Class Update with New Drug Evaluation: Influenza Antiviral Agents

Date of Review: September 2015
Generic Name: peramivir

Current Status of PDL Class:
See Appendix 1.

Brand Name (Manufacturer): Rapivab™ (BioCryst Pharmaceuticals)
Dossier Received: no

Date of Last Review: January 2012

Purpose for Class Update:
Rapivab (peramivir) was approved by the United States (U.S.) Food and Drug Administration (FDA) to treat uncomplicated influenza in adults.

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 moderate quality evidence that neuraminidase inhibitors (oral oseltamivir, inhaled zanamivir, and intravenous peramivir) have small, non-specific reduction in time to alleviation of influenza symptoms in previously healthy adults by about 1 day if the drug is started within 48 hour of symptom onset. Efficacy of these agents diminish as treatment is delayed.6
- There is moderate quality evidence that oseltamivir can similarly reduce the time to alleviation of influenza symptoms in children as in adults, but oseltamivir has no effect on children with asthma.2,3 There is moderate quality evidence that zanamivir does not affect time to alleviation of influenza symptoms in children.1,3 There is insufficient evidence for peramivir in this population.5
- There is low-quality evidence from randomized controlled trials (RCTs) that treatment with oseltamivir and zanamivir do not reduce complications from influenza in any population, including confirmed pneumonia, sinusitis and otitis media.1-3 There is insufficient evidence to determine if peramivir reduces complications from influenza.
- There is low-quality evidence from RCTs that treatment with oseltamivir does not reduce hospitalizations.2,3 There is insufficient evidence to determine if treatment with zanamivir or peramivir affects rates of hospitalizations.1,3,5
- Observational data, which are limited by high risk of bias and lack of control groups, but captured many more patients than those enrolled in RCTs, suggest oseltamivir may reduce mortality and hospitalizations in high risk (i.e., hospitalized) patients.6 Treatment with oseltamivir reduced hospitalizations by 0.34%
(odd ratio [OR]=0.75; 95% Confidence Interval [CI], 0.66 to 0.89) and reduced mortality by 17.3% (OR 0.23; 95% CI, 0.13 to 0.43) compared to no treatment, which may have resulted in 173 fewer deaths per 1000 patients treated. The quality of evidence is insufficient to low, but these data underscore the need for high-quality evidence to inform appropriate use of these drugs in high risk populations.

- There is moderate quality evidence that the prophylactic use of either oseltamivir or zanamivir reduces the risk of developing symptomatic influenza by about 2-4% but does not reduce complications of influenza if it develops.  
- There is moderate quality evidence that the prophylactic use of oseltamivir does not reduce hospitalizations. There is insufficient evidence to determine if prophylactic use of zanamivir reduces hospitalizations. Peramivir for prophylaxis of influenza is not recommended.
- There is insufficient evidence to support the use of amantadine and rimantadine for the prevention or treatment of influenza A. Lack of knowledge about the safety of amantadine, inactivity against influenza B virus, and complete resistance to influenza A virus preclude use of these drugs for influenza.
- The use of oseltamivir increases the risk of adverse effects, such as nausea, vomiting, and psychiatric effects in adults and vomiting in children. Zanamivir and peramivir are well tolerated without serious harms identified.
- There is insufficient evidence to directly compare the efficacy and safety of neuraminidase inhibitors.

**Recommendations:**
- Designate amantadine and rimantadine non-preferred due to lack of efficacy for influenza and other conditions (e.g., Parkinson’s disease), and possible increased harms.
- Maintain oseltamivir suspension and tablets as preferred agents on the PDL because of ease of use.
- No specific recommendations for peramivir are necessary at this time.
- Approve modified Prior Authorization criteria in Appendix 4 and receive drug costs in the executive session.

**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. Influenza can be described as uncomplicated or complicated influenza, and can also become a progressive disease. 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.
The current report of influenza activity in the U.S. can be found online at CDC Weekly FluView.\textsuperscript{10} 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.\textsuperscript{11} Hospitalizations for influenza were double the incidence seen in the 2013-14 season with 65.5 hospitalizations per 100,000 persons.\textsuperscript{11} Deaths from pneumonia or influenza were at or above epidemic level for 8 consecutive weeks.\textsuperscript{11}

The annual influenza vaccine is the primary method to prevent influenza.\textsuperscript{12} The vaccination is recommended for all persons 6 months of age and older who do not have contraindications.\textsuperscript{12} 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.\textsuperscript{12} Five influenza antiviral medications are also available in the U.S. However, only 3 are recommended for use: oral oseltamivir (Tamiflu\textsuperscript{®}) and inhaled zanamivir (Relenza\textsuperscript{®}) are recommended for acute treatment of influenza or prevention of influenza in susceptible individuals, and injectable peramivir (Rapivab\textsuperscript{™}), approved in December 2014, is recommended for the treatment of acute uncomplicated influenza in adults.\textsuperscript{9,11} Each of these drugs are known as neuraminidase inhibitors and have activity against both influenza A and B.\textsuperscript{8} Amantadine and rimantadine are antiviral drugs known as adamantanes, which are not active against influenza B, but are also not recommended for treatment prevention of currently circulating influenza A viruses.\textsuperscript{8} Since the 2005-06 season, resistance to amantadine and rimantadine have been widespread.\textsuperscript{9} In the 2014-15 season, circulating viruses remained highly resistant (>99\%) to amantadine and rimantadine.\textsuperscript{11}

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.\textsuperscript{14-16} Treatment effects in controlled clinical trials showed about 1-day improvement in time to alleviation of a constellation of symptoms rated as “none” or “mild” including: nasal congestion, sore throat, headache, aches, or chills.\textsuperscript{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.\textsuperscript{14,15} Oseltamivir and zanamivir are also FDA-approved for prophylaxis of influenza.\textsuperscript{14,15} Oseltamivir is approved in patients 1 year and older and zanamivir is approved in patients 5 years and older.\textsuperscript{14,15} Neuraminidase inhibitors may reduce symptoms duration by about 1 day in adults and by 0.5-3 days in children.\textsuperscript{9} Oseltamivir is most studied and does to 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.\textsuperscript{9} 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.\textsuperscript{9} Besides high rates of resistance, use of amantadine and rimantadine are limited by high rates of adverse events, particularly central nervous system adverse events.\textsuperscript{9}

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.

Author: A. Gibler, Pharm.D. Date: September 2015
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. 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. Trial registries and several electronic databases were searched, in addition to regulatory archives and correspondences with the manufacturer. 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. 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. All trials identified were sponsored by the manufacturer. Variations in reporting quality of the studies were identified: only 1 study showed adequate randomization technique; adequateblinding of participants and personnel was reported in only 2 studies, and 24 studies showed adequate blinding of outcome assessors.

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; $\bar{I}^2=9\%$), 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. However, the treatment effect of zanamivir in children was not significant (mean difference -1.08 days; 95% CI, -2.32 to 0.15 days). In subgroup analysis, there was no significant difference in treatment effects by infection status for time to first alleviation of symptoms in adults. The treatment effect for patients was 0.67 days 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 influenza. Zanamivir treatment reduced the risk of bronchitis in adults (Relative Risk [RR]=0.75; 95% CI, 0.61 to 0.91; $\bar{I}^2=3\%$; 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; $\bar{I}^2=0\%$) and sinusitis (RR=1.12; 95% CI, 0.84 to 1.48; $\bar{I}^2=30\%$). No data were reported on the effect of zanamivir treatment on rates of hospitalizations. No studies defined pneumonia, but studies that used strict definitions of pneumonia did not find zanamivir treatment reduced incidence of pneumonia (RR=1.02; 95% CI, 0.35 to 3.02; $\bar{I}^2=39\%$). Studies that used self-reported investigator-mediated unverified pneumonia also did not find zanamivir reduced incidence of pneumonia (RR=0.90; 95% CI, 0.58 to 1.40; $\bar{I}^2=0\%$).

For prevention of influenza, zanamivir significantly reduced the risk of symptomatic influenza by 1.98% versus placebo (RR=0.39; 95% CI, 0.22 to 0.70; $\bar{I}^2=45\%$; 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; $\bar{I}^2=40\%$; NNT=7). No data were reported on the effect of zanamivir prophylaxis on prevention of hospitalizations. Zanamivir prophylaxis had no effect on reduction of complications from influenza in adults or children. However, prophylaxis with zanamivir reduced the risk of self-reported, unverified pneumonia in adults by 0.32% versus placebo (95% CI, 0.09 to 0.41%; NNT=331).

Studies reported zanamivir was well tolerated with no evidence of increased risk of adverse events.
Oseltamivir

A systematic review with meta-analysis of oseltamivir for influenza in adults and children was also conducted by the same Cochrane Collaboration group that conducted the review of zanamivir. The same methodology applied to the previous systematic review was also applied to this review. Studies of previously healthy adults and children and patients with a chronic illness (e.g., asthma, diabetes, etc.) were included; however, patients with immunosuppression were excluded from the analysis. About 48% (11/23) of studies adequately reported random sequence generation, and 65% showed adequate allocation concealment. Forty-eight percent showed adequate blinding of outcome assessors. 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. 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.

In the 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). This difference represents a reduction in time to first alleviation of symptoms by 7 days to 6.3 days in the oseltamivir group versus the placebo group. 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. Because of strong selection bias in treatment trials, an analysis was not performed by influenza-infected status. 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). Oseltamivir treatment also did not affect hospitalizations in children. Oseltamivir had no significant treatment effect in adults or children for sinusitis, bronchitis, otitis media, or any serious complications. No studies adequately defined pneumonia, but in treatment of adults, oseltamivir reduced investigator-mediated unverified pneumonia by 1.00% versus placebo (95% CI, 0.22 to 1.49%; NNT=100). There was no significant difference in studies that used more detailed definitions of pneumonia (e.g., radiologically confirmed pneumonia).

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). In these trials, oseltamivir did not reduce incidence of pneumonia in children or adults versus placebo. In addition, prophylaxis with oseltamivir did not reduce rates of hospitalizations in adults or children.

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). Other adverse effects that occurred significantly more with oseltamivir use in adults were headache and vomiting. 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.

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. Nine systematic reviews were identified and were based on randomized controlled trials restricted to ITT results and assessed review (AMSTAR) and study quality (GRADE). In healthy adults, prophylaxis against influenza with oseltamivir demonstrated 76% efficacy (95% CI, 42 to 90%) (GRADE moderate), with an absolute risk reduction (ARR) of 3.6% (95% CI, 2.0 to 4.3%). Prophylaxis with zanamivir demonstrated 68% efficacy (95% CI, 37 to 83%) (GRADE moderate), with an ARR of 4.4% (95% CI, 2.3 to 5.1%). Similar efficacy was also observed for post-exposure prophylaxis in adults who received oseltamivir. In children, only post-exposure prophylaxis studies were performed, which found and ARR of 12.1% (95% CI, 3.0 to 16.1%) with oseltamivir. 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 on elderly was observed. Similar to the Cochrane analyses previously noted, treatment with oseltamivir or zanamivir in adults and children alleviated symptoms of influenza less than 1 day sooner than with placebo (GRADE moderate). No evidence was available on the treatment benefits of neuraminidase inhibitors in elderly and at-risk groups and their effects on hospitalization and mortality. In oseltamivir trials, nausea, vomiting and diarrhea were significant adverse effects. Zanamivir was well tolerated.

Antivirals for Influenza (Oseltamivir, Zanamivir, Amantadine and Rimantidine)
A systematic review of only observational studies that evaluated neuraminidase inhibitors (oseltamivir, zanamivir) and adamantanes (amantadine, rimantidine) was conducted to inform World Health Organization (WHO) guidelines. The review was conducted because of lack of high-quality evidence for clinically relevant outcomes from randomized controlled trials (RCTs). Observational studies were evaluated to determine if they provide additional information to supplement evidence provided by the RCTs. The majority of studies (n=74) reported comparisons of oral oseltamivir with no antiviral treatment. Low-quality evidence suggests oseltamivir may reduce mortality in high-risk populations, such as hospitalized patients, compared with no antiviral treatment (7.1% vs. 24.4%, respectively; adjusted odd ratio [OR]=0.23; 95% CI, 0.13 to 0.43), which corresponded to 172 fewer deaths per 1000 patients treated. This effect became less pronounced, however, when pooling data from unadjusted studies (OR=0.51; 95% CI, 0.23 to 1.14). Low-quality evidence also suggests oseltamivir may reduce hospitalizations compared with no antiviral treatment (0.86% vs. 1.2%, respectively; OR=0.75; 95% CI, 0.66 to 0.89), which corresponded to 3 fewer hospitalizations per 1000 patients treated. Similar to previous systematic reviews, observational studies also showed treatment with oseltamivir reduces duration of influenza symptoms. The benefits of oseltamivir are more pronounced when initiated within 48 hours of symptom onset. When comparing zanamivir to no treatment, there was moderate-quality evidence that zanamivir reduced duration of symptoms relative to no treatment by 23 hours (95% CI, 17 to 28 hours) but there was no significant reduction in hospitalizations observed (OR 0.66; 95% CI, 0.37 to 1.18). In direct comparisons of oseltamivir and zanamivir, inconsistent evidence suggests that zanamivir may have slight advantage in reducing the duration of symptoms by 7 hours (95% CI, 2 to 12 hours). Low-quality evidence showed that the 2 treatments may not differ with respect to mortality, hospitalization, intensive care unit (ICU) admission, critical adverse events or viral shedding. The authors concluded high-quality evidence is needed to inform treatment guidelines because of the overall low-quality evidence for these drugs.

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

New Guidelines:
The CDC antiviral recommendations were last published in January 2015. 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. Oral oseltamivir (Tamiflu®), 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. Table 1 lists the antiviral drugs recommended by the CDC, which may not reflect official labeling of the drugs.

Author: A. Gibler, Pharm.D. Date: September 2015
### Table 1. Centers for Disease Control and Prevention (CDC) Recommendations for Antiviral Use in Influenza (2014-2015 Season).\(^8\)

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

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 inhibitor:\(^8\):

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/Alaska Natives
   - Morbidly obese (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.\(^8\)

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.\(^8\)

The CDC does not recommend widespread or routine use of antiviral medications for chemoprophylaxis due to risk of emergence of antiviral resistant viruses.\(^8\)

Antiviral medications for chemoprophylaxis are 70-90% effective in preventing influenza and may be useful adjuncts to the vaccine.\(^8\) 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.\(^8\)
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.16

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, with supplemental data from the other studies.5 Principal 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 patients 18 to 65 years of age (n=297) with acute uncomplicated influenza.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 within 48 hours of enrollment.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

Author: A. Gibler, Pharm.D.
Date: September 2015
Table 2. Median Time to Alleviation of Symptoms by Treatment Group in Subjects with Confirmed Influenza.\textsuperscript{5}

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

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.\textsuperscript{5} Among the 664 patients who received peramivir 600 mg, the most commonly observed adverse reaction was diarrhea (8% vs. 7% with placebo).\textsuperscript{5} No serious adverse events were reported in the trials.\textsuperscript{5} One death due to meningitis occurred in the clinical trials and was deemed unlikely to be related to the study drug.\textsuperscript{5} Clinically significant laboratory abnormalities that occurred more frequently with peramivir 600 mg than placebo are listed in Table 3.\textsuperscript{5}

Table 3. Laboratory Abnormalities Occurring in \(\geq 2\%\) of Patients Treated with Peramivir 600 mg.\textsuperscript{5}

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Peramivir 600 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine Aminotransferase ((&gt;2.5 \times \text{ULN}))</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Serum Glucose ((&gt;160 \text{mg/dL}))</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Creatine Phosphokinase ((\geq 6.0 \times \text{ULN}))</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Neutrophils ((&lt;1.000 \times 10^7/L))</td>
<td>8%</td>
<td>6%</td>
</tr>
</tbody>
</table>

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


15. RELENZA (zanamivir) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline, October 2013.

Appendix 1: Current Status on Preferred Drug List

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

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

Author: A. Gibler, Pharm.D.  Date: September 2015
### Antivirals - Influenza

**Goal(s):**
- To ensure evidence-based extended use of influenza antiviral drug use by authorizing utilization in specified patient population.

**Length of Authorization:**
- Date of Service

**Requires PA:**
- Non-preferred drugs
- Oseltamivir therapy for greater than 5 days

**Covered Alternatives:**
- Preferred alternatives listed at [http://www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

### Approval Criteria

<table>
<thead>
<tr>
<th>Step</th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>What diagnosis is being treated?</td>
<td>Record ICD9 code.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Is this an OHP-funded diagnosis?</td>
<td>Yes: Go to #3</td>
<td>No: Pass to RPH. Deny; not funded by the OHP</td>
</tr>
<tr>
<td>3.</td>
<td>Is the antiviral agent to be used to treat current influenza infection?</td>
<td>Yes: Go to #4</td>
<td>No: Go to #6</td>
</tr>
<tr>
<td>4.</td>
<td>Will the prescriber consider a change to a preferred product?</td>
<td>Yes: Inform provider of covered alternatives in class.</td>
<td>No: Go to #5</td>
</tr>
</tbody>
</table>

Message:
- Preferred products do not require a PA.
- Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.
## Approval Criteria

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Is the antiviral prescribed amantadine or rimantadine?</td>
<td>Yes: Pass to RPh. Deny for medical appropriateness</td>
<td>No: Approve for length of therapy or 5 days, whichever is less.</td>
</tr>
<tr>
<td>6. Is the antiviral prescribed oseltamivir or zanamivir?</td>
<td>Yes: Go to #7</td>
<td>No: Pass to RPh. Deny for medical appropriateness.</td>
</tr>
</tbody>
</table>
| 7. Does the patient have any of the following CDC and IDSA criteria* that may place them at increased risk for complications requiring chemoprophylaxis? | Yes: Approve for duration of prophylaxis.  
  Current recommended duration of prophylaxis:  
  Oseltamivir and zanamivir: 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. |

- 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