% or 0.45% Sodium Chloride Injection, USP that does not contain dextrose or other electrolytes [see DIRECTIONS FOR USE OF PERAMIVIR INJECTION]. There are no data to support dilution of Peramivir IV with dextrose containing solutions or solutions containing electrolytes other than sodium chloride.

Table 2: Pediatric Daily Dosage Recommendations*

Age	Dose (mg/kg)
Birth through 30 Days	6 mg/kg
31 Days through 90 Days	8 mg/kg
91 Days through 180 Days	10 mg/kg
181 Days through 5 Years	12 mg/kg
6 Years through 17 Years	10 mg/kg

***Maximum Daily Dose is 600 mg IV**

2.4 Pediatric Patients with Impaired Renal Function:

Dosing instructions for pediatric patients were derived based on modeling and simulation of pharmacokinetic data from adult healthy volunteers and adult

patients with influenza and information on renal maturation and body weight. The dose of Peramivir IV should be adjusted in **pediatric** patients with different degrees of renal impairment as follows: [see *Special Populations, Renal Impairment— Pediatric Patients*]

Table 3: Pediatric Impaired Renal Function Dosage Recommendations

Age	Creatinine Clearance (CrCl ¹) or Estimated Clearance (CL _{CRRT} ² + Residual Renal CL)				
	50-80 mL/min/1.73 m ²	31-49 mL/min/1.73 m ²	10-30 mL/min/1.73m ²	< 10 mL/min/1.73 m ² and NOT on Intermittent HD or CRRT	ESRD (<10 mL/min/ 1.73 m ²) on Intermittent HD
Birth through 30 days	6 mg/kg QD	1.5 mg/kg QD	1 mg/kg QD	1 mg/kg on Day 1, then 0.15 mg/kg QD	1 mg/kg on Day 1, then 1 mg/kg given 2 hrs after each HD session on dialysis days only
31 Days through 90 Days	8 mg/kg QD	2 mg/kg QD	1.3 mg/kg QD	1.3 mg/kg on Day 1, then 0.2 mg/kg QD	1.3 mg/kg on Day 1, then 1.3 mg/kg given 2 hrs after each HD session on dialysis days only
91 Days through 180 Days	10 mg/kg QD	2.5 mg/kg QD	1.6 mg/kg QD	1.6 mg/kg on Day 1, then 0.25 mg/kg QD	1.6 mg/kg on Day 1, then 1.6 mg/kg given 2 hrs after each HD session on dialysis days only
181 Days through 5 Years	12 mg/kg QD	3.0 mg/kg QD	1.9 mg/kg QD	1.9 mg/kg on Day 1, then 0.3 mg/kg QD	1.9 mg/kg on Day 1, then 1.9 mg/kg given 2 hrs after each HD session on dialysis days only
6 Years through 17 Years	10 mg/kg QD	2.5 mg/kg QD	1.6 mg/kg QD	1.6 mg/kg on Day 1, then 0.25 mg/kg QD	1.6 mg/kg on Day 1, then 1.6 mg/kg given 2 hrs after each HD session on dialysis days only

¹ Calculated using Schwartz equation when serum creatinine represents a steady state of renal function.

² Calculated using equation applicable to type of CRRT. See equations under **Calculation of CRRT Clearance for Various Types of CRRT.**

To estimate creatinine clearance in children, the Schwartz formula³ may be used. The serum creatinine should represent a steady state of renal function. A link to a website using the Schwartz formula to calculate creatinine clearance in children can be found at:

<http://www-users.med.cornell.edu/~spon/picu/calc/crclschw.htm>

Pediatric patients undergoing continuous veno-venous hemofiltration (CVVH) or other continuous renal replacement therapy (CRRT)

Very limited data available for Peramivir IV in the setting of CVVH and CVVHD in adult patients indicate peramivir is efficiently cleared by CRRT. There are inadequate data from pediatric patients administered Peramivir IV while on CRRT to confirm whether this observation is also true for children.

For renally impaired pediatric patients receiving CRRT, the Peramivir IV dose should be selected according to Table 3, but using the CRRT clearance (CL_{CRRT} , as outlined below) instead of calculated CrCl determined with the Schwartz equation. If the patient has any residual renal function while on CRRT, an estimate of the patient's renal clearance should be added to CL_{CRRT} in order to estimate total clearance before using Table 3.

Consultation with the health care provider managing the CRRT is recommended to most accurately estimate the patient's total clearance, including CRRT clearance, on a case-by-case basis.

The following equations were derived from previously published recommendations for drug dosing in the setting of CRRT,² and are based on several assumptions [See 2.2 Adults with Impaired Renal Function].

Calculation of CRRT Clearance for Various Types of CRRT

For slow continuous ultrafiltration (SCUF) or continuous arterio-venous hemofiltration (CAVH) or continuous veno-venous hemofiltration (CVVH):

$$CL_{CRRT} = Q_f$$

For continuous arterio-venous hemodialysis (CAVHD) or continuous veno-venous hemodialysis (CVVHD):

$$CL_{CRRT} = Q_d$$

For continuous arterio-venous hemodiafiltration (CAVHDF) and continuous veno-venous hemodiafiltration (CVVHDF):

$$CL_{CRRT} = Q_f + Q_d$$

Where Q_f = ultrafiltration rate (mL/min) and Q_d = dialysate flow rate (mL/min)

Dose modifications should be made, as appropriate, for changes in renal function (CrCl), changes to ultrafiltrate or dialysate flow rate, or initiation, discontinuation or changes to CRRT.

Impaired Hepatic Function:

Based on the available data, Peramivir IV is not significantly metabolized by the liver. Therefore, no dose adjustment is necessary for patients with impaired hepatic function.

3. DIRECTIONS FOR PREPARING PERAMIVIR INJECTION

Method of Preparation: See the following detailed preparation directions for adult and pediatric use.

Preparation of Peramivir IV infusion should be done under aseptic conditions.

3.1 Adult Dose Preparation Directions:

Follow the steps below to prepare a diluted solution of Peramivir IV 600 mg for adult patients with normal renal function. The dose of Peramivir IV should be adjusted in adult patients with renal impairment according to Table 1. Peramivir injection must be diluted in 0.9% or 0.45% Sodium Chloride Injection, USP that does not contain dextrose or other electrolytes. There are no data to support dilution of Peramivir IV with dextrose containing solutions or solutions containing electrolytes other than sodium chloride.

1. Transfer 600 mg (60 mL, or appropriate volume based on recommended dose for patients with renal impairment in Table 1) of Peramivir injection to an empty sterile container for IV use.
2. Add 40 mL (or appropriate volume to reach a total of 100 mL based on the adjusted renal dose) of 0.9% or 0.45% Sodium Chloride Injection, USP to the container. The total volume of diluted solution should be 100 mL with a maximum final concentration of 6 mg/mL.

3.2 Pediatric Dose Preparation Directions: (age birth through 17 years of age)

Follow the steps below to prepare a diluted solution of Peramivir injection. Peramivir injection must be diluted in 0.9% or 0.45% Sodium Chloride Injection, USP that does not contain dextrose or other electrolytes. There are no data to support dilution of Peramivir IV with dextrose containing solutions or solutions containing electrolytes other than sodium chloride.

1. Calculate the recommended age-based dose according to Table 2. Refer to Table 3 to calculate the recommended dose for pediatric patients with known or suspected renal insufficiency.

2. Dilute the calculated dose using 0.9% or 0.45% Sodium Chloride Injection, USP in an empty sterile container for IV use. The final concentration of the diluted solution should not exceed 6 mg/mL. The diluted solution should be administered intravenously over 60 minutes.

OR

3. An undiluted dose must be administered using an infusion device, e.g., a piggy back system, timed syringe system or pump, which allows infusion into an open IV line with Sodium Chloride Injection, USP over 60 minutes.

3.3 Storage: Vials of Peramivir injection should be stored at ambient temperature (15°C-30°C or 59°F-86°F). However, temperature extremes encountered during shipment and storage (including freezing) would likely not adversely affect the quality of this product. Once a diluted solution has been prepared, it should be administered immediately or stored under refrigerated conditions (2°C-8°C or 36°F-46°F). If refrigerated, the refrigerated diluted solution should be allowed to reach room temperature prior to administration. The diluted solution should be administered within 24 hours following preparation. Any unused diluted solution must be discarded after 24 hours.

IMPORTANT:

Any unused portion of a single use Peramivir injection vial should be discarded after a diluted solution is prepared. Maintain adequate records showing receipt, use, and disposition of Peramivir. For unused intact vials, maintain adequate records showing use and disposition of Peramivir.

Peramivir injection is a clear-colorless solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Should either be observed, the solution should be discarded and fresh solution prepared.

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of Peramivir injection with IV solutions and medications other than Sodium Chloride Injection, USP is not known. **To the extent possible, a separate IV line or separate IV lumen in a multilumen catheter is recommended for infusion of Peramivir IV [see *Dosage and Administration*].** Peramivir injection must be diluted in 0.9% or 0.45% Sodium Chloride Injection, USP that does not contain dextrose or other electrolytes [see *DIRECTIONS FOR USE OF PERAMIVIR INJECTION*]. There are no data to support dilution of Peramivir IV with dextrose containing solutions or solutions containing electrolytes other than sodium chloride.

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible. The diluted solution of Peramivir IV must be discarded after 24 hours.

4. DOSAGE FORMS AND STRENGTHS

Intravenous (IV) Injection:

- Each vial of Peramivir injection contains 200 mg per 20 mL (10 mg per mL)

5. CONTRAINDICATIONS

Do not use Peramivir IV in patients with history of severe allergic reaction to any other neuraminidase inhibitors (Relenza or Tamiflu) or any ingredient of Peramivir IV [see *Product Description*].

6. WARNINGS AND PRECAUTIONS

Limited multiple dose data are available for Peramivir IV 600 mg. The clinical trial experience for Peramivir IV 600 mg is limited to three clinical trials in which 478 patients received a single 600 mg dose. The Warnings and Precautions described here are based on the limited controlled clinical data. Most of the data are from patients who received either multiple doses less than 600 mg IV or only received single doses of Peramivir [see *Limitations of Populations Studied*]. Serious and unexpected adverse events may occur that have not been previously reported with Peramivir use.

Completion of FDA MedWatch Form to report all medication errors and selected adverse events occurring during Peramivir IV treatment is mandatory. Please see the Adverse Reactions and Medication Errors Reporting Requirements and Instructions section below for details on FDA MedWatch reporting.

6.1 Gastrointestinal Side Effects

Patients should be monitored for development of diarrhea and have appropriate evaluation and/or treatment, as indicated, including evaluation for other causes of diarrhea as clinically warranted.

In Trial BCX1812-201 of hospitalized patients with serious influenza receiving either Peramivir IV 200 mg (n=41) or 400 mg (n=40) for 5 days or oral oseltamivir 75 mg bid (n=41) for 5 days, the following events were observed:

- Gastrointestinal (GI) adverse events were reported in 33% of patients receiving Peramivir IV 200 mg, 28% of patients receiving Peramivir IV 400 mg, and 15% of patients receiving oseltamivir.
- Diarrhea was reported in 13% patients receiving Peramivir IV 200 mg or 400 mg compared to 2% patients receiving oseltamivir.
- One serious adverse event of severe diarrhea was reported by a patient receiving Peramivir IV 400 mg daily and was judged as probably related to Peramivir IV. All diarrhea events resolved.

Similar rates of diarrhea, nausea and vomiting in patients receiving Peramivir and placebo were observed in other phase 1 and 2 trials. All GI events, regardless of causality, were seen in 12.4% of patients receiving Peramivir IV 600 mg compared to 18.1% of patients receiving oseltamivir. In the phase 3 trial, the incidence of diarrhea was similar between Peramivir IV 600 mg and oseltamivir.

6.2 Bacterial Infections

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or develop as complications during the course of influenza illness. Patients should be monitored, evaluated and treated for suspected bacterial infections as clinically warranted while being treated with Peramivir IV. Consult an infectious disease specialist when appropriate.

6.3 Allergic Reactions

Serious allergic-like reactions have not been reported in clinical trials in patients receiving Peramivir to date. However, allergic-like reactions, including oropharyngeal edema, serious skin rashes and anaphylaxis have been reported with use of neuraminidase inhibitors including Relenza (zanamivir) and Tamiflu (oseltamivir). Peramivir IV should be stopped and appropriate treatment instituted if an allergic reaction occurs or is suspected.

6.4 Neuropsychiatric Events

Influenza infection itself can be associated with a variety of neurologic and behavioral symptoms which can include events such as seizures, hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without clinically apparent severe disease.

There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who were receiving the approved neuraminidase inhibitors, Tamiflu or Relenza. These events appear to be uncommon based on usage data, have been reported primarily

among pediatric patients and often had an abrupt onset and rapid resolution. Because Peramivir IV is also a neuraminidase inhibitor, and based on limited data from clinical trials, it is possible that these types of reactions or other types of neurologic and behavior events could occur in patients receiving Peramivir IV. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

In Trial BCX1812-201 of hospitalized patients with serious influenza receiving either Peramivir IV 200 mg (n=41) or 400 mg (n=40) for 5 days or oral oseltamivir 75 mg bid (n= 41) for 5 days, the following events were observed.

- Psychiatric adverse events were reported in 11% of patients receiving Peramivir IV 200 or 400 mg compared to 4% of patients receiving oseltamivir.
- Other adverse events reported by patients treated with Peramivir IV were depression (n=2), confusion (n=1), insomnia (n=4), delirium (n=1), restlessness (n=1), anxiety (n=2), nightmare (n=1), and alteration of mood (n=1). Of these adverse events, approximately half were judged as related to study treatment.

7. OVERALL SAFETY SUMMARY

From the available phase 1, 2 and 3 data the more common adverse events related to administration of Peramivir are:

- diarrhea
- nausea
- vomiting
- neutrophil count decreased

From the available phase 1 and 2 data, other less common adverse events related to administration of Peramivir are:

- dizziness
- headache
- somnolence
- nervousness
- insomnia
- feeling agitated
- depression
- nightmares
- hyperglycemia
- hyperbilirubinemia
- elevated blood pressure
- cystitis
- ECG abnormalities (prolonged QTc interval observed in one patient in a phase 1 trial)
- anorexia
- proteinuria
- hematuria

Patients should have appropriate clinical and laboratory monitoring to aid in early detection of any potential adverse events. The decision to continue or discontinue Peramivir IV therapy after development of an adverse event should be made based on the clinical risk benefit assessment for the individual patient.

[See CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA]

8. PATIENT MONITORING RECOMMENDATIONS

Given the limited experience with Peramivir IV at the recommended dose and duration, the following procedures for monitoring patients are recommended during Peramivir IV therapy. **Additionally, completion of FDA MedWatch Form to report all medication errors and selected adverse events is mandatory.** Please see the Adverse Reactions and Medication Errors Reporting Requirements and Instructions section 9 for details on submitting MedWatch Forms.

Assessment	Laboratory Parameter	Timing
Complete blood count with differential and a basic metabolic profile	glucose, calcium, sodium, potassium, chloride, serum bicarbonate, creatinine, and blood urea nitrogen	On initiation, Day 3 of therapy and end of therapy
Liver associated tests	alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total and direct bilirubin	On initiation and conclusion of therapy and during therapy if clinically indicated
Urinalysis*		On initiation and conclusion of therapy and during therapy, if clinically indicated. <i>If significant proteinuria develops while on therapy then appropriate further evaluation including laboratory testing, 24-hour urine collection and possible nephrology consultation should be considered</i>
Assessment of renal function	serum creatinine (at a minimum)	completed prior to initiation of dosing and followed carefully throughout dosing as clinically appropriate
Vital Signs	body temperature, noninvasive blood pressure, heart rate, respiratory rate, and	Daily (at a minimum)

	oxygen saturation	
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*[Note: Because renal abnormalities were observed in animal studies, renal parameters including proteinuria were closely monitored in phase 1 and 2 studies. Based on the limited data, no dose related proteinuria and other renal abnormalities possibly related to Peramivir were observed; however, monitoring is recommended].

- It is especially important for patients in whom abnormal laboratory values are noted at the time Peramivir IV treatment is initiated to be monitored through the duration of therapy for worsening.
- Patients with significant or serious metabolic abnormalities should be assessed continually with regard to the risks and potential benefits of continued Peramivir IV therapy.
- Patients with abnormal laboratory parameters should have careful follow-up and, at a minimum, repeat assessment within 1-2 weeks of the conclusion of therapy to assess normalization.

9. ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

See Warnings and Precautions for information about risk of serious adverse events such as gastrointestinal events, bacterial infections, allergic-like reactions, and neuropsychiatric events.

The prescribing health care provider and/or their designee is/are responsible for the **mandatory** reporting of all medication errors and the following selected adverse events occurring during Peramivir IV treatment within 7 calendar days from the onset of the event:

- a. Deaths
- b. Neuropsychiatric Events
- c. Renal Adverse Events
- d. Serious Skin Adverse Events (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)
- e. Hypersensitivity Reactions Adverse Events (e.g., anaphylaxis, urticaria, angioedema)
- f. Severe Intravenous site or Intravenous Administration Adverse Events (e.g. septic phlebitis, infiltrated IV)
- g. Other Serious Adverse Events*

*Serious Adverse Event 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.

The MedWatch FDA Form 3500 must be completed either online at www.fda.gov/medwatch/report.htm or by using a postage-paid FDA Form 3500 (available at http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf) and returning by fax (1-800-FDA-0178) or by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787). If you do not have online internet access call 1-800-FDA-1088. Audits for compliance for completion and return of the MedWatch Form will be performed. FDA or their designee may contact health care providers for additional information about the adverse events or medication errors. In addition, response to follow-up inquiries requesting information regarding selected adverse events and medication errors associated with Peramivir IV administration is mandatory.

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient Demographics (e.g., Peramivir Request number, patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of Peramivir IV
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available (use the same Peramivir Request number when completing the report).

The following steps are highlighted to provide the necessary information for safety tracking:

1. In section A, box 1 provide the Peramivir Request number and the patient's initials in the Patient Identifier
2. In section A, box 2 provide the patient's date of birth
3. In section B, box 5 description of the event provide:
 - a. Write "Peramivir IV EUA" as the first line
 - b. Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.

4. In section G, box 1 name and address:
 - a. Provide the name and contact information of the prescribing health care provider or institutional designee who is responsible for the report
 - b. Provide the address of the treating institution (NOT the health care provider's office address).

10. DRUG INTERACTIONS

Peramivir IV is primarily eliminated by the kidneys; coadministration of Peramivir IV with drugs that reduce renal function or compete for active tubular secretion may increase plasma concentrations of Peramivir and/or increase the concentrations of other renally eliminated drugs.

Drug-drug interaction trials of Peramivir IV and other concomitant medications have not been conducted. Use with caution with other medications which are eliminated by the kidneys and monitor the patient's renal function as appropriate.

11. USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

No adequate and well-controlled studies of Peramivir use in pregnant women have been conducted. Peramivir IV should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

No teratogenicity was detected in fertility and developmental studies conducted in both rats and rabbits. When comparing to systemic Peramivir exposures at the 600 mg IV dose in humans (predicted AUC = 90 $\mu\text{g}\cdot\text{h}/\text{ml}$), the exposures in rats are 8.4 times the human exposure and the exposures in rabbits are 1.5 times the human exposure at the 600 mg dose given intravenously. Peramivir administered intravenously at 200 mg/kg, caused severe maternal toxicity (dose-limiting nephrosis) in pregnant rabbits, and an increased incidence of abortion and embryotoxicity, considered to be related to the maternal toxicity. Rabbits are considered a sensitive species and nephrotoxicity has been observed in non-pregnant rabbits in general toxicology studies. The margin of safety for nephrotoxicity in non-pregnant rabbits, as compared with predicted AUC of 90 $\mu\text{g}\cdot\text{h}/\text{ml}$ at 600 mg IV dose in humans, is less than 1. In contrast to rabbits, Peramivir did not produce significant maternal toxicity nor embryotoxicity (up to 600 mg/kg) in pregnant rats.

11.2 Nursing Mothers

Peramivir has not been studied in nursing mothers. Studies in rats demonstrated Peramivir is excreted in milk. Lactating rats excreted Peramivir into the milk, at levels below the mother's plasma drug concentrations. However, nursing

mothers should be instructed that it is not known whether Peramivir is excreted in human milk.

11.3 Pediatric Use

Peramivir has not been administered to any pediatric patients (age <18 years) in clinical trials. However, limited use of Peramivir IV in adults and children has been allowed for Peramivir IV 600 mg once daily for 5 to 10 days under emergency IND procedures.

The safety and effectiveness of Peramivir IV for treatment of influenza has not been assessed in pediatric patients. Dosing instructions for pediatric patients were derived based on modeling and simulation of pharmacokinetic data from adult healthy volunteers and adult patients with influenza and information on renal maturation and body weight [see *Dose Rationale*].

11.4 Geriatric Use

Clinical studies of Peramivir do not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, appropriate caution should be exercised in the administration of Peramivir IV and monitoring of elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Sixteen healthy volunteers ≥ 65 years of age received twice-daily doses of 4 mg/kg for 1, 5, and 10 days. Too few patients ≥ 65 years of age have received Peramivir to make conclusions about the overall safety profile compared to adult patients < 65 years of age [see *Special Populations*].

12. OVERDOSAGE

There is no human experience of acute overdosage with Peramivir. Treatment of overdose with Peramivir IV should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Peramivir IV.

Peramivir is cleared by hemodialysis.

13. CLINICAL PHARMACOLOGY

13.1 Pharmacokinetics

The pharmacokinetics of Peramivir IV have been evaluated in adults in several phase 1 trials. The pharmacokinetic parameters following IV administration of Peramivir (dose range 0.5 mg/kg up to 8 mg/kg) showed a linear relationship

between dose and the exposure parameters (C_{max} and AUC). The half-life of Peramivir following administration of 0.5 mg/kg to 8 mg/kg as a single dose or 4 mg/kg twice daily for 1 day ranged from 7.7 hours to 20.8 hours. Table 4 shows the summary of the pharmacokinetic parameters of Peramivir at various IV doses across multiple studies.

Table 4: Summary of the PK Parameters of Peramivir after Intravenous (IV) Administration of Peramivir Across Multiple Studies

Study Number	Dose(s) Administered Intravenously	Number of Patients	Mean C_{max} ng/mL	Mean $AUC_{0-\infty}$ ng*hr/mL
Hi-06-101	0.5 mg/kg single dose	6	1925.8	4975.2
Hi-06-102	0.5 mg/kg BID x one day	6	2549.2 ^a	6035.9 ^a
BCX1812-103	1 mg/kg single dose	6	5531.7	12246.7
	2 mg/kg single dose	6	11346.7	22689.7
	4 mg/kg single dose	6	20491.7	49902.2
	8 mg/kg single dose	6	44666.7	90666.0
	4 mg/kg BID X one day	7	21933.3 ^a	47776.2 ^a
	2 mg/kg BID X 10 days	9	12935.6 ^b	26132.1 ^b
BCX1812-104 (healthy elderly patients \geq 65 years of age)	4 mg/kg BID X one day	20	23600.0	ND
	4 mg/kg BID X 5 days	6	22608.3 ^c	78950.1 ^c
	4 mg/kg BID X 10 days	6	22933.3 ^d	67425.4 ^d
BCX1812-105 (patients with renal impairment)	2.0 mg/kg single dose CrCL > 80 mL/min	6	12775.0	25932.1
	2.0 mg/kg single dose CrCL 50-80 mL/min	6	11900.8	32103.4
	2.0 mg/kg single dose CrCL 30-49 mL/min	6	13698.3	109233.9
	2.0 mg/kg single dose CrCL < 30 mL/min	6	12325.0	136918.3
	2.0 mg/kg (pre-dialysis)	6	11020	137819.5 ^e
	2.0 mg/kg (after dialysis)	6	15475.0	1013660.9 ^f
BCX1812-111	75 mg single dose	9	4652.2	10843.2
	150 mg single dose	9	9400.6	24198
	300 mg single dose	9	17166.7	47241.1

- a. C_{max} and $AUC_{0-12hours}$ after the second infusion
- b. $AUC_{0-72hours}$ after the second dose on Day 10
- c. C_{max} and $AUC_{0-48hours}$ after the second infusion on Day 5
- d. C_{max} and $AUC_{0-48hours}$ after the second infusion on Day 10
- e. PK measurements before dialysis

f. PK measurements after dialysis

The major route of elimination of Peramivir is via the kidney. Renal clearance of unchanged Peramivir accounts for ~90% of total clearance. In patients with normal renal function, the apparent elimination half-life of intravenously administered Peramivir ranged from 7.7 to 20.8 hours.

Special Populations

Gender, Race and Age

Pharmacokinetic differences for gender and race have not been evaluated.

Comparisons of the pharmacokinetics of Peramivir administered intravenously in healthy young volunteers with data from healthy volunteers (≥ 65 years of age) suggest patients ≥ 65 years of age group had approximately a 46% increase in dose-normalized AUC and on average, approximately 26% lower clearance of Peramivir primarily due to decrease in kidney function. Peramivir C_{\max} was independent of age and dose adjustment is not currently recommended for patients ≥ 65 years of age.

Pediatric Patients

Peramivir has not been administered to any pediatric patients (age <18 years) in clinical trials.

The pharmacokinetics in pediatric patients have not been studied. Dosing recommendations for pediatric patients (birth to 17 years of age) are based on modeling and simulation of pharmacokinetic data from adult healthy volunteers and adult patients with influenza and patient pharmacokinetic data and information on renal maturation and body weight [see *Dose Rationale*].

Renal Impairment – Adults

Peramivir pharmacokinetics were studied in healthy adult patients with mild, moderate, and severe renal impairment and patients undergoing hemodialysis. Based on the results of the study the dose of Peramivir IV should be adjusted in adult patients with renal impairment as follows:

Mild Renal Impairment (CrCl 50-80 mL/min)

The mean systemic exposures in patients with mild renal impairment are expected to be approximately 24% higher than the systemic exposures in patients with normal renal function. These higher exposures in patients with mild renal impairment are not expected to be clinically relevant. Therefore, no dose adjustments of Peramivir IV are needed for patients with mild renal impairment.

Moderate Renal Impairment (CrCl 30-49 mL/min)

The mean systemic exposures in patients with moderate renal impairment are expected to be approximately 3.4-fold higher than the exposures in patients with normal renal function. Therefore, the dose of Peramivir IV is reduced to 150 mg in order to achieve exposures similar to the exposures in patients with normal renal function after administration of a single 600 mg IV dose [see *DOSAGE AND ADMINISTRATION*].

Severe Renal Impairment (CrCl 10-30 mL/min)

The mean systemic exposures in patients with severe renal impairment are expected to be approximately 6-fold higher than the exposures in patients with normal renal function. Therefore, the dose of Peramivir IV is reduced to 100 mg in order to achieve exposures similar to the exposures in patients with normal renal function after administration of a single 600 mg IV dose [see *DOSAGE AND ADMINISTRATION*].

Patients with ESRD on Intermittent Hemodialysis

For patients with ESRD receiving intermittent hemodialysis (HD), the recommended dose is 100 mg on Day 1, followed by 100 mg administered 2 hours after completion of each HD session, on HD days only. Based on simulations, this dose is predicted to provide comparable Peramivir exposure (AUC_{0-24}) as patients with normal renal function, while C_{max} will be lower and C_{min} higher (Table 5 and Figure 1). The AUC_{0-24} values over the dosing period are predicted to be relatively stable for this dosing regimen (range 93,400 – 106,000 ng·h/mL). The simulations were performed assuming a 4-hour HD session and a Q48h HD schedule. However, the same dosing recommendation (100 mg after each HD session) is appropriate if HD is administered on two consecutive days. [See *DOSAGE AND ADMINISTRATION*]

Table 5. Predicted Peramivir PK Parameters in Patients with ESRD on Intermittent Hemodialysis (HD)

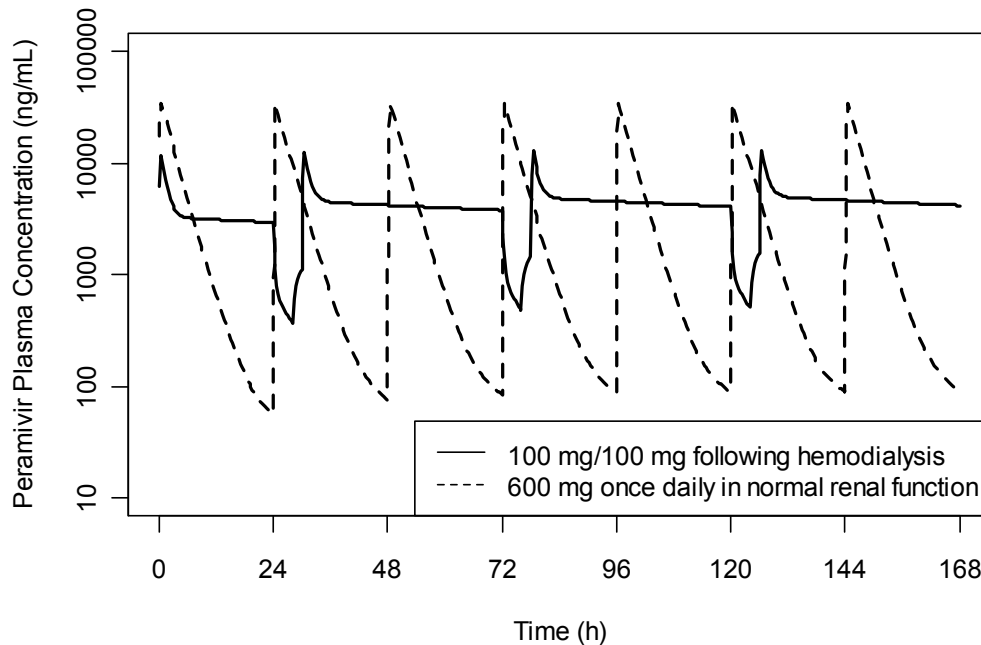
	Normal Renal Function (600 mg QD)	Intermittent HD (100 mg on Day 1, then 100 mg Given 2 Hrs After Each HD Session)
AUC_{0-24} (average ¹) (ng·h/mL)	107,000	98,000
C_{max} (ng/mL) ²	34,100	13,100
C_{min} (ng/mL) ²	56	370

Note: Simulations were performed assuming a 4-hour HD session, every 48 hours. Simulations were performed for a 7-day dosing duration.

¹ Average AUC_{0-24} is the average of all AUC_{0-24} values predicted for the 7-day treatment duration.

² C_{max} is the highest predicted C_{max} and C_{min} is the lowest predicted C_{min} for the simulated dosing period.

Figure 1. Predicted Peramivir Concentrations in Patients on Intermittent Hemodialysis (HD)



Patients with CrCL < 10 mL/min who are NOT receiving Intermittent Hemodialysis or CRRT

For patients with CrCl < 10 mL/min who are not receiving intermittent hemodialysis (HD) or continuous renal replacement therapy (CRRT), the recommended dose of Peramivir IV is 100 mg on Day 1, followed by 15 mg QD.. This dosing regimen is predicted to provide average AUC_{0-24} values similar to patients with normal renal function receiving 600 mg QD. Peramivir C_{max} and C_{min} for this regimen are predicted to be lower and higher, respectively, relative to patients with normal renal function (Table 6 and Figure 2). The initial 100 mg dose on Day 1 is intended to bring Peramivir concentrations to levels similar to those in patients with normal renal function beginning on Day 1.

Table 6. Predicted Peramivir PK Parameters in Patients with CrCl < 10 mL/min and NOT on Intermittent Hemodialysis or Continuous Renal Replacement Therapy

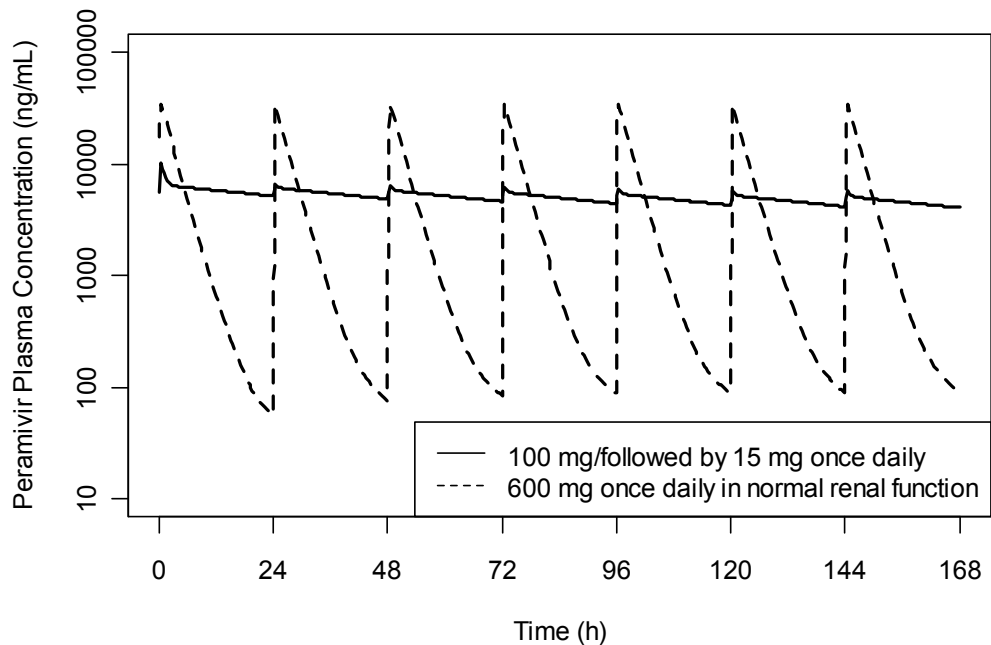
	Normal Renal Function	CrCl < 10 mL/min and NOT receiving intermittent HD or CRRT
	600 mg QD	100 mg on Day 1, followed by 15 mg QD
AUC ₀₋₂₄ (average) ¹ (ng·h/mL)	107,000	122,000
AUC ₀₋₂₄ (Day 1) (ng·h/mL)	106,000	142,000
C _{max} ² (ng/mL)	34,100	10,300
C _{min} ² (ng/mL)	56	4,060

Note: Simulations were performed assuming a 7-day dosing duration.

¹ Average AUC₀₋₂₄ is the average of all AUC₀₋₂₄ values predicted for the 7-day treatment duration.

² C_{max} is the highest predicted C_{max} and C_{min} is the lowest predicted C_{min} for the simulated dosing period

Figure 2. Predicted Peramivir Concentrations in Patients with CrCl < 10 mL/min and NOT on Intermittent Hemodialysis or Continuous Renal Replacement Therapy



Patients Undergoing Continuous Veno-Venous Hemofiltration (CVVH) or Other Continuous Renal Replacement Therapy (CRRT)

Very limited data are available from patients on CVVH or CVVHD who received Peramivir IV under emergency IND procedures. The pharmacokinetic sampling from these patients was sparse (2-4 samples per patient), timing of samples with respect to dose or CRRT is not well documented, and no information is provided regarding filter type, flow rate, or duration of renal replacement therapy. Ultrafiltrate concentrations from a single adult patient on CVVH revealed a high sieving coefficient (~80%), consistent with peramivir's low protein binding (<30%).

Recognizing the urgent need for dosing recommendations for patients receiving Peramivir IV while on CRRT, the dose recommendations provided in this document were derived from previously published recommendations for drug dosing in the setting of CRRT.² The equations provided under Section 2.2 are based on several assumptions about Peramivir, including low or negligible protein binding ($f_u = 1$) and a high sieving coefficient (SC = 100%). These assumptions may result in over-estimation of clearance depending on actual protein binding or sieving coefficient. For CRRT methods with a diffusive component (CVVHD and CAVHD), the equation provided does not account for dialysate saturation, which may result in a higher CL_{CRRT} estimation than is actually observed.

Drug clearance in patients on CRRT may be affected by multiple variables, including type of filter, dialysate flow, ultrafiltration rate, blood flow, replacement solution rates and residual renal function. Drug dosing should be adjusted taking into account these parameters. Consultation with the health care provider managing the CRRT is recommended in order to accurately estimate peramivir clearance on a case-by-case basis.

Renal Impairment – Pediatric Patients

Dose recommendations for pediatric patients with renal impairment are based on based on modeling pharmacokinetic data from healthy adults with mild, moderate, and severe renal impairment and patients undergoing hemodialysis. Very limited data available for Peramivir IV in the setting of CVVH and CVVHD in adult patients indicate Peramivir is efficiently cleared by CRRT. There are inadequate pediatric data from patients undergoing CRRT. The current dosing recommendations for pediatrics are based on adult data [see *Patients Undergoing Continuous Veno-Venous Hemofiltration (CVVH) or Other Continuous Renal Replacement Therapy (CRRT) and DOSAGE AND ADMINISTRATION*].

14. MICROBIOLOGY

Mechanism of Action

Peramivir is a cyclopentane analogue which binds to the active site of influenza virus neuraminidase. It has inhibitory activity against human influenza A and influenza B viruses. Peramivir inhibited the neuraminidase activity of several influenza A and B strains in a biochemical assay with median IC₅₀ values of 0.2 nM (range 0.09 to 1.4 nM, n=15) for influenza A strains and 1.3 nM (range 0.60 to 11 nM, n=8) for influenza B strains. The IC₅₀ values of Peramivir against several 2009 H1N1 influenza A (swine flu) isolates ranged from 0.06-0.26 nM.

Antiviral Activity

The antiviral activity of Peramivir against laboratory strains and clinical isolates of influenza virus was determined in cell culture assays. The 50% effective concentrations (EC₅₀) were 1 µM (range 0.09 to 21 µM, n=5) for seasonal influenza A H1N1 isolates, 0.07 µM (range <0.01 to 0.16 µM, n=12) for influenza A H3N2 isolates, and 2.2 µM (range 0.06 to 3.2 µM, n=5) for influenza B isolates. The relationship between the antiviral activity in cell culture, the inhibitory activity in neuraminidase assays, and the inhibition of influenza virus replication in humans has not been established. Limited biochemical, cell culture, and animal model data are available on the combination antiviral activity antiviral relationships of Peramivir with oseltamivir. No data are available on the combination activity with zanamivir. In a mouse influenza A virus challenge model study, the combination of Peramivir with oseltamivir demonstrated additive antiviral activity. The clinical significance of this data is currently unknown.

Resistance

No clinical data are available on the development of resistance to Peramivir. Characterization of virus selected in cell culture for resistance to Peramivir identified the H275Y substitution in influenza A/WSN/33 (H1N1). The H1N1 influenza A clinical isolates expressing the oseltamivir resistance-associated substitution H275Y appear to be resistant to Peramivir. The H275Y substitution has been observed in 2009 H1N1 in patients exposed to oseltamivir. As of September 5, 2009, the frequency of resistance in isolates from treated and untreated patients has been < 1% (Source: <http://www.cdc.gov/flu/weekly/index.htm#whomap>). To date, the resistance pathways for Peramivir have not been fully described.

Cross-Resistance

Cross-resistance has been observed among influenza virus neuraminidase inhibitors. The oseltamivir resistance-associated substitutions E119V (A/H3N2), D198N (B), H275Y (A/H1N1), and R292K (H2N2) conferred 1, 4.8, 100 and 80 fold reductions in susceptibility to Peramivir in a neuraminidase assay,

respectively. The zanamivir resistance-associated substitutions E119A (H4N2), E119D (H4N2), E119G (H4N2), R152K (B) conferred 1, 33, 2 and 400 fold reductions in susceptibility to Peramivir, respectively. The relationship between susceptibility to Peramivir inhibition in biochemical assays and clinical efficacy has not been established. Current information on neuraminidase inhibitor resistance-associated substitutions in 2009 H1N1 can be found at www.cdc.gov/h1n1flu/recommendations.htm.

15. NONCLINICAL TOXICOLOGY

Carcinogenesis

No long-term animal carcinogenicity studies have been conducted with Peramivir.

Animal Studies: Target Organs of Toxicity

In studies of rabbits and rats, kidney related events including increases in creatinine, increases in ALT and AST and hematologic abnormalities including decreased red blood cell counts were observed. The events observed in animals are easily monitored in humans. Based on the limited data, no dose related laboratory abnormalities including proteinuria and other renal abnormalities possibly related to Peramivir were observed.

16. CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

Peramivir is an unapproved antiviral drug. Limited safety and efficacy data from phase 1, 2 and 3 trials are available to support use for treatment of 2009 H1N1 infection under an EUA. The following table provides the total number of patients who received Peramivir in phase 1, 2 and 3 trials, including available data from the Shionogi development program.

Dose, Formulation, Duration	Total Number of Exposed Patients
Any dose, Any formulation, Any Duration	1891
Any Dose, IV Formulation, Any Duration	1213
≥ 600 mg, Any Formulation, Any Duration	847
≥ 600 mg, Intramuscular, Single Dose	287
600 mg, IV, Single Dose	478
600 mg, IV, ≥ 5 Day Duration	33
400 mg, IV, 5 Day Duration	85

16.1 Clinical Trial Safety Information

Safety of Intravenous (IV) Peramivir in Hospitalized Patients Treated for 5 Days

Trial BCX1812-201

Trial BCX1812-201 was a phase 2, multicenter, randomized, double-blind trial conducted by BioCryst in the United States, Canada, South Africa, Australia, New Zealand, Hong Kong and Singapore comparing the efficacy and safety of Peramivir administered intravenously once daily for 5 days versus oral oseltamivir 75 mg twice daily for 5 days in adults with acute serious or potentially life-threatening influenza. The doses of Peramivir IV used were 200 mg and 400 mg [see *Clinical Trials*]. The safety population, consisting of patients who received study drug [Peramivir IV 200 mg (n=45), Peramivir IV 400 mg (n=46), or oseltamivir (n=46)], totaled 137 patients.

Serious adverse events (SAEs) were reported by 10% of all patients; 4% of patients who received Peramivir IV 200 mg; 17% of patients who received Peramivir IV 400 mg; 9% of patients who received oseltamivir. Overall, the most frequently reported SAEs were pneumonia (2%) and chronic obstructive pulmonary disease (1%). One patient who received Peramivir IV but was not infected with influenza died during the trial with viral myocarditis confirmed at post-mortem exam.

Three patients withdrew from the trial. The adverse events leading to withdrawal were anxiety and altered mood (Peramivir IV 200 mg), acute respiratory failure (Peramivir IV 400 mg), and angioedema (oseltamivir).

Adverse Events:

- Overall, 54% of patients treated with Peramivir IV developed an adverse event compared to 41% of patients treated with oral oseltamivir.
- Diarrhea was reported in 13% of patients receiving Peramivir IV 200 mg or 400 mg compared to 2% of patients receiving oseltamivir.
- Psychiatric adverse events were reported in 11% of patients receiving Peramivir IV 200 or 400 mg compared to (4%) of patients receiving oseltamivir.
- Psychiatric adverse events reported by patients treated with Peramivir IV either 200 mg or 400 mg were depression (n=2), confusion (n=1), insomnia (n=4), delirium (n=1), restlessness (n=1), anxiety (n=2), nightmare (n=1), and alteration of mood (n=1). Half the events were judged as related to Peramivir IV.

Laboratory Abnormalities:

At the time of enrollment, lymphopenia and elevated glucose levels were common. Three patients had increases in creatinine over enrollment values during or after the treatment period. Evaluation of 24-hour urine collection for protein and creatinine levels did not reveal a trend for renal toxicity for Peramivir when compared to oseltamivir. No laboratory evidence for hematologic or liver toxicity for patients exposed to Peramivir was seen. The laboratory results for the enrolled patients generally reflected the spectrum of underlying co-morbid conditions and severity of illness in the trial population.

Safety of Intravenous Peramivir in Outpatients Treated with Single Dose

I. A phase 2 trial conducted by Shionogi & Co. Ltd in Japan (Study 0722T0621) was a randomized, multicenter, blinded trial to evaluate a single administration of placebo, Peramivir 300 mg IV, or Peramivir 600 mg IV in patients with acute uncomplicated influenza infection. The overall safety population, consisting of patients administered study drug (Peramivir IV or placebo), totaled 298 patients. The safety population by treatment arm was: Peramivir IV 300 mg (N=99); Peramivir IV 600 mg (N=99); placebo (N=100).

- No deaths or serious adverse events were reported in this trial.
- Gastrointestinal Disorders were the most frequently reported adverse events:
 - Peramivir IV 300 mg (19%), Peramivir IV 600 mg (23%), and placebo (22%)
- Diarrhea accounted for the majority of these adverse events:
 - Peramivir IV 300 mg (14%), Peramivir IV 600 mg (15%), and placebo (17%)
 - Most diarrhea adverse events were reported as mild and 7 cases were reported as moderate. None were reported as severe.
- Nausea:
 - Ten patients reported nausea: 3 patients receiving Peramivir IV 300 mg, 6 patients receiving Peramivir IV 600 mg and 1 receiving placebo. With the exception of 1 case of moderate nausea in the Peramivir IV 600 mg group, all cases of nausea were reported as mild.
- Psychiatric events were infrequent
 - 1% Peramivir IV 300 mg (insomnia) and 0 patients in the Peramivir IV 600 mg group
 - 2% placebo (anger (1), insomnia (1))

There was no clinical trend or safety concern observed in the laboratory results for the patients with acute uncomplicated influenza receiving single doses of Peramivir 300 mg or 600 mg intravenously compared with the limited data derived from patients receiving placebo in Study 0722T0621.

The most common laboratory abnormalities were an increased monocyte percentage: 20% in the Peramivir IV 300 mg group, 18% in the Peramivir IV 600 mg group and 31% in the placebo group.

Also increased lymphocyte percentage was commonly seen: 4% in the Peramivir IV 300 mg group, 14% in the Peramivir IV 600 mg group and 5% in the placebo group.

Because renal abnormalities were observed in animal studies, renal parameters including proteinuria were closely monitored in phase 1 and 2 studies. Based on the limited data, no dose related proteinuria or other renal abnormalities possibly related to Peramivir IV were observed.

Proteinuria:

- 9% for the Peramivir IV 300 mg group, 11% for the Peramivir IV 600 mg group, and 18% for the placebo group

No cases of hypersensitivity reaction, septic phlebitis, necrosis of IV administration site or other serious local skin reactions have been reported during the clinical trials.

II. A phase 3 trial conducted by Shionogi & Co. Ltd in Japan, Korea and Taiwan (Trial 0815T0631) was a randomized, multicenter, double-blinded comparative trial to evaluate a single administration of Peramivir 300 mg IV, or Peramivir 600 mg IV and Tamiflu 75 mg twice daily for five days in patients with acute uncomplicated influenza infection. A total of 1093 subjects were included in the safety analyses.

The safety findings include the following:

Preliminary Safety Findings From Phase 3 Trial (0815T0631)

System Organ Class _Preferred Term	Peramivir 300 mg N=364	Peramivir 600 mg N=364	Oseltamivir N=365
Adverse Events – More than 10 cases [number of patients (cases) incidence]			
Gastrointestinal disorders	41 (44) 11.3%	45 (49) 12.4%	66 (79) 18.1%
_Diarrhea	24 (24) 6.6%	30 (30) 8.2%	27 (27) 7.4%
_Nausea	8 (8) 2.2%	8 (8) 2.2%	20 (20) 5.5%
_Vomiting	2 (2) 0.5%	6 (6) 1.6%	15 (15) 4.1%
Investigations	112 (153) 30.8%	111 (155) 30.5%	109 (139) 29.9%
_alanine aminotransferase increased	10 (10) 2.7%	10 (10) 2.7%	5 (5) 1.4%

_ Blood glucose increased	11 (11) 3%	14 (14) 3.8%	12 (12) 3.3%
_ Electrocardiogram QT prolonged	5 (5) 1.4%	8 (8) 2.2%	10 (10) 2.7%
_ Neutrophil count decreased	39 (39) 10.7%	38 (38) 10.4%	34 (34) 9.3%
_ White blood cells urine positive	14 (14) 3.8%	8 (8) 2.2%	16 (16) 4.4%
_ Protein urine present	17 (17) 4.7%	16 (16) 4.4%	22 (22) 6%

Adverse Drug Reactions – More than 10 cases [number of patients (cases) incidence]			
Gastrointestinal disorders	18 (19) 4.9%	28 (37) 7.7%	42 (51) 11.5%
_ Diarrhea	14 (14) 3.8%	20 (20) 5.5%	19 (19) 5.2%
_ Nausea	2 (2) 0.5%	7 (7) 1.9%	16 (16) 4.4%
Investigations	32 (47) 8.8%	30 (48) 8.2%	33 (43) 9%
_ Neutrophil count decreased	9 (9) 2.5%	14 (14) 3.8%	13 (13) 3.6%
_ Protein urine present	7 (7) 1.9%	4 (4) 1.1%	10 (10) 2.7%

III. Shionogi & Co., Ltd. provided preliminary results on a trial in patients at high-risk for serious influenza complications. The trial enrolled 42 patients with either poorly controlled diabetes, chronic respiratory disease requiring pharmacotherapy or patients who were currently on immunosuppressant medication. Patients were randomized to receive 300 mg IV or 600 mg IV for one to five days depending on clinical criteria. Only the incidences of adverse events and adverse drug reactions were provided. No individual cases reporting significant events were observed. The incidence of adverse events and adverse drug reactions were as follows:

Preliminary Safety Summary from Trial in Patients at High Risk for Serious Influenza Complications

	Combined N=42	Peramivir 300 mg N=21	Peramivir 600 mg N=21
Adverse Events			
Number of Patients	31	15	16
Number of Events	(82)	(44)	(38)
Percentage of Patients	73.8%	71.4%	76.2%
Adverse Drug Reactions			
Number of Patients	14	6	8
Number of Events	(21)	(11)	(10)
Percentage of Patients	33.3%	28.6%	38.1%

Phase 1 Safety Data

No serious adverse events and no adverse events leading to discontinuation have been reported from any phase 1 study for either IV or intramuscular formulation.

Overall, 133 patients were exposed to Peramivir IV during the phase 1 studies and 29 patients (22%) reported adverse events. The most commonly reported adverse event was somnolence experienced by 6% of patients receiving Peramivir IV and no placebo patients. Hematuria was reported by 3% of patients receiving Peramivir IV and 7% of patients receiving placebo. Proteinuria was reported by 1% of patients receiving Peramivir IV. There were no dose related trends in the incidence of reported adverse events. Of note, there were no increased reports of adverse events in the trials conducted in the special populations of renal insufficiency and elderly patients.

Besides reports of adverse events related to the injection site (injection site anesthesia, discomfort, irritation, pain), there were no other clinically significant safety findings or trends observed in the phase 1 or phase 2 trials of the intramuscular formulation of Peramivir that were not described above.

16.2 Clinical Trial Efficacy Information

Four IV trials were completed, three single dose trials in acute uncomplicated influenza and one multiple dose trial in hospitalized patients. Additionally, two single dose intramuscular trials were completed. The following table summarizes the phase 2 and 3 trials of Peramivir administered intravenously or intramuscularly. The table below includes the number of patients who completed the trial and are included in the safety analyses and the number of patients evaluable for efficacy. Because only patients who have laboratory confirmed influenza infection are included for evaluation of efficacy, the number of patients evaluated for efficacy differs from the number of patients evaluated for safety (which includes all subjects who had a least one dose of study drug). Additionally, the sections below provide the preliminary efficacy results:

Table 5: Phase 2 and 3 Trials with Peramivir Administered Intravenously or Intramuscularly

Type of Trial	Trial Identifier	Population (N)	Trial Design and Type of Control	Dosage Regimen Route of Administration Duration; Test Product(s)	Trial Results
Intravenous Trials – Acute Uncomplicated Influenza					
Phase 2	Shionogi Trial 0722T0621	Patients aged 20 to 65 years of age with symptoms of influenza	A double-blind, placebo-controlled multicenter with dynamic allocation using the minimization method	Peramivir 300 mg or 600 mg IV, single dose, compared to placebo	Completed (n=298; n=296 efficacy analyses) A statistically significant difference for both doses of Peramivir compared with placebo was observed for time to alleviation of symptoms
Phase 3	Shionogi Trial 0815T0631	Patients with symptoms of influenza	Double blind, randomized	Single IV dose Peramivir 300 mg or 600 mg compared to oseltamivir 75 mg twice daily for 5 days	Completed (n=1093; n=1091 efficacy analyses) The time to alleviation of symptoms, the primary endpoint, was similar for all 3 treatment groups, but a non-inferiority margin has not been established for acute uncomplicated influenza, so the results cannot be interpreted.

Type of Trial	Trial Identifier	Population (N)	Trial Design and Type of Control	Dosage Regimen Route of Administration Duration; Test Product(s)	Trial Results
Intravenous Trials – Hospitalized					
Phase 2 Efficacy and Safety	BCX1812-201	Hospitalized men and women, 18 years or older, with RAT + test for acute influenza infection, and complications of influenza.	Randomized, double-mask, double-dummy comparing the efficacy and safety of Peramivir 200mg or 400mg administered intravenously QD for 5 days v. oseltamivir administered orally BID x 5 days in adults hospitalized with acute serious or potentially life-threatening influenza. Adaptive study design with interim analysis.	Each patient receives IV study drug (Peramivir or placebo) QD for 5 days and receives oral suspension study drug (oseltamivir or placebo) BID for 5 days.	completed (n=137; n=122 efficacy analyses) The results of this trial did not show superiority of either Peramivir dose over oseltamivir or a dose response for Peramivir for the primary endpoint.

Type of Trial	Trial Identifier	Population (N)	Trial Design and Type of Control	Dosage Regimen Route of Administration Duration; Test Product(s)	Trial Results
Intramuscular Trials – Acute Uncomplicated Influenza					
Phase 2 Efficacy and Safety	BCX1812-211	Men and women, 18 years or older, with RAT + test for acute uncomplicated influenza infection.	Multicenter, Double-blind, randomized, placebo-controlled	150 mg, 300 mg, placebo Intramuscular injection, single dose	completed (n=344) no statistically significant differences between treatment groups were observed for the primary efficacy endpoint of time to alleviation of symptoms.
Phase 2	BCX1812-212	The study was planned to include 320 to treatment to ensure enrollment of a minimum of 252 patients who were positive for influenza A (by RT-PCR) and up to 50 patients who were positive for influenza B.	Multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of a single dose of intramuscular Peramivir (600 mg) versus placebo in adults with uncomplicated acute influenza.	Patients received a single dose intramuscular of Peramivir 600 mg or placebo	Completed (n=402; n=334 for efficacy) no statistically significant differences between treatment groups were observed for the primary efficacy endpoint of time to alleviation of symptoms.

The efficacy of Peramivir has not been established in adequate and well-controlled studies.

Four trials are available to evaluate the efficacy of Peramivir IV. Three of the trials were completed in the outpatient setting and a fourth trial was completed in

hospitalized patients. The first trial evaluated a single dose of Peramivir (300 mg and 600 mg) administered intravenously compared to placebo in 298 patients with acute uncomplicated influenza. The second trial evaluated a single dose of Peramivir (300 mg and 600 mg) administered intravenously compared to Tamiflu 75 mg twice daily for five days in 1,093 patients with acute uncomplicated influenza. The third trial provides limited preliminary data in patients at high-risk for serious influenza complications (poorly controlled diabetes, chronic respiratory disease requiring pharmacotherapy or currently on drug medication which suppresses the patient's natural immune responses). Patients were randomized to receive Peramivir IV 300 mg or 600 mg for one to five days depending on clinical criteria.

The fourth trial enrolled hospitalized patients infected with influenza and compared Peramivir IV 200 mg and 400 mg once daily for five days to oral oseltamivir 75 mg twice daily for five days. The results of this trial are not interpretable because the treatment effect of oseltamivir for the primary endpoint of time to clinical stability has not been established for the treatment of influenza in hospitalized patients and the results did not show superiority of either Peramivir IV dose over oseltamivir or a dose response for Peramivir IV for the primary endpoint.

Experience with Peramivir IV at the 600 mg once daily dose for five days in clinical trials is limited to 33 adult patients [see *Warnings and Precautions, Limitations of Populations Studied*]. However, limited use of Peramivir IV in adults and children has been allowed for Peramivir IV 600 mg once daily for 5 to 10 days under emergency IND procedures

Acute Uncomplicated Influenza:

A randomized, multicenter, blinded trial was conducted in Japan to evaluate a single IV treatment with either Peramivir 300 mg, Peramivir 600 mg, or placebo in 298 patients with acute uncomplicated influenza. A total of 296 patients had influenza confirmed by virus culture or PCR assay. The inclusion criteria required that patients be enrolled in the trial within 2 days of symptom onset.

The primary endpoint was time to alleviation of symptoms and was defined as the number of hours from initiation of study drug until the start of the 24 hour period in which all seven symptoms of influenza (cough, sore throat, nasal congestion, headache, feverishness, myalgia and fatigue) were either absent or present at a level no greater than mild for at least 24 hours.

A statistically significant difference for both doses of Peramivir IV compared with placebo was observed for time to alleviation of symptoms. An approximately one day treatment benefit was observed. The trial results are as follows:

Trial 0722T0621 Results – Time to Alleviation of Symptoms

Kaplan-Meier Estimates	Peramivir 300 mg (n=99)	Peramivir 600 mg (n=97)	Placebo (n=100)
Median (hours)	59.1	59.9	81.8
95% CI	50.9, 72.4	54.4, 68.1	68.0, 101.5
Median Improvement over placebo (hours)	22.7	21.1	
95% CI*	(2.75, 43.492)	(4.233, 41.442)	
one sided P value	0.0046	0.0030	
Cox Proportional hazards model			
Hazard ratio	0.681	0.666	--
(95% CI)	(0.511, 0.909)	(0.499, 0.890)	--

* Based on bootstrap estimation of 7500 samples

A phase 3 trial conducted by Shionogi & Co. Ltd in Japan, Korea and Taiwan (Trial 0815T0631) was a randomized, multicenter, double-blinded comparative trial to evaluate a single administration of Peramivir IV 300 mg, or Peramivir IV 600 mg and Tamiflu 75 mg twice daily for five days in 1093 patients with acute uncomplicated influenza infection. A total of 1091 patients were included in the efficacy analyses.

The primary endpoint was time to alleviation of symptoms. BioCryst recently provided preliminary results via a slide set and press release. The final study report is being drafted. The time to alleviation of symptoms was similar for all three treatment groups as shown below.

Trial 0722T0631 Time to Alleviation of Symptoms (Hours) – ITTI Population

	Peramivir 300 mg (n=364)	Peramivir 600 mg (n=362)	Tamiflu (n=365)
Median (hours)	78.0	81.0	81.8
95% CI	(68.4, 88.6)	72.7, 91.5)	(73.2, 91.1)
Improvement over Tamiflu (hours)	-3.8	-0.8	--
Cox Proportional hazards model			
Hazard ratio	0.946	0.970	--
(97.5% CI)	(0.793, 1.129)	(0.814, 1.157)	--
P value	0.4836	0.7015	--

The overall trial results are challenging to interpret because appropriate non-inferiority margins have not been established in trials of acute uncomplicated influenza. Placebo-controlled rather than noninferiority designs are preferred for studies evaluating treatment of uncomplicated mild to moderate influenza because the risks of receiving placebo are low and the efficacy of available treatment is modest (1-day difference in time-to-alleviation of symptoms), variable, and cannot be predicted well enough to support a noninferiority margin.

Additionally, BioCryst provided preliminary results of a trial conducted by Shionogi in patients at high-risk for serious influenza complications. Trial 0816T0632 enrolled 42 patients with either poorly controlled diabetes, chronic respiratory disease requiring pharmacotherapy or currently on drug medication which suppresses the patient's natural immune responses. Patients were randomized to receive 300 mg IV or 600 mg IV for one to five days depending on clinical criteria. The primary endpoint was time to alleviation of symptoms. The table below summarizes how many doses were administered by dose group. Thirty seven patients were included in the efficacy analyses.

Trial 0816T0632 Number of Peramivir IV Doses Received by Dose Group

# of doses	Combined N=37	300 mg N=18	600 mg N=19
1	10	7	3
2	23	9	14
3	2	1	1
4	1	0	1
5	1	1	0

The following results were presented in a slide set and press release. The results are presented for all patients combined, comparison between single-dose and multiple-dose groups and comparison between doses.

Trial 0816T0632 Time to Alleviation of Symptoms

	All Patients Combined	Single Dose	Multiple Dose	300 mg	600 mg
N	37	10	27	18	19
Median (hrs)	68.6	92	64.1	114.4	42.3
(90% confidence interval)	(41.5, 113.4)	(14.6, 235.3)	41.5, 111.2)	(40.2, 235.3)	(30, 82.7)

Shionogi states time to alleviation of symptoms was shorter for the 600mg IV group than the 300 mg IV group. In addition, time to alleviation of symptoms was shorter in multiple-dosed patients than single-dosed patients based on time to alleviation of symptoms. Of note, an imbalance in the number of patients receiving single or multiple doses within a dose cohort was seen. More patients received single IV administration in the 300 mg group compared to the 600 mg group (7 versus 3) and more patients received multiple doses in the 600 mg group compared to the 300 mg group (16 versus 11). Based on the limited data, the impact of this imbalance on the overall results is unknown and we await the individual data to verify the overall study results.

Intramuscular Administration for Acute Uncomplicated Influenza:

A single dose intramuscular trial (Trial 211) was conducted to compare Peramivir 150 mg and 300 mg and placebo in adult patients with acute uncomplicated influenza. The primary efficacy endpoint was time to alleviation of symptoms defined as the number of hours from initiation of study drug until the start of the 24 hour period in which all 7 symptoms of influenza (cough, sore throat, nasal congestion, headache, feverishness, myalgia and fatigue) were either absent or present at a level no greater than mild for at least 24 hours. The results from the intent-to-treat infected (ITTI) population are shown in the table below.

Trial BCX1812-211 Time to Alleviation of Symptoms (Hours) – ITTI Population

Kaplan–Meier Estimates	Placebo (N=108)	Peramivir 150 mg (N=104)	Peramivir 300 mg (N=105)
Mean (SD)	150.3 (7.91)	136.2 (8.15)	131.0 (8.79)
Median	136.2	114.1	117.4
95% CI	114.3, 165.8	95.2, 145.5	78.0, 135.9
Median Improvement over placebo (Hrs)		22.1	18.8
95% CI ¹		(-19.5, 63.3)	(-14.3, 63.7)
Cox Proportional hazards model²			
Hazard ratio	--	0.859	0.816
(95% CI)	--	(0.606, 1.156)	(0.606, 1.098)
P value	--	0.315	0.180

1 Based on bootstrap estimation of 7500 samples

2 Cox proportional hazard model with factors for treatment, influenza season, and smoking status

While there were differences in the point estimates for the Peramivir treatment groups compared to placebo, no statistically significant differences between treatment groups were observed for the primary efficacy endpoint of time to alleviation of symptoms.

In another phase 2 trial (Trial 212) of intramuscular Peramivir 600 mg compared to placebo in patients with acute uncomplicated influenza, a statistically significant treatment effect was not observed for the primary endpoint (time to alleviation of symptoms) or secondary endpoints. Potential reasons for the lack of treatment difference are the circulating virus in the community during this trial and the single dose design. All seasonal influenza A H1N1 viruses tested had the H275Y mutation. Current data supports the conclusion that a single administration of Peramivir will not have adequate activity against viruses with H275Y substitution. No clinical data are available on the development of resistance to Peramivir.

Hospitalized Patients:

A double-blind, randomized, multinational trial was conducted to compare two IV doses of Peramivir (200 mg once daily and 400 mg once daily) and oral oseltamivir 75 mg twice daily for five days in hospitalized adults with serious or potentially life-threatening influenza.

No difference between the three treatment groups was reported for the primary endpoint of time to clinical stability or for the secondary endpoints. Clinical stability was defined as:

<u>Sign of Clinical Resolution</u>	<u>Normalization Criteria</u>
Temperature	≤ 37.2° C (≤ 99° F) oral
Oxygen saturation	≥ 92%
Respiration rate	≤ 24/minute
Heart rate	≤ 100/minute
Systolic BP	≥ 90 mm Hg

Note: Both temperature and oxygen saturation must meet Normalization Criteria in order for the clinical stability endpoint to be met in the clinical trial

The following table summarizes the results.

BCX1812-201 Trial Results

Parameter	Peramivir 200 mg (n=41)	Peramivir 400 mg (n=40)	Oseltamivir (n=41)
Time to Clinical Stability	23.7 hours	37 hours	28.1 hours
Time to Resumption of Usual Activities (days)	8.2 days	9.2 days	13.2 days
Clinical Relapse	None	None	None
Time to Hospital Discharge (days)	6.3 days	4.5 days	4.3 days
Overall mean change log ₁₀ in viral load from nasopharyngeal specimens at 48 hours	-2.3	-2.5	-2.2
Influenza A subgroup: Mean change log ₁₀ in viral load from nasopharyngeal specimens at 48 hours	-2.0 (n=24)	-2.3 (n=28)	-2.2 (n=28)
Influenza B subgroup: Overall mean change log ₁₀ in viral load from nasopharyngeal specimens at 48 hours	-2.7 (n=15)	-3.3 (n=6)	-2.2 (n=11)

Based on the results of this trial FDA cannot conclude Peramivir IV demonstrated a clinical effect in this population for several reasons:

- The treatment effect of oseltamivir in hospitalized patients with serious influenza has not been established. Therefore, findings for the primary endpoint of time to clinical stability for all treatment groups are inconclusive.
- The results did not show superiority of either Peramivir IV dose over oseltamivir for the primary endpoint nor did it show a dose-response for Peramivir IV 200 mg over Peramivir IV 400 mg.

Overall, because of the trial design, valid conclusions cannot be determined regarding whether Peramivir IV had a clinically meaningful impact on clinical disease in hospitalized patients infected with influenza virus.

16.3 Dose Rationale:

Adults:

Peramivir administered intravenously at a dose of 600 mg once daily for 5 to 10 days is recommended for the emergency use of Peramivir IV under EUA based on the following available data and assumptions.

- A treatment benefit was observed in a phase 2 trial (0722T0621) conducted by Shionogi & Co. Ltd in Japan. The results showed 300 mg and 600 mg single doses of Peramivir given intravenously to patients with acute uncomplicated influenza had statistically significant shorter time to alleviation of symptoms compared to placebo (approximately one day treatment benefit).
- The results from two other trials (one in hospitalized patients and one in outpatients with acute uncomplicated influenza) are challenging to interpret, in part, because oseltamivir was the comparator. The treatment effect of oseltamivir in hospitalized patients has not been established and insufficient information is available to establish a noninferiority margin for the acute uncomplicated influenza trial. In the phase 2 trial in hospitalized patients and the phase 3 trial in outpatients with acute uncomplicated influenza, the individual study results did not show superiority of either Peramivir IV dose over oseltamivir for the primary endpoint nor did it show a dose-response for either Peramivir IV dose (200 mg versus 400 mg and 300 mg versus 600 mg, respectively).
- Safety data from phase 1, 2, and 3 clinical trials support emergency use under EUA.
- Pharmacokinetic data suggest Peramivir will show a dose proportional increase in exposures when the dose is increased from 300 mg to 600 mg. Dose proportional increases in exposures were observed at single IV doses from 75 to 300 mg and from 1 mg/kg to 8 mg/kg (560 mg for a 70 kg patient).

- No accumulation of Peramivir was observed after multiple dose administration.
- The exposure parameter that correlates with antiviral activity is not known for Peramivir or for the other approved neuraminidase inhibitors. Data for antiviral products indicated to treat viral infections show that maintaining sufficient exposures throughout the dosing interval is important for antiviral activity and minimizes development of resistance.

The objective is to provide a sufficient Peramivir IV dose and exposure throughout the course of infection in an attempt to improve clinical outcome. A treatment benefit was observed with single doses of IV administration of Peramivir in patients with acute uncomplicated influenza. It is reasonable to expect a proportional increase in exposure when the Peramivir IV dose is increased from 300 mg to 600 mg once daily. Therefore, a longer duration of therapy at the 600 mg IV dose which already showed a treatment benefit, albeit in a different population, is reasonable for certain hospitalized patients infected with 2009 H1N1 infection.

The information presented above along with the currently available safety information support the use of Peramivir IV under EUA. The 600 mg daily dose of Peramivir IV for 5 to 10 days is being evaluated in phase 3 clinical development. Given the currently available safety and pharmacokinetic data for Peramivir IV, FDA believes the 600 mg dose once daily is appropriate for treating certain patients with 2009 H1N1 infection under EUA. Initial treatment courses of 5 days or 10 days are permitted. Patients with critical illness (such as 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. Additional treatment beyond 10 days is permitted depending on clinical presentation such as continued viral shedding or unresolved clinical influenza illness.

Pediatrics

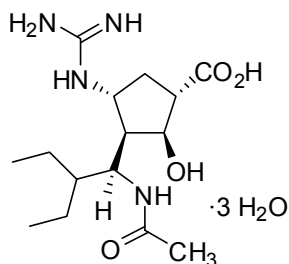
No patients less than 18 years of age have received Peramivir IV in clinical trials. However, limited use of Peramivir IV in children has been allowed for Peramivir IV 600 mg once daily for 5 to 10 days under emergency IND procedures. The pediatric dosing recommendations are derived from a model based analysis of data available from 36 healthy adults (age: 18-46 yrs; weight: 49-113 kg; females: 12) and 198 acute uncomplicated influenza infected patients (age: 20-62 yrs; weight: 39-109 kg; females: 97). In the absence of pharmacokinetic (PK) data in pediatric patients (17 years and younger), the model for pediatric patients was derived from the published literature on renal function maturation and the knowledge of other renally eliminated drugs.³ The estimated exposures of the recommended doses for pediatric patients reasonably approximate the exposures in adults.

Peramivir clearance was found to be 7.58 L/hr/70 kg in influenza infected patients and 6.19 L/hr/70 kg in healthy adults. The effect of body size on Peramivir clearance was described using an allometric function with an exponent of $\frac{3}{4}$. The effect of renal maturation on Peramivir clearance was described with a sigmoid hyperbolic model described by Rhodin et. al. ⁵.

Based on the adult data (body size model) and pediatric model (renal function maturation), the proposed dosing recommendations were derived to reasonably match exposures (AUC = 80 $\mu\text{g}\cdot\text{hr}/\text{mL}$) in adult influenza patients. The target exposures were defined from an AUC for a typical 70 kg patient from the 0722T0621 study after 600 mg IV dose of Peramivir. The dose of 600 mg IV for 5 days will be administered in phase 3 trials in adults.

17. PRODUCT DESCRIPTION

Peramivir is a neuraminidase inhibitor for influenza virus. The chemical name is (1S,2S,3R,4R)-3-[(1S)-1-(acetylamino)-2-ethylbutyl]-4-[(aminoiminomethyl)amino]-2-hydroxycyclopentanecarboxylic acid, trihydrate. The empirical formula is $\text{C}_{15}\text{H}_{34}\text{N}_4\text{O}_7$, representing a molecular weight of 382.45. The molecular structure is as follows.



18. HOW SUPPLIED/STORAGE AND HANDLING

Peramivir Injection is a clear, iso-osmotic, sterile, nonpyrogenic solution in 200 mg per 20 mL (10 mg/mL) glass vials fitted with rubber stoppers and aluminum flip-off seals with blue buttons. Each mL of solution contains 10 mg Peramivir and 9 mg sodium chloride in Water for Injection. The pH is adjusted with sodium hydroxide, NF and/or hydrochloric acid, NF.

No preservative or bacteriostatic agent is present in the product.

Peramivir Injection is supplied in a 200 mg/20 mL single use vial. Five (5) single use vials, are packaged in a carton

Vials should be stored at room temperature (15 to 30°C; 59 to 86°F). [see *Dosage and Administration*]

19. PATIENT COUNSELING INFORMATION

See Fact Sheet for Patients and Parents/Caregivers

20. REFERENCES

- (1) Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16:31-4.
- (2) Joy MS, Matzke GR, Armstrong DK, et al. A primer on continuous renal replacement therapy for critically ill patients. *Annals Pharmacotherapy* 1998;32:362-375
- (3) Schwartz GJ, Gauthier B. *JPediatric* 1985 March;106(3):522-6.
- (5) Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Chatelut E, Grubb A, Veal GJ, Keir MJ, Holford NH.; Human renal function maturation: a quantitative description using weight and postmenstrual age.; *Pediatr Nephrol*. 2009 Jan; 24(1):67-76.