

Class Update with New Drug Evaluation: Influenza Antiviral Agents

Date of Review: September 2015
Generic Name: peramivir injection

Date of Last Review: January 2012
Brand Name (Manufacturer): Rapivab™ (BioCryst Pharmaceuticals)
Dossier Received: no

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:

Rapivab™ (peramivir) is a neuraminidase inhibitor approved by the United States (U.S.) Food and Drug Administration (FDA) to treat uncomplicated influenza in adults. This class has not been reviewed since 2012 and both updated systematic reviews and guidelines are available.

Research Questions:

1. What is the comparative efficacy/effectiveness between antiviral agents to treat and prevent influenza?
2. What are the comparative harms between antiviral agents?
3. Are there any populations in which a specific antiviral agent for influenza is more effective or associated with greater harms than other agents?

Conclusions:

- There is insufficient comparative evidence between neuraminidase inhibitors to assess relative safety and efficacy between these drugs.
- There is moderate quality evidence that influenza symptoms are alleviated sooner with neuraminidase inhibitors (oral oseltamivir, inhaled zanamivir, and intravenous peramivir) compared to placebo in previously healthy adults if the drug is started within 48 hours of onset of symptoms.¹⁻⁵ Time to alleviation of symptoms were reduced by 14 to 21 hours (a 10% reduction in time to alleviation) depending on the drug.¹⁻⁵ However, the clinical significance of such a modest effect is not well defined.
- In previously healthy children, there is moderate quality evidence that oseltamivir can reduce the time to alleviation of influenza symptoms by about 1 day relative to placebo; however, oseltamivir does not appear to have any effect in children with asthma.^{2,3} There is moderate quality evidence that treatment with zanamivir is ineffective in children.^{1,3} There is insufficient evidence for peramivir in this population.⁵
- There is low quality evidence that treatment with oseltamivir and zanamivir do not reduce complications from influenza in children or adults.¹⁻³ There is insufficient evidence to determine if peramivir can reduce complications from influenza.
- There is low quality evidence that treatment with oseltamivir may not reduce risk for hospitalization.^{2,3} There is insufficient evidence to determine if treatment with zanamivir or peramivir can decrease rates of hospitalizations.^{1,3,5}

- There is moderate quality evidence that prophylactic use of oseltamivir or zanamivir in previously healthy adults and children can reduce risk of developing influenza symptoms, but by only 2% to 4% compared to placebo. These drugs do not reduce complications of influenza if it develops.¹⁻⁴
- There is moderate quality evidence that the prophylactic use of oseltamivir does not reduce rates of hospitalizations.^{2,3} There is insufficient evidence to determine if prophylactic use of zanamivir can reduce hospitalizations.^{1,3} Peramivir for prophylaxis of influenza is not recommended.
- Use of amantadine and rimantadine for prevention or treatment of influenza is not recommended. Safety concerns with amantadine, inactivity of both drugs against influenza B virus, and complete resistance to influenza A virus preclude use of these drugs for influenza.^{6,7}
- The use of oseltamivir increases the risk of adverse effects, such as nausea, vomiting, and psychiatric effects in adults and vomiting in children.¹⁻³ Zanamivir and peramivir were well tolerated in clinical trials.^{1,3,5}

Recommendations:

- Designate amantadine and rimantadine non-preferred because of lack of efficacy for influenza and insufficient evidence for use in other conditions (eg, dyskinesias, Parkinson's disease), and possible increased harms with amantadine.
- Move amantadine from the Influenza Antiviral drug class to the Parkinson's Drug Class. Two drugs used for dyskinesias, benzotropine and trihexyphenidyl, are already preferred within the Parkinson's Drugs Class.
- Designate peramivir non-preferred at this time due to limited evidence.
- No other changes to the PDL are recommended at this time.
- Approve modified prior authorization (PA) criteria (see **Appendix 4**). Restrict PA to neuraminidase inhibitors only.

Previous Conclusions:

- Vaccination is the primary method of preventing influenza infection.
- Amantadine or rimantadine are not recommended for the treatment or prophylaxis of influenza A due to high prevalence of resistance.
- Zanamivir uses a complex administration device for inhalation and should not be used in patients with pre-existing respiratory disorders.

Previous Recommendations:

- Recommend taking into account current public health recommendations for appropriate populations, duration and dosing schedules.

Background:

Influenza is a respiratory infection caused by influenza viruses A and B, the primary viruses that result in influenza epidemics in humans.⁸ Influenza can be described as uncomplicated or complicated influenza, and can also become a progressive disease.⁸ Persons with uncomplicated influenza may present with influenza-like symptoms (e.g., fever, cough, sore throat, muscle pain, malaise, etc.) but without shortness of breath (SOB). Though it can be a self-limited disease, there can be serious complications. Persons with complicated influenza may present with sinusitis, otitis media, or pneumonia (SOB, tachypnea, hypoxia and/or radiologic signs), which can also be associated with altered mental status, severe dehydration, secondary complications (e.g., multiorgan failure, septic shock), or exacerbation of an underlying chronic disease.⁸

The current report of influenza activity in the U.S. can be found online at CDC Weekly FluView.⁹ During the 2014-15 influenza season, 83.5% of circulating influenza viruses were influenza A (nearly all subtyped were H3N2) and 16.5% were influenza B.¹⁰ Hospitalizations for influenza were double the incidence seen

in the 2013-14 season with 65.5 hospitalizations per 100,000 persons.¹⁰ Deaths from pneumonia or influenza were at or above epidemic level for 8 consecutive weeks.¹⁰

The annual influenza vaccine is the primary method to prevent influenza.¹¹ The vaccination is recommended for all persons 6 months of age and older who do not have contraindications.¹¹ No vaccine is preferred over any other in adults for whom multiple versions are appropriate, including trivalent or quadrivalent inactivated influenza vaccines, live attenuated influenza vaccines, or recombinant influenza vaccines.¹¹ Five influenza antiviral medications are also available in the U.S. However, only 3 are recommended for use: oral oseltamivir (Tamiflu®) and inhaled zanamivir (Relenza®) are recommended for acute treatment of influenza or prevention of influenza in susceptible individuals (eg, severe immune deficiency); injectable peramivir (Rapivab™), approved in December 2014, is recommended for the treatment of acute uncomplicated influenza in adults.^{7,12} Each of these drugs are known as neuraminidase inhibitors and have activity against both influenza A and B.⁷ Amantadine and rimantadine are antiviral drugs known as adamantanes, which are not active against influenza B, but are also not recommended for treatment or prevention of currently circulating influenza A viruses.⁷ Since the 2005-06 season, resistance to amantadine and rimantadine have been widespread.⁸ In the 2014-15 season, circulating viruses remained highly resistant (>99%) to amantadine and rimantadine.¹⁰

Oseltamivir, zanamivir and peramivir are approved by the U.S. Food and Drug Administration treatment of acute, uncomplicated influenza in patients who have had symptoms for up to 48 hours.¹³⁻¹⁵ Treatment effects in controlled clinical trials showed improvement in time to alleviation of a constellation of symptoms rated as “none” or “mild” including: nasal congestion, sore throat, headache, aches, or chills.⁵ Oseltamivir received FDA approval for patients as young as 14 days, while zanamivir is limited to patients aged 7 years and older and peramivir is limited to adult use only.^{13,14} Oseltamivir and zanamivir are also FDA-approved for prophylaxis of influenza.^{13,14} Oseltamivir is approved in patients 1 year and older and zanamivir is approved in patients 5 years and older.^{13,14} Neuraminidase inhibitors may reduce symptom duration by about 1 day in adults and by 0.5-3 days in children.⁸ Oseltamivir is the most studied drug and does not appear to reduce likelihood of hospitalization or pneumonia in adults and adolescents with influenza-like illness; however, oseltamivir may reduce complications and hospitalization in children with influenza and chronic medical conditions.⁸ At the time these drugs were last reviewed in January 2012, there was no evidence these drugs reduced mortality.

Amantadine has been used as an antiparkinsonian agent in the past but there is insufficient evidence of efficacy for its use.⁸ Besides high rates of resistance, use of amantadine and rimantadine are limited by high rates of adverse events, particularly central nervous system adverse events.⁸

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Zanamivir

A Cochrane systematic review with meta-analysis of zanamivir for influenza in adults and children was conducted.^{1,3} Eligible studies were published or unpublished and limited to randomized, placebo-controlled trials testing the effects of zanamivir for prophylaxis, post-exposure prophylaxis, and treatment of influenza in previously healthy adults and children.^{1,3} Trial registries and several electronic databases were searched, in addition to regulatory archives and correspondences with the manufacturer.^{1,3} The effects of zanamivir on time to first alleviation of symptoms, influenza outcomes, complications, hospitalizations and adverse events in the intention-to-treat (ITT) population were analyzed.^{1,3} Twenty-eight studies were identified that met explicit inclusion criteria: 6 compared zanamivir with usual care in the prevention of influenza A and B among populations exposed to a local epidemic, 2 studies for the prevention of transmission of influenza among households, and 20 trials for the treatment of influenza A and B.^{1,3} All trials identified were sponsored by the manufacturer.^{1,3} Quality of the studies varied and posed large threats that introduce biases: only 1 study showed adequate randomization technique; adequate blinding of participants and personnel was reported in only 2 studies, and 24 studies showed adequate blinding of outcome assessors.^{1,3}

For treatment of influenza, zanamivir reduced time to first alleviation of symptoms in adults by 0.60 days (95% Confidence Interval [CI], 0.39 to 0.81 days; $p < 0.001$; $I^2 = 9\%$), which translated to an average 14.4-hour time reduction, or a 10% reduction in the mean duration of symptoms from 6.6 days to 6.0 days.^{1,3} However, the treatment effect of zanamivir in children was not significant (mean difference -1.08 days; 95% CI, -2.32 to 0.15 days).^{1,3} In subgroup analysis, there was no significant difference in treatment effects by infection status for time to first alleviation of symptoms in adults.^{1,3} The treatment effect was an improvement by 0.67 days in patients with confirmed influenza (95% CI, 0.35 to 0.99 days) compared to 0.52 days (0.18 to 0.86 days) in patients without confirmed influenza.^{1,3} Zanamivir treatment reduced the risk of bronchitis in adults (Relative Risk [RR]=0.75; 95% CI, 0.61 to 0.91; $I^2 = 3\%$; NNT=56), but there were no significant reduction found for serious complications of influenza, nor in incidence of otitis media (RR=0.81; 95% CI, 0.54 to 1.20; $I^2 = 0\%$) and sinusitis (RR=1.12; 95% CI, 0.84 to 1.48; $I^2 = 30\%$).^{1,3} No data were reported on the effect of zanamivir treatment on rates of hospitalizations.^{1,3} No studies specifically defined pneumonia, but self-reported, investigator-mediated verified and unverified pneumonia was not reduced with zanamivir (RR=0.90; 95% CI, 0.58 to 1.40; $I^2 = 0\%$).^{1,3}

For prevention of influenza, zanamivir reduced the risk of symptomatic influenza by 2% versus placebo (RR=0.39; 95% CI, 0.22 to 0.70; $I^2 = 45\%$; Number Needed-to-Treat [NNT]=51), as well as in post-exposure prophylaxis of households by 14.84% (RR=0.33; 95% CI, 0.18 to 0.58; $I^2 = 40\%$; NNT=7).^{1,3} No data were reported on the effect of zanamivir prophylaxis on prevention of hospitalizations.^{1,3} Zanamivir prophylaxis had no effect on reduction of complications from influenza in adults or children.^{1,3}

Studies reported zanamivir was well tolerated with no evidence of increased risk of adverse events.^{1,3}

Oseltamivir

A systematic review with meta-analysis^{2,3} of oseltamivir for influenza in adults and children was also conducted by the same Cochrane Collaboration group that conducted the review of zanamivir^{1,3}. The same methodology applied to the previous systematic review was also applied to this review.¹⁻³ Studies of previously healthy adults and children and patients with a chronic illnesses (e.g., asthma, diabetes, etc.) were included; however, patients with immunosuppression were excluded from the analysis.^{2,3} About 48% (11/23) of studies adequately reported random sequence generation, and 65% showed adequate allocation concealment.^{2,3} Forty-eight percent showed adequate blinding of outcome assessors.^{2,3} There was high risk of bias for included outcomes as a result of missing data, selective reporting, potentially active placebo, lack of outcome definitions, suboptimal measurement, and incomplete reporting in the study reports.^{2,3}

There were inadequate measures in place to protect 11 studies from performance bias due to non-identical placebo products, which may have included active substances. In addition, attrition bias was high across the studies.^{2,3}

In treatment of adults, oseltamivir reduced the time to first alleviation of symptoms by 16.7 hours (95% CI, 8.4 to 25.1 hours; $p < 0.001$).^{2,3} This difference represents a 10% reduction in time to first alleviation of symptoms from 7 days to 6.3 days in the oseltamivir group versus the placebo group.^{2,3} In previously healthy children, oseltamivir reduced the time to first alleviation of symptoms by 29 hours (95% CI, 12 to 27 hours; $p = 0.001$), but there was no significant effect for children with asthma ($p = 0.53$).^{2,3} Because of strong selection bias in treatment trials, an analysis was not performed by influenza-infected status.^{2,3} In treatment of adults, there was a non-significant difference of 0.15% in rate of hospitalization between oseltamivir and placebo groups (RR=0.92; 95% CI, 0.57 to 1.50; $I^2 = 0\%$; $p = 0.84$).^{2,3} Oseltamivir treatment also did not affect hospitalizations in children.^{2,3} Oseltamivir had no significant treatment effect in adults or adults or children for sinusitis, bronchitis, otitis media, or any serious complications.^{2,3} Oseltamivir reduced unverified pneumonia by 1% versus placebo when used as treatment in adults (95% CI, 0.22 to 1.49%; NNT=100).^{2,3} There was no significant difference in studies that used more detailed definitions of pneumonia (e.g., radiologically confirmed pneumonia).^{2,3}

In prophylaxis trials, oseltamivir reduced symptomatic influenza in subjects by 3.05% versus placebo (95% CI, 1.83 to 3.88; NNT=33) and in households by 13.6% (95% CI, 9.52 to 15.47%; NNT=7).^{2,3} In these trials, oseltamivir did not reduce incidence of pneumonia in children or adults versus placebo.^{2,3} In addition, prophylaxis with oseltamivir did not reduce rates of hospitalizations in adults or children.^{2,3}

Treatment of oseltamivir was associated with increased risk of nausea in adults (RR=1.57; 95% CI, 1.14 to 2.51) and children (RR=1.70; 95% CI, 1.23 to 2.35).^{2,3} Other adverse effects that occurred significantly more with oseltamivir use in adults were headache and vomiting.^{2,3} In addition, oseltamivir appeared to be associated with increased risk of 1.06% for psychiatric adverse events (including depression, confusion, hallucinations, and psychosis) versus placebo in prophylaxis trials (RR=1.80; 95% CI, 1.05 to 2.08; Number Needed to Harm =94). This observation was not found at treatment doses.^{2,3}

Neuraminidase Inhibitors Oseltamivir and Zanamivir

A systematic review of high-quality reviews of neuraminidase inhibitors (oseltamivir, zanamivir) using the Cochrane Database of Systematic Reviews, Health Technology Assessment Database, Database of Abstracts of Reviews of Effects, and Medline (January 2006 to July 2012) was also conducted.⁴ Nine systematic reviews were identified and were based on randomized controlled trials restricted to ITT results and assessed review (AMSTAR) and study quality (GRADE).⁴ In healthy adults given oseltamivir as prophylaxis, risk of developing influenza symptoms by reduced by an absolute risk reduction (ARR) of 3.6% compared to placebo (95% CI, 2.0 to 4.3%) (GRADE moderate).⁴ Prophylaxis with zanamivir reduced risk of developing influenza symptoms by an ARR of 4.4% (95% CI, 2.3 to 5.1%) versus placebo (GRADE moderate).⁴ Similar efficacy was also observed for post-exposure prophylaxis in adults who received oseltamivir.⁴ In children, only post-exposure prophylaxis studies were performed, which found an ARR of 12.1% (95% CI, 3.0 to 16.1%) with oseltamivir.⁴ In at-risk adults and adolescents, prophylaxis with zanamivir reduced risk of influenza (ARR 4.0%; 95% CI, 1.6 to 4.4%) (GRADE moderate); however, no effect in elderly patients was observed.⁴ Similar to the Cochrane analyses previously noted,¹⁻³ treatment with oseltamivir or zanamivir in adults and children alleviated symptoms of influenza less than 1 day sooner than with placebo (GRADE moderate).⁴ No evidence was available on the treatment benefits of neuraminidase inhibitors in elderly and at-risk groups and their effects on hospitalization and mortality.⁴ In oseltamivir trials, nausea, vomiting and diarrhea were significant adverse effects.⁴ Zanamivir was well tolerated.⁴

Amantadine and Rimantidine

A Cochrane review did not find sufficient evidence for the use of amantadine and rimantadine for the prevention or treatment of influenza A in children and the elderly.⁶ The lack of knowledge about the safety of amantadine and the limited benefit of rimantadine were of particular concern to the reviewers.⁶

New Guidelines:

The CDC antiviral recommendations were last published in January 2015.^{7,12} The CDC recognizes clinical trials and observational data that show early antiviral treatment can shorten the duration of fever and symptoms, and may reduce the risk of complications from influenza. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hours of influenza illness onset.⁷ Oral oseltamivir (Tamilfu[®]), inhaled zanamivir (Relenza[®]) and intravenous peramivir (Rapivab[™]) are the antiviral medications recommended by the CDC for treatment against influenza A and B for the 2014-15 season. Amantadine and rimantadine are not recommended for treatment or prevention of influenza due to high levels of resistance (>99%).⁷ **Table 1** lists the antiviral drugs recommended by the CDC, which may not reflect official labeling of the drugs.

Table 1. Centers for Disease Control and Prevention (CDC) Recommendations for Antiviral Use in Influenza (2014-2015 Season).⁷

Antiviral Agent	Use	Recommended	NOT Recommended	Dose
Oseltamivir #	Treatment	Any age	N/A	75 mg BID** x5 days
	Chemo-prophylaxis	Age ≥3 months	N/A	75 mg once daily** x7 days
Zanamivir *	Treatment	Age ≥7 years	Patients with underlying respiratory disease (e.g., asthma, COPD)	10 mg BID x5 days
	Chemo-prophylaxis	Age ≥5 years		10 mg once daily x7 days
Peramivir ^	Treatment	Age ≥18 years	N/A	One dose
	Chemo-prophylaxis	N/A	N/A	N/A

Abbreviations: COPD = chronic obstructive pulmonary disease; N/A = not applicable.

Oseltamivir is the preferred treatment of pregnant women.

* Relenza is contraindicated in patients with history of allergy to milk protein.

^ Peramivir efficacy is based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled.

**See current prescribing information for dosing in patients ≤40 kg or in patients with renal impairment.

Briefly, any of the following patients with suspected or confirmed influenza should be treated as early as possible, without laboratory confirmation of influenza, after illness onset with a neuraminidase inhibitor⁷:

1. All hospitalized patients
2. Severe, complicated or progressive illness (e.g., prolonged progressive symptoms or pneumonia complications)
3. High risk for influenza complications
 - Children <2 years of age
 - Adults ≥65 years of age
 - Chronic pulmonary, cardiovascular, renal, hepatic, hematologic, and neurologic/neurodevelopment conditions
 - Immunosuppression
 - Pregnancy or immediate post-partum
 - Persons ≤18 years on long-term aspirin
 - American Indians/Alaskan Natives

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- Morbid obesity (body mass index ≥ 40)
 - Residents of nursing homes and other chronic care facilities

A history of influenza vaccination does not rule out the possibility of influenza virus infection in an ill patient with clinical signs and symptoms of influenza.⁷ Antiviral treatment can also be considered in previously healthy, symptomatic outpatients not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.⁷

The CDC does not recommend widespread or routine use of antiviral medications for chemoprophylaxis due to risk of emergence of antiviral resistant viruses.⁷ Antiviral medications for chemoprophylaxis are 70-90% effective in preventing influenza and may be useful adjuncts to the vaccine.⁷ The CDC suggests patients with severe immune deficiencies or at high risk for complications of influenza who cannot receive the influenza vaccine, or during the first 2 weeks following vaccination, may be appropriate for chemoprophylaxis with antiviral agents.⁷

New Safety Alerts:

None identified.

New Formulations or Indications:

No new formulations or indications were identified. However, a new neuraminidase inhibitor was identified. Rapivab™ (peramivir) for injection was approved in December 2014 for treatment of influenza.¹⁵

Randomized Controlled Trials:

Two hundred fifty-five potentially relevant clinical trials or systematic reviews were evaluated from the literature search (see **Appendix 2**). After further review, none of the trials were randomized, head-to-head trials that compared one antiviral drug to another, and were therefore excluded.

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Peramivir is the third drug in the neuraminidase class and is recommended for use in adult patients with acute uncomplicated illness based primarily on data from the 4 placebo-controlled Phase 2 or 3 trials in adults with acute uncomplicated influenza (studies 621, 211, 212 and 311).⁵ The analysis of safety was based chiefly on data from Study 621,¹⁶ with supplemental data from the other studies.⁵ Study 621 was a 3-arm randomized, multi-centered, blinded trial conducted in Japan that evaluated a single intravenous (IV) dose of peramivir 300 mg, peramivir 600 mg, or placebo administered over 30 minutes in previously healthy patients 20 to 64 years of age (n=297) with acute uncomplicated influenza that had developed within the previous 48 hours.⁵ Patients were eligible if they had fever greater than 38 °C, a positive rapid antigen test for influenza virus, with at least 2 symptoms (cough, nasal symptoms, sore throat, myalgia, chills/sweats, malaise, fatigue, or headache) of moderate severity.⁵ All enrolled patients were allowed to take medication for fever during the study.⁵ The primary endpoint was time to alleviation of symptoms (TTAS), 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, fever, myalgia and fatigue) were either absent or present at a level no greater than “mild” for at least 21.5 hours.⁵ The group assigned to 600 mg of peramivir demonstrated significant improvement.⁵ In the group assigned to peramivir 600 mg

(n=98), alleviation of symptoms occurred a median of 21 hours sooner than those receiving placebo.⁵ The median time to recover to normal temperature in the 600 mg group was approximately 12 hours sooner compared to placebo.⁵ In the 600 mg peramivir group, 55% were male; 34% were smokers; and 99% were infected with influenza A virus (1% were infected with influenza B virus).⁵ Pooled analysis of all the placebo-controlled trials in acute uncomplicated influenza are described in **Table 2**, which shows the duration of influenza symptoms was shortest in patients treated with peramivir 300 mg and 600 mg.⁵

Table 2. Median Time to Alleviation of Symptoms by Treatment Group in Subjects with Confirmed Influenza.⁵

	Paramivir 150 mg	Paramivir 300 mg	Paramivir 600 mg	Paramivir Overall	Placebo
N (number censored)	100 (17)	255 (33)	256 (22)	611 (72)	399 (41)
Median TTAS in hours (95% CI)	120.7 (96.1 to 148.1)	81.7 (68.1 to 102.0)	79.4 (68.1 to 91.6)	87.6 (78.3 to 96.1)	107.3 (95.7 to 115.2)

Abbreviations: CI = confidence interval; N = number of patients; TTAS = time to alleviation of symptoms.

Clinical Safety:

Across controlled clinical trials in adults with uncomplicated influenza, a total of 1,399 patients were exposed to at least 1 dose of peramivir.⁵ Among the 664 patients who received peramivir 600 mg, the most commonly observed adverse reaction was diarrhea (8% vs. 7% with placebo).⁵ No serious adverse events were reported in the trials.⁵ One death due to meningitis occurred in the clinical trials and was deemed unlikely to be related to the study drug.⁵ Clinically significant laboratory abnormalities that occurred more frequently with peramivir 600 mg than placebo are listed in **Table 3**.⁵

Table 3. Laboratory Abnormalities Occurring in ≥2% of Patients Treated with Peramivir 600 mg.⁵

Laboratory Parameter	Peramivir 600 mg	Placebo
Alanine Aminotransferase (>2.5 x ULN)	3%	2%
Serum Glucose (>160 mg/dL)	5%	3%
Creatine Phosphokinase (≥ 6.0 x ULN)	4%	2%
Neutrophils (<1.000 x10 ⁹ /L)	8%	6%

Abbreviations: dL = deciliters; L = liters; ULN = upper limit of normal range.

References:

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11. Key Facts About Seasonal Flu Vaccine. Centers for Disease Control and Prevention. Available at <http://www.cdc.gov/flu/protect/keyfacts.htm>. Accessed July 27, 2015.
12. CDC Health Update Regarding Treatment of Patients with Influenza with Antiviral Medications - January 2015. Health Alert Network, Centers for Disease Control and Prevention. Available at <http://emergency.cdc.gov/han/han00375.asp>. Accessed July 24, 2015.
13. TAMIFLU (oseltamivir phosphate) [prescribing information]. South San Francisco, CA: Genentech, Inc., November 2014.

14. RELENZA (zanamivir) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline, October 2013.
15. RAPIVAB (peramivir injection) [prescribing information]. Durham, NC: BioCryst Pharmaceuticals, Inc., December 2014.
16. Kohno S, Kida H, Mizuguchi M, Shimada J. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrobial Agents and Chemotherapy*. 2010;54:4568-4574. doi:10.1128/AAC.00474-10.

Appendix 1: Current Status on Preferred Drug List

Generic Name	Brand Name	Form	PDL Status	Current Drug Use Criteria
AMANTADINE HCL	AMANTADINE	CAPSULE	Y	
AMANTADINE HCL	AMANTADINE	SOLUTION	Y	
AMANTADINE HCL	AMANTADINE	TABLET	Y	
OSELTAMIVIR PHOSPHATE	TAMIFLU	CAPSULE	Y	Quantity Limit
OSELTAMIVIR PHOSPHATE	TAMIFLU	SUSP RECON	Y	Quantity Limit
RIMANTADINE HCL	RIMANTADINE HCL	TABLET	Y	
RIMANTADINE HCL	FLUMADINE	TABLET	Y	
ZANAMIVIR	RELENZA	BLST W/DEV	N	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 4 2015

- 1 exp Amantadine/ 2973
- 2 exp Rimantadine/ 259
- 3 exp Oseltamivir/ 2154
- 4 exp Zanamivir/ 816
- 5 peramivir.mp. 210
- 6 1 or 2 or 3 or 4 or 5 5501
- 7 limit 6 to (yr="2012 -Current" and (clinical trial, all or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 255

Appendix 3: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RAPIVAB safely and effectively. See full prescribing information for RAPIVAB.

RAPIVAB™ (peramivir injection), for intravenous use
Initial U.S. Approval: [2014]

INDICATIONS AND USAGE

RAPIVAB is an influenza virus neuraminidase inhibitor indicated for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than two days. (1)

Limitations of Use:

- Efficacy based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled
- Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use. (1)
- Efficacy could not be established in patients with serious influenza requiring hospitalization. (1)

DOSAGE AND ADMINISTRATION

- Administer as a single dose within 2 days of onset of influenza symptoms (2.1)
- Recommended dose is 600 mg, administered by intravenous infusion for a minimum of 15 minutes (2.1)
- Renal Impairment: Recommended dose for patients with creatinine clearance 30-49 mL/min is 200 mg and the recommended dose for patients with creatinine clearance 10-29 mL/min is 100 mg (2.2)
- Hemodialysis: Administer after dialysis. (2.2)
- RAPIVAB must be diluted prior to administration (2.3)
- See the Full Prescribing Information for drug compatibility information (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 200 mg in 20 mL (10 mg/mL) in a single-use vial (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Serious skin/hypersensitivity reactions such as Stevens-Johnson syndrome and erythema multiforme have occurred with RAPIVAB. (5.1)
- Neuropsychiatric events: Patients with influenza may be at an increased risk of hallucinations, delirium and abnormal behavior early in their illness. Monitor for signs of abnormal behavior. (5.2)

ADVERSE REACTIONS

Most common adverse reaction (incidence >2%) is diarrhea (6)

To report SUSPECTED ADVERSE REACTIONS, contact BioCryst Pharmaceuticals, Inc. at 1-844-273-2327 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Live attenuated influenza vaccine (LAIV), intranasal: Avoid use of LAIV within 2 weeks before or 48 hours after administration of RAPIVAB, unless medically indicated (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use if benefit outweighs risk.(8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2014

Appendix 4: Proposed Prior Authorization Criteria

Author: Andrew Gibler, PharmD

Date: January 2016

Antivirals – Influenza

Goal:

- Restrict use of extended prophylactic influenza antiviral therapy to high risk populations recognized by the Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA).

Length of Authorization:

- Up to 30 days

Requires PA:

- Non-preferred neuraminidase inhibitors
- Oseltamivir therapy for greater than 5 days

Covered Alternatives:

Preferred alternatives listed at <http://www.orpdl.org/drugs/>

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an OHP-funded diagnosis?	Yes: Go to #3	No: Pass to RPH. Deny; not funded by the OHP
3. Is the antiviral agent to be used to treat a current influenza infection (ICD10 J1100, J129, J111-112, J1181, J1189; J09X1-J09X9)?	Yes: Go to #4	No: Go to #5
4. Will the prescriber consider a change to a preferred product? <u>Message:</u> <ul style="list-style-type: none"> • Preferred products do not require a PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee. 	Yes: Inform prescriber of covered alternatives in class and approve for length of therapy or 5 days, whichever is less.	No: Approve for length of therapy or 5 days, whichever is less.
5. Is the antiviral prescribed oseltamivir or zanamivir?	Yes: Go to #6	No: Pass to RPh. Deny for medical appropriateness.

Approval Criteria

6. Does the patient have any of the following CDC¹ and IDSA² criteria that may place them at increased risk for complications requiring chemoprophylaxis?

- Persons at high risk of influenza complications during the first 2 weeks following vaccination after exposure to an infectious person (6 weeks in children not previously vaccinated and require 2 doses of vaccine)
- Persons with severe immune deficiencies or others who might not respond to influenza vaccination, such as persons receiving immunosuppressive medications, after exposure to an infectious person
- Persons at high risk for complications from influenza who cannot receive influenza vaccine after exposure to an infectious person
- Residents of institutions, such as long-term care facilities, during influenza outbreaks in the institution.
- Pregnancy and women up to 2 weeks postpartum who have been in close contact with someone suspected or confirmed of having influenza

Yes: Approve for duration of prophylaxis or 30 days, whichever is less.

Current recommended duration of prophylaxis: 7 days (after last known exposure; minimum 2 weeks to control outbreaks in institutional settings and hospitals, and continue up to 1 week after last known exposure.

No: Pass to RPh. Deny for medical appropriateness.

References:

1. Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. <http://www.cdc.gov/flu/pdf/professionals/antivirals/antiviral-summary-clinician.pdf>. Accessed June 2, 2015.
2. Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children – diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2009; 48:1003-32.

P&T/DUR Review: 1/16 (AG); 1/12; 9/10
Implementation: TBD; 1/11