Guidance for Use and Dosing of Peramivir in Hospitalized Adults

Background:
Peramivir is an intravenous neuraminidase inhibitor that is FDA-approved for the treatment of acute uncomplicated influenza in adults 18 years and older.[1] Prior to its approval, the FDA had authorized emergency use of peramivir to treat certain hospitalized patients with known or suspected 2009 H1N1 influenza.[2]

Criteria for Use:
Peramivir is restricted for use to ID only. **In addition, its use should be limited to patients who are unable to take oseltamivir due to an inability to ingest or absorb oral medication.** Examples of these situations would include severe GVHD or mucositis, ileus, or patient intubated with no enteral access. Once medications may be given enterally, patients should be changed oseltamivir to complete therapy as oseltamivir has shown to be well absorbed even when provided through a nasogastric tube.[3]

Dosing Recommendations:
Peramivir is approved as a single dose regimen based on studies of uncomplicated influenza in outpatients.[4] There is less data available on peramivir use for hospitalized patients with influenza; however this population may benefit from repeated dosing of peramivir, especially those that are immunocompromised.

- An uncontrolled study of peramivir in high risk patients with influenza found that the duration of illness tended to be shorter in patients receiving multiple daily doses (up to 5 days) compared to a single dose.[5]
- An open-label, randomized study conducted during the 2009 H1N1 pandemic found that two dosing regimens of peramivir (300 mg twice daily or 600 mg once daily) given for 5-10 days were associated with a decrease in viral shedding and clinical improvement. [6]
- The largest randomized study in hospitalized patients failed to find a significant benefit for peramivir compared to placebo plus standard of care, although there was a more pronounced benefit in patients admitted to the ICU or enrolled within 48 hours of symptom onset.[7] There are many limitations with this study, notably that standard of care therapy could include other neuraminidase inhibitors.

We generally recommend that peramivir be given as a **600 mg daily dose for 5 days** in patients hospitalized due to influenza, primarily the immunocompromised. This is consistent with how it was previously utilized for H1N1 influenza. Dose adjustments should be made for renal function as highlighted below.[8]

Renal Dose Adjustments:

	Creatinine Clearance				Hemodialysis (HD)
Recommended Dose	> 50 mL/min	31-50 mL/min	10-30 mL/min	< 10 mL/min, not on any dialysis	Give maintenance dose 2 hours after HD on dialysis days only
Adults	600 mg daily	150 mg daily	100 mg daily	100 mg on Day 1, then 15 mg daily	100 mg on Day 1, then 100mg after each HD
Birth through 30 days	6 mg/kg daily	1.5 mg/kg daily	1 mg/kg daily	1 mg/kg on Day 1, then 0.15 mg/kg daily	1 mg/kg on Day 1, then 1mg/kg after each HD
31 Days through 90 Days	8 mg/kg daily	2 mg/kg daily	1.3 mg/kg daily	1.3 mg/kg on Day 1, then 0.2 mg/kg daily	1.3 mg/kg on Day 1, then 1.3 mg/kg after HD
91 days through 180 days	10 mg/kg daily	2.5 mg/kg daily	1.6 mg/kg daily	1.6 mg/kg on Day 1, then 0.25 mg/kg	1.6 mg/kg on Day 1, then 1.6 mg/kg after HD
181 days through 5 years	12 mg/kg daily	3 mg/kg daily	1.9 mg/kg daily	1.9 mg/kg on Day 1, then 0.3 mg/kg daily	1.9 mg/kg on Day 1, then 1.9 mg/kg after HD
6 years through 17 years	10 mg/kg daily	2.5 mg/kg daily	1.6 mg/kg daily	1.6 mg/kg on Day 1, then 0.25 mg/kg daily	1.6 mg/kg on Day 1, then 1.6 mg/kg after HD

References:

1. Rapivab™ (peramivir injection) [package insert]. Durham, NC: Biocryst Pharmaceuticals, Inc. December 2014.
2. Mancuso CE, Gabay MP, Steinke LM, VanOsdol SJ. Peramivir: an intravenous neuraminidase inhibitor for the treatment of 2009 H1N1 influenza. *Ann Pharmacother*. 2010;44:1240-9.

3. Taylor WR, Thinh BN, Anh GT et al. Oseltamivir is adequately absorbed following nasogastric administration to adult patients with severe H5N1 influenza. *PLoS One*. 2008;3410:e3410.
4. Kohno S, Yen Muh-Yong, Cheong H, et al. Phase III randomized, double-blind study comparing single-dose intravenous peramivir with oral oseltamivir in patients with seasonal influenza virus infection. Antimicrob Agents Chemother. 2011;55(11):5267-76.
5. Ison MG, Fraiz J, Heller B, et al. Intravenous peramivir for treatment of influenza in hospitalized patients. *Antivir Ther*. 2014;19(4):349-61.
6. Kohno S, Kida H, Mizuguchi M, et al. Intravenous peramivir for treatment of influenza A and B virus infection in high-risk patients. *Antimicrob Agents Chemother.* 2011;55(6):2803-12.
7. De Jong MD, Ison MG, Monto AS, et al. Evaluation of intravenous peramivir for treatment of influenza in hospitalized patients. *Clin Infect Dis.*2014;59(12):e172-82.
8. Food and drug administration. Emergency Use Authorization for Providers. 2009. [Accessed March 24, 2017] https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM190601.pdf

Peramivir Injection (Rapivab™, Biocryst Pharmaceuticals) Reviewed February 2015

Efficacy
Peramivir is a neuraminidase inhibitor that was approved by the FDA in December 2014 for treatment of uncomplicated influenza in adults. Prior to its approval, permivir was used to treat critically ill patients during the 2009 H1N1 epidemic under an FDA emergency use authorization. Efficacy was established in a randomized trial in adults with acute uncomplicated influenza, with findings consistent with other neuraminidase inhibitors. Efficacy was not established in patients with serious influenza requiring hospitalization.

Safety
The most common side effect associated with use of peramivir is diarrhea. Rare but serious side effects include hypersensitivity reactions, such as Stevens-Johnson syndrome and erythema multiforme.

Uniqueness
Peramivir is the first neuraminidase inhibitor approved as an intravenous formulation. This is advantageous for patients unable to take medications enterally. It is also unique in that it was approved as a single dose; however it was given as a daily dose for 5 days during the H1N1 epidemic.

Introduction[1,2,3]
Influenza virus, a member of the Orthomyxoviridae family, is responsible for causing an acute but self-limited respiratory illness. Influenza viruses are classified into three distinct types, A, B, and C, with illness primarily caused by A and B strains of virus. Due to annual epidemics and unpredictable pandemics, influenza has the potential for causing significant morbidity and mortality. Approximately 5-20% of Americans are affected by seasonal influenza, resulting in over 200,000 hospitalizations and 36,000 deaths per year from influenza-related complications. Cost is estimated to be greater than $12 billion. In 2009, a new strain of influenza virus A was isolated. The H1N1 virus, or “swine flu”, became the first influenza A outbreak to reach a worldwide pandemic status in over 40 years.

There are only two drug classes of anti-influenza agents approved by the FDA for both prophylaxis and treatment of seasonal influenza. These are the adamantanes and neuraminidase inhibitors. Prior to the approval of peramivir, an intravenous neuraminidase inhibitors, the only other agents in this class were oseltamivir, which is available as an oral capsule and oral suspension, and zanamivir,

which is available as an inhalation. During the H1N1 pandemic, peramivir was still undergoing phase III clinical trials. However, the FDA granted an Emergency Use Authorization (EUA) for the emergency use of peramivir to treat hospitalized patients with suspected or confirmed H1N1 influenza. This marked the first time that a EUA was authorized for an unapproved medication.

Pharmacokinetics[1]

Absorption	Cmax 46.8 mcg/mL following IV infusion
Distribution	< 30% bound to human plasma proteins; volume of distribution 12.56 L
Metabolism	Not significantly metabolized in humans
Elimination	Primarily renally eliminated (90%); elimination half-life 20 hours

Pharmacodynamics[1]

Peramivir does not prolong the QTc interval (at twice the maximum recommended dose) to any clinically relevant extent.

Pharmacology[1]

Peramivir is an inhibitor of influenza virus neuraminidase, the enzyme responsible for releasing viral particles from the plasma membrane of infected cells. It is only active against influenza virus.

FDA Approved Indications[1,2]

Peramivir is indication for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than 2 days. It was approved by the FDA on December 19, 2014.

Clinical Trials[4,5,6,7]

Study 621

<table>
<tr><th>Study Design</th><th>Methods</th><th>Results</th><th>Conclusions/ Comments</th></tr>
<tr>
<td>Kohno et al, Nov. 2010

Randomized, multicenter, blinded trial conducted in 75 centers in Japan

Total n = 296

Intervention: Single dose of peramivir 300 mg (n=99), peramivir 600 mg (n=97), or placebo (n=100)

Dec. 2007 – April 2008</td>
<td>Inclusion criteria: Previously healthy adults aged 20-65 with onset of influenza-like illness within the previous 48 hours, diagnosis of influenza (positive rapid antigen test, fever ≥ 38ºC, and ≥ 2 of 7 symptoms)

Exclusion criteria: Respiratory dysfunction, convulsions or neurologic symptoms, chronic illness, HIV, hemodialysis, suspected bacterial infection, treatment with steroids or immunosuppressants, use of anti-influenza drugs within the past 7 days, pregnant or breast feeding

Efficacy analysis performed on ITT population; safety analysis performed on all subjects who took one dose of medication

Per-group sample size of 67 estimated to have 80% power to detect difference in mediate time to symptom alleviation of 87 hours in treatment group and 137 hours in placebo group</td>
<td>Primary efficacy variable:
Time to alleviation of symptoms
<table>
<tr><th>Population</th><th>Parameter</th><th>P 300 mg</th><th>P 600 mg</th><th>Placebo</th></tr>
<tr><td rowspan="4">Overall</td><td>n</td><td>99</td><td>97</td><td>100</td></tr>
<tr><td>Median (h) (95% CI)</td><td>59.1 (50.9-72.4)</td><td>59.9 (54.4-68.1)</td><td>81.8 (68.0-101.5)</td></tr>
<tr><td>HR (95% CI)</td><td>0.681 (0.511-0.909)</td><td>0.666 (0.499-0.89)</td><td></td></tr>
<tr><td>P value</td><td>0.0092</td><td>0.0092</td><td></td></tr>
<tr><td colspan="5">Subtype</td></tr>
<tr><td rowspan="4">A/HI</td><td>n</td><td>74</td><td>69</td><td>72</td></tr>
<tr><td>Median (h) (95% CI)</td><td>52.5</td><td>62.6</td><td>81.4</td></tr>
<tr><td>HR (95% CI)</td><td>0.779</td><td>0.899</td><td></td></tr>
<tr><td>P value</td><td>0.1458</td><td>0.5384</td><td></td></tr>
<tr><td rowspan="4">A/H3</td><td>n</td><td>21</td><td>25</td><td>24</td></tr>
<tr><td>Median (h) (95% CI)</td><td>76.1</td><td>50.5</td><td>81.0</td></tr>
<tr><td>HR (95% CI)</td><td>0.542</td><td>0.326</td><td></td></tr>
<tr><td>P value</td><td>0.0556</td><td>0.0008</td><td></td></tr>
<tr><td colspan="5">Symptom duration before study</td></tr>
<tr><td rowspan="4">0-24 h</td><td>n</td><td>59</td><td>51</td><td>48</td></tr>
<tr><td>Median (h) (95% CI)</td><td>57.2</td><td>56.1</td><td>86.7</td></tr>
<tr><td>HR (95% CI)</td><td>0.653</td><td>0.663</td><td></td></tr>
<tr><td>P value</td><td>0.0516</td><td>0.0516</td><td></td></tr>
<tr><td rowspan="4">24-48 h</td><td>n</td><td>40</td><td>46</td><td>52</td></tr>
<tr><td>Median (h) (95% CI)</td><td>69.1</td><td>64.7</td><td>70.8</td></tr>
<tr><td>HR (95% CI)</td><td>0.708</td><td>0.694</td><td></td></tr>
<tr><td>P value</td><td>0.1118</td><td>0.1118</td><td></td></tr>
</table>
Adverse events:
One subject withdrew from study
No serious adverse events reported</td>
<td>Author's conclusion:
Single dose IV peramivir is effective and well-tolerated in acute uncomplicated influenza virus infection

Comments:
Can only be generalized to previously healthy outpatients, therapy was started within 48 hours of symptom onset, efficacy only shown for influenza A virus</td>
</tr>
</table>

Study 301

Study Design	Methods	Results	Conclusions/ Comments
De Jong et al, Dec. 2014 Randomized (2:1), double-blind, multicenter, placebo-controlled trial conducted at 323 hospitals in 21 countries Safety population, n=398 ITT population, n=338 Intervention: Standard of care plus peramivir 600 mg (n=217) or placebo (n=121)given daily for 5 days) Sept. 2009 – Nov. 2012	Inclusion criteria: Serious influenza requiring hospitalization (fever and/or reduced oxygen saturation, ≥ 2 of 3 vital signs abnormal, ≥ 1 respiratory symptom for < 72 h, ≥ 1 constitutional symptom for < 72 h, ≥ 1 risk factor) Exclusion criteria: hospitalization > 24 hours at screening, prior neuraminidase inhibitor or amantadine treatment, confirmed bacterial infection Intervention started within 72 hours of start of symptoms Sample size of 160 in the non-NAI SOC group estimated to have 90% power to detect hazard ratio of 0.57	Results from pre-planned interim analysis. Primary efficacy variable: Time to clinical resolution Subjects: ITTI Non-NAI SOC (Placebo + SOC; Peramivir + SOC); ITT NAI SOC (Placebo + SOC; Peramivir + SOC) All: 49.5 (40.0-61.9); 42.5 (34.0-57.9); 48.9 (31.0-65.8); 41.9 (30.9-56.8) Symptoms ≤ 48 h at randomization: 58.2 (37.0-71.1); 42.9 (35.4-63.0); 48.4 (35.7-80.1); 41.8 (27.8-67.3) Symptoms > 48 h at randomization: 40.0 (20.0-42.5); 36.0 (23.3-65.0); 31.0 (18.9-62.0); 36.0 (25.0-61.4) Admitted to ICU at baseline Yes: 50.2 (7.8-61.9); 31.5 (22.8-47.5); 49.5 (37.0-65.5); 46.3 (38.3-64.0) No: 49.5 (37.0-65.5); 46.3 (38.3-64.0); 38.8 (25.0-60.8); 36.2 (27.8-48.3) Adverse events: 28 serious adverse events reported, majority related to underlying influenza infection. COPD (n=4) and pneumonia (n=4) reported most frequently, similar for peramivir and placebo.	Author's conclusion: Study terminated after pre-planned interim analysis for futility. Significant clinical benefit was not demonstrated but peramivir was safe and well tolerated. Challenging to designed studies to evaluate influenza antiviral agents in hospitalized patients. Comments: No clinical endpoints have been validated in this patient population. Therapy was started within 72 hours of symptom onset

Study Design	Methods	Results	Conclusions/ Comments
Kohno et al, June 2011 Multicenter, uncontrolled, randomized, double-blind study at 37 centers in Japan Per protocol set, n=74 Intervention: Peramivir 300 mg (n=18) or 600 mg (n=19) once daily for 1-5 days Jan. 2009 – May 2009	Inclusion criteria: Age ≥ 20 years, rapid antigen test positive for influenza, ≥ 1 risk factor (poorly controlled diabetes, pharmacotherapy for chronic respiratory tract disease, immunosuppression), symptom onset within the previous 48 h, ≥ 2 of 7 symptoms of at least moderate severity Exclusion criteria: chronic respiratory failure requiring artificial ventilation, diabetes with HbA1C ≥ 10%, organ or hematopoietic stem cell transplant within previous 12 months, dialysis or nephropathy, CHF as complication, ischemic heart disease or serious arrhythmia, QTc ≥ 480 ms, presence of major circulatory system disease, CNS disease, metabolic disease, cancer, hepatitis, or cirrhosis, treatment with immunoglobulin or colony-stimulating factor 90% CIs and median values used to assess primary endpoint; target number of patients receiving peramivir was 100 so 90% CI could be expected to lie within a 72 h interval	Primary efficacy variable: Duration of influenza illness Parameter: Combined; 300 mg; 600 mg Duration of influenza illness n: 37; 18; 19 Median (h) (90% CI): 68.6 (41.5, 113.4); 114.4 (40.2, 235.2); 42.3 (30.0, 82.7) HR (90% CI): ; ; 0.497 (0.251, 0.984) Adverse events: Most common adverse event clinical symptoms: diarrhea (n=2), pneumonia (n=3), oral herpes infection (n=3)	Author's conclusion: Duration of illness was significantly shorter in the 600 mg group compared to the 300 mg group. No adverse events were problematic clinically. Potentially useful treatment for high-risk patients. Comments: Used repeated doses instead of a single dose. Not placebo-controlled.

<table>
<tr><th>Study Design</th><th>Methods</th><th>Results</th><th>Conclusions/ Comments</th></tr>
<tr>
<td>Kohno et al, Nov. 2011

Multinational, multicenter, double-blind, double-dummy, randomized controlled trial at 146 centers in South Korea, Japan, and Taiwan

ITT population, n=1091

Intervention: Peramivir 300 mg (n=364) or 600 mg (n=362) for 1 dose vs. oseltamivir 75 mg twice daily for 5 days (n=365)

Nov. 2008 – April 2009</td>
<td>Inclusion criteria: Age ≥ 20 years, rapid antigen test positive for influenza, available for treatment within 48 h of symptom onset, fever ≥ 38°C, ≥ 2 of 7 symptoms of at least moderate severity,

Exclusion criteria: Impaired respiratory function, CHF, poorly controlled diabetes, immunosuppressive therapy, immunodeficiency disorder, renal disorder, ischemic heart disease or serious arrhythmia, QTc ≥ 480 ms or bradycardia, infection requiring antibiotics

Hazard model analysis and noninferiority margin of 0.170. Planned to recruit 1050 patients.</td>
<td>Primary efficacy variable:
Time to alleviation of influenza symptoms
<table>
<tr><th>Population and treatment</th><th>Median time to alleviation</th><th>Hazard ratio (97.5 CI)</th></tr>
<tr><td>Overall</td><td></td><td></td></tr>
<tr><td>Peramivir 300 mg</td><td>78.0 (68.4, 88.6)</td><td>0.946 (0.793, 1.129)</td></tr>
<tr><td>Peramivir 600 mg</td><td>81.0 (72.7, 91.5)</td><td>0.970 (0.814, 1.157)</td></tr>
<tr><td>Oseltamivir</td><td>81.8 (73.2, 91.1)</td><td></td></tr>
<tr><td>A/H1</td><td></td><td></td></tr>
<tr><td>Peramivir 300 mg</td><td>80.2 (69.3, 90.6)</td><td>0.854 (0.672, 1.085)</td></tr>
<tr><td>Peramivir 600 mg</td><td>83.6 (72.7, 101.9)</td><td>0.927 (0.730, 1.176)</td></tr>
<tr><td>Oseltamivir</td><td>88.8 (73.1, 102.2)</td><td></td></tr>
<tr><td>A/H3</td><td></td><td></td></tr>
<tr><td>Peramivir 300 mg</td><td>69.9 (54.4, 97.1)</td><td>1.039 (0.745, 1.448)</td></tr>
<tr><td>Peramivir 600 mg</td><td>70.6 (47.7, 91.9)</td><td>0.958 (0.687, 1.335)</td></tr>
<tr><td>Oseltamivir</td><td>75.1 (63.4, 92.6)</td><td></td></tr>
<tr><td>B</td><td></td><td></td></tr>
<tr><td>Peramivir 300 mg</td><td>55.3 (43.9, 86.4)</td><td>0.445 (0.202, 0.982)</td></tr>
<tr><td>Peramivir 600 mg</td><td>92.8 (57.4, 116.1)</td><td>0.706 (0.341, 1.460)</td></tr>
<tr><td>Oseltamivir</td><td>92.7 (70.2, 138.5)</td><td></td></tr>
</table>
Adverse events:
Serious adverse events occurred in 4 patients receiving 300 mg peramivir (myalgia, bronchitis, influenza with acute exacerbation, and pneumonia) and two patients receiving oseltamivir (pneumonia and vomiting). Of these, only vomiting in the oseltamivir group was considered to be an adverse drug reaction.</td>
<td>Author's conclusion: Both peramivir groups were noninferior to the oseltamivir group and the incidence of adverse drug reactions was significant lower in the 300 mg peramivir group.

Comments:
Incidence of severe adverse reactions in either peramivir group was not different compared to the oseltamivir group.</td>
</tr>
</table>

Warnings, Precautions, and Adverse Effects[1]

The following warnings and precautions are included in the prescribing information:

- Serious skin/hypersensitivity reactions – Rare cases of serious skin reactions, including erythema multiforme, have been reported in clinical studies and post-marketing experience with peramivir. Stevens-Johnson syndrome has also been reported in post-marketing experience.
- Neuropsychiatric events – Patients with influenza may be an increased risk of hallucinations, delirium, and abnormal behavior early in their illness and should be monitored for signs of abnormal behavior.
- Risk of bacterial infections – Serious bacterial infections may coexist with or occur as complications during the course of influenza. Prescribers should be alert to the potential for secondary bacterial infections and treat with antibiotics as appropriate.

The most commonly observed adverse reaction to peramivir is diarrhea, occurring in 8% of subjects in clinical trials.

Peramivir is pregnancy category C as there are no adequate and well-controlled trials of peramivir in pregnant women. It has been shown to cross the placenta in animal studies.

Interactions[1]

Peramivir does not inhibit or induce the cytochrome P450 enzyme system and has a low potential for CYP-mediated drug interactions. There is no evidence of drug interactions with oral rimantadine, oseltamivir, or oral contraceptives containing ethinyl estradiol or levonorgestrel.

Inactivated influenza vaccine may be administered at any time relative to administration of peramivir. Live attenuated influenza vaccine should be avoided within 2 weeks before or 48 hours after administration of peramivir.

Dosage and Administration[1]
The recommended dose in adult patients is a single 600 mg dose administered via intravenous infusion for 15-30 minutes. Dose should be reduced for patients with a baseline creatinine clearance less than 50 mL/min. For patients on hemodialysis, the dose should be adjusted based on renal function and administered after dialysis.

	Creatinine Clearance		
	≥ 50 mL/min	30-49 mL/min	10-29 mL/min
Recommended dose	600 mg single dose	200 mg single dose	100 mg single dose

Monitoring Parameters
None

How Supplied/Cost

	Inpatient/Outpatient Cost ($)
3 x 20 mL vials (10 mg/mL)	950.00

Prepared by: Kiri M. Rolek, PharmD, BCPS
Reviewed by: Trevor Van Schooneveld, MD, FACP
Updated by: Scott Bergman, PharmD, FIDSA, BCPS-AQ ID
Last reviewed: March 2017