Drug Class Update: Influenza

Date of Review: December 2022
Date of Last Review: Jan 2019
Dates of Literature Search: 11/01/2018 - 10/07/2022

Current Status of PDL Class:
See Appendix 1.

Plain Language Summary:
- This review looks at new evidence for medicines that are used to treat or prevent seasonal flu (influenza).
- New evidence shows that:
  - People treated with peramivir or oseltamivir for seasonal flu had similar rates of poor outcomes and of pneumonia.
  - Children between 1 year and 12 years old taking oseltamivir for seasonal flu had slightly more side effects compared to baloxavir. Side effects of oseltamivir were usually mild.
  - People 12 years and older prescribed baloxavir or oseltamivir to treat seasonal flu had similar rates of side effects. These medicines also had the same impact on the time it takes for flu symptoms to disappear.
- The Food and Drug Administration (FDA) has updated the approved reasons to use certain medications for seasonal flu.
  - Peramivir can now be used to treat seasonal flu in people as young as 6 months.
  - Baloxavir can now be used to treat seasonal flu in people as young as 5 years.
  - Baloxavir can now be used to prevent seasonal flu in people as young as 5 years if they are in close contact with someone who has seasonal flu.
- The Infectious Diseases Society of America (IDSA) recommends medications called neuraminidase inhibitors (NAI) to treat and prevent seasonal flu, especially in people who are most likely to become very unwell from seasonal flu because of other health conditions. Oseltamivir is a common neuraminidase inhibitor.
- Under the current policy, providers must explain to the Oregon Health Authority why someone needs a non-preferred flu medicine or a preferred flu medicine for more than 5 days before Medicaid will pay for it. This process is called prior authorization (PA). We recommend changes to this policy to match new FDA indications and age ranges.

Purpose for Class Update:
The purpose of this class update is to review the literature for new comparative evidence since the last class update for influenza antivirals.

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Research Questions:
1) Is there new comparative evidence related to efficacy for the influenza antivirals for important outcomes (e.g., clinical cure, hospitalizations, mortality)?
2) Is there new comparative evidence for harms for the influenza antivirals?
3) Are there any subpopulations which would receive more benefit or suffer more harm from specific influenza antivirals?

Conclusions:
- There are 1 guideline, 1 systematic review, and 3 new comparative randomized controlled trials (RCTs) included in this review.
- Guidelines from the Infectious Diseases Society of America (IDSA) include recommendations for influenza treatment, post-exposure prophylaxis, and in rare cases pre-exposure prophylaxis.
  - Treatment for outpatients at higher risk of influenza complications are supported by high quality evidence, while treatment for those at lower risk, even if symptomatic and likely to come into contact with higher risk individuals, is supported by low-quality evidence.
  - Neuraminidase inhibitors (NAI) are recommended for influenza treatment. Combination NAI and routine use of doses higher than Food and Drug Administration (FDA) approval are not recommended (high quality evidence).
  - Short-term and longer term (duration of season) preexposure prophylaxis with oseltamivir or zanamivir should be considered in select groups of patients at high risk for morbidity and mortality (evidence level varies by patient group).
  - Postexposure prophylaxis starting within 48 hours of exposure and continuing 7 days can be considered in select patient populations at high risk for morbidity and mortality. (moderate-quality evidence)
- A high-quality systematic review comparing a single dose of intravenous (IV) peramivir 600 mg to oral oseltamivir 75 mg twice daily for 5 days found no statistical differences in rate of influenza complications (peramivir 2.5% vs. oseltamivir 4.1%; relative risk [RR]=0.70; 95% confidence interval [CI] 0.36 to 1.38; I²=0%) or pneumonia (peramivir 2.2% vs oseltamivir 2.7%; RR=0.74; 95% CI 0.37 to 1.51; I²=0%).
- A single randomized controlled trial (RCT) of weight-based, single dose baloxavir versus weight based, twice daily oseltamivir given for 5 days for influenza treatment in children aged 1 year to less than 12 years (N=176) which looked at safety as the primary outcome, found slightly higher rates of adverse events (AE) in oseltamivir (2.6% vs. 8.6%, statistics not performed). There were no deaths, serous AEs, or hospitalizations.
- A single RCT of baloxavir (single, weight-based 40 mg or 80 mg dose) versus oseltamivir 75 mg twice daily for 5 days for influenza treatment in patients 12 years and older (N=1163) found no statistical difference in time to symptom improvement (baloxavir 73.2 hours vs. oseltamivir 81.1 hours; median difference -7.7 hours; 95% CI -7.9 to 22.7) and similar AE rate (25% vs. 28%, respectively).
- A single open-label, randomized trial of IV peramivir 600 mg daily for two days (P600), IV peramivir 300 mg as a single dose (P300), or oseltamivir 75 mg twice daily for 5 days (O75) in patients 16 to 70 years with influenza and pre-existing chronic respiratory diseases (N=214) found no statistical difference in the cumulative rate of time versus symptoms (CATVS; an index area under the curve of the total score of cough, sore throat, and nasal congestion for 2 weeks) for the higher peramivir dose (P600 vs. O75, estimated difference -78.36; 95% CI -215.69 to 58.96), although the lower dose did reach statistical significance (P300 vs O75 estimated difference -145.07; 95% CI -284.57 to -5.56; p=0.0416). The AE rate was highest with high-dose peramivir (25.7%) compared to lower-dose peramivir (13.4%) or oseltamivir (13.9%). Neither of these peramivir dosing strategies are FDA approved.
- High quality direct comparisons between various antiviral agents remains limited.
- There is insufficient evidence to support combination therapy of NAIs and other antivirals in outpatients.
- Peramivir (RAPIVAB) received an expanded FDA-approved indication for treatment of acute uncomplicated influenza in patients as young as 6 months.
- Baloxavir marboxil (XOFLUZA) has a new suspension formulation, received an expanded indication for postexposure prophylaxis, and expanded age indications down to 5 years for both postexposure prophylaxis and for influenza treatment in otherwise healthy patients.
**Recommendations:**
- No changes to preferred drug list (PDL) are recommended based on the review of clinical evidence.
- Update prior authorization (PA) criteria with expanded indications and age ranges for peramivir and baloxavir (*Appendix 5*).
- Evaluate costs in executive session.

**Summary of Prior Reviews and Current Policy:**
- Evidence assessment of antivirals for treatment of influenza with a new drug evaluation for baloxavir marboxil was presented to the Pharmacy and Therapeutics (P & T) Committee in 2019. At that time, there was no new comparative evidence assessing the efficacy or safety of antivirals for treatment or prevention of influenza. Low strength evidence found that baloxavir marboxil reduced the median time to symptom improvement by 26.5 hours compared to placebo. There was insufficient evidence in patients with comorbid medical conditions or patients with severe influenza. Adverse events observed with baloxavir are similar to influenza disease and include diarrhea, bronchitis, nausea, nasopharyngitis, and headache. Resistance mutations were documented in 11% of patients in clinical trials.
- Prior reviews found insufficient direct comparative evidence between NAIs to assess the comparative efficacy or safety of these drugs. Compared to placebo, the average time to symptom improvement has been documented as 14 to 21 hours in otherwise healthy adults if NAIs were started within 48 hours of symptom onset (based on moderate-quality evidence). With prophylactic use of oseltamivir or zanamivir in adults or children, the risk of developing influenza is decreased by 2-4% compared to placebo, and there is low to insufficient quality evidence that treatment with NAIs does not impact risk of complications or rate of hospitalization. At the time of the last review, rimantadine was made non-preferred due to lack of evidence for influenza and insufficient evidence for use in other conditions. Similarly, peramivir was non-preferred due to limited available evidence.
- Prior authorization is required for all non-preferred products and for more than 5 days of preferred products to limit prophylactic use to patients at increased risk of complications from influenza. Preferred drug list (PDL) status for all influenza antivirals is presented in Appendix 1.

**Background:**
Influenza is a common respiratory viral infection spread through respiratory particles. Common symptoms of influenza are generally mild for many patients and include fever, chills, myalgia, headache, nausea, and fatigue. In some patients, influenza infection is severe and may result in death. It is estimated that approximately 140,000 to 710,000 yearly hospitalizations are associated with influenza, and 12,000 to 52,000 patients die from influenza yearly. The 2020-2021 season had minimal influenza activity, likely due to coronavirus-19 related lockdowns. Similarly, the symptomatic cases in 2021-2022 were about one-third to one-fourth of normal years, with 98.6% being influenza A and the H3N2 strain predominating. Complications of influenza can include pneumonia, bronchitis, otitis media, and death. Complications may arise from the influenza virus itself or may be caused by comorbid infections or conditions which worsen with influenza infection.

Influenza viruses are classified based on viral types (influenza A and B). Influenza A is further classified into viral subtypes based on surface proteins hemagglutinin (H) and neuraminidase (N). The primary preventive treatment for influenza is vaccination. Influenza vaccines are recommended for all patients over 6 months of age who do not have contraindications to the vaccine. Formulations include inactivated vaccines, live attenuated vaccines, and recombinant vaccines. Vaccines may be administered via intradermal injection, intramuscular injection, jet injection, or nasal spray. For the 2022-2023 influenza vaccines, no changes were made to the A(H1N1)pdm09 or the B/Yamagata egg-based, cell-based, or recombinant vaccine recommended components. The recommended A(H3N2) component was changed to an A/Darwin/9/2021 (H3N2)–like virus for egg-based vaccines and an A/Darwin/6/2021 (H3N2)–like virus for cell-based or recombinant vaccines. The B/Victoria component recommendation was changed to a B/Austria/1359417/2021–like virus.

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*December 2022*
Antiviral treatment may be considered in acute uncomplicated influenza infection within 48 hours of symptom onset to reduce duration of symptoms. The Centers for Disease Control and Prevention (CDC) recommend treatment with antivirals for any patient with confirmed or suspected influenza who is hospitalized; has severe, complicated or progressive illness; or is at higher risk for influenza complications. Patients considered to be at high risk for complications from influenza include patients greater than 65 years of age, children less than 2 years of age, people with chronic comorbid conditions (including those with respiratory, cardiovascular, metabolic, neurologic, immunosuppressive, endocrine, kidney or liver disease), pregnant or postpartum individuals, Native Americans, patients with BMI greater than 40, and patients residing in long-term care facilities. Prophylactic treatment with antivirals is not routinely recommended by the CDC, but may be considered in the following circumstances after exposure to a person with influenza: patients at high risk of complications who cannot receive the vaccine, patients with severe immune deficiencies or those who may not respond to influenza vaccination, or patients at high risk of influenza during the first 2 weeks after vaccination. Only oseltamivir, zanamivir, and baloxavir are indicated as prophylactic agents. Antivirals have the best evidence of benefit if no more than 48 hours have elapsed since the initial exposure and, if started prophylactically, should be continued for 7 days after the last known exposure.

Antivirals FDA-approved for treatment of acute uncomplicated influenza include NAIs (oseltamivir, zanamivir, and peramivir), adamantanes (amantadine and rimantadine), and a polymerase acidic (PA) cap-dependent endonuclease inhibitor (baloxavir marboxil). Ages of approval for treatment and prophylaxis vary by agent. The CDC recommends use of oseltamivir for ages below its FDA approval for treatment in infants less than 14 days old and prophylaxis as young as 3 months. When treating pre-term infants, CDC recommends American Academy of Pediatrics (AAP) guidance for lower weight-and-gestational-age-based dosing, due to their presumed slower drug clearance due to immature renal function. In persons who are pregnant, oseltamivir is the preferred antiviral treatment. Baloxavir marboxil is not recommended due to lack of evidence in pregnancy. Circulating influenza A viruses continue to have high levels of resistance to amantadine and rimantadine and these antivirals are not recommended for treatment or prevention of influenza. The CDC has tested 314 of 1782 influenza viruses genetically characterized for susceptibility to NAIs, and 3 strains (influenza A H1N1pdm09 viruses with NA-H275Y amino acid substitution known to convey oseltamivir resistance) were not inhibited normally by NAIs when tested phenotypically. When testing 535 of 1757 influenza viruses genetically characterized for susceptibility to baloxavir were tested phenotypically, one strain (influenza A H3N2 with PA-138M amino acid substitution) had reduced susceptibility.

The most common outcome evaluated in influenza antiviral clinical trials is symptom improvement. Symptom severity and time to symptom improvement is often self-reported and evaluated using numeric rating scales with alleviation of symptoms defined as complete resolution or presence of only mild symptoms. Other clinically meaningful outcomes of interest include prevention of influenza complications, morbidity, mortality, hospitalizations, and serious AEs.

Usage of medications for influenza is seasonally driven and varies between years based on local and regional outbreaks. In Oregon Medicaid Fee-for-Service patients, use from October 2021 through May of 2022 varied from 6 to 60 claims in each quarter and preferred agents were most commonly used.

Methods:
A Medline literature search for new systematic reviews and 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 3, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews.

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December 2022
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.

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:**

**Intravenous Peramivir Versus Oseltamivir For Patients With Influenza**

A 2021 review compared the efficacy of IV peramivir and oral oseltamivir for treatment of polymerase chain reaction or rapid antigen test confirmed influenza. The primary outcomes of interest were incidence of complications and pneumonia. Seven RCTs with sample sizes ranging from 34 to 562 participants were included in the analysis. Most studies restricted to adults or older children, and influenza clinical symptom definitions varied. Peramivir dosing varied somewhat, with 4 studies using the FDA-approved 600 mg single dose regimen, while oseltamivir dosing matched standardized 75 mg twice daily for 5 days (weight based for children). Four studies required symptom presentation within 48 hours, while the remaining included patients with onset 72 to 96 hours prior to enrollment. There were some concerns for bias in 4 studies, low risk in 2 studies, and high risk of bias in a single study. This single study had the lowest patient enrollment of any included RCT.

The incidence of total complications between 600 mg peramivir and the standard oseltamivir regimen found no significant difference between the two therapies (peramivir 2.5% vs. oseltamivir 4.1%; RR=0.70; 95% CI 0.36 to 1.38; $I^2=0\%$). Meta-analysis of the 4 RCTs using the 600 mg peramivir dose compared to standard oseltamivir found no differences in overall incidence in rate of pneumonia (peramivir 2.2% vs oseltamivir 2.7%; RR=0.74; 95% CI 0.37 to 1.51; $I^2=0\%$).

After review, 12 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

**New Guidelines:**

**High Quality Guidelines:**

**Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza**

The IDSA published a December 2018 update of previous 2009 guidelines. The focus was on the care of children, pregnant and postpartum individuals, and nonpregnant adults as well as patients who are severely immunocompromised (e.g., hematopoietic stem cell and solid organ transplant recipients). Consultation is recommended with the CDC website for most up to date information regarding influenza vaccines, influenza tests, and approved antiviral medications. The literature and regulatory website search was conducted through January 2018. Of note, initial baloxavir approval was in October 2018. Recommendations were graded as described in Table 1. Recommendations relevant to outpatient treatment and prophylaxis are summarized below.

<table>
<thead>
<tr>
<th>Table 1. Infectious Diseases Society of America–US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category and Grade</strong></td>
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<tr>
<td>Strength of recommendation</td>
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<td>A</td>
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</tbody>
</table>

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December 2022
In patients with confirmed or suspected influenza, the following should be treated with antivirals:

- Adults and children with documented or suspected influenza, irrespective of influenza vaccination history:
  - Persons of any age who are hospitalized with influenza, regardless of illness duration prior to hospitalization (A-II).
  - Outpatients of any age with severe or progressive illness, regardless of illness duration (A-III).
  - Outpatients who are at high risk of complications from influenza, including those with chronic medical conditions and immunocompromised patients (A-II).
  - Children younger than 2 years and adults ≥65 years (A-III).
  - Pregnant individuals and those within 2 weeks postpartum (A-III).

- Adults and children who are not at high risk of influenza complications, with documented or suspected influenza, irrespective of influenza vaccination history:
  - Outpatients with illness onset ≤ 2 days before presentation (C-I).
  - Symptomatic outpatients who are household contacts of persons who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised (C-III).
  - Symptomatic healthcare providers who care for patients who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised (C-III).

IDSA recommends that patients who meet treatment criteria should receive a NAI such as oseltamivir, inhaled zanamivir, or IV peramivir, but not a NAI combination (A-I) and not routinely at higher doses than FDA approved (A-I). Uncomplicated influenza in otherwise healthy outpatients should include 5 days of oseltamivir or inhaled zanamivir, or a single IV dose of peramivir (A-I). Longer durations may be considered in some patients including with documented or suspected immunocompromising condition or those requiring hospitalization for severe lower respiratory tract disease (C-III).

Patients who should be considered for antiviral chemoprophylaxis in the absence of an exposure or institutional outbreak are included below. Oseltamivir or inhaled zanamivir should be used rather than amantadine (A-II). Duration of the season (to begin as soon as influenza activity is detected in community and continued for duration of community influenza activity [A-II]).

- Adults and children aged ≥ 3 months who are at very high risk of developing complications from influenza and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., persons who are severely immunocompromised) (C-II).
- Adults and children aged ≥ 3 months who have the highest risk of influenza-associated complications, such as recipients of hematopoietic stem cell transplant in the first 6 to 12 months post-transplant and lung transplant recipients (B-II).
• Short-term duration
  o With prompt administration of inactivated influenza vaccine for unvaccinated adults and children aged ≥ 3 months who are at high risk of developing complications from influenza in whom influenza vaccination is expected to be effective when influenza activity has been detected in the community (C-II).
  o In unvaccinated adults, including healthcare personnel, and for children aged ≥ 3 months who are in close contact with persons at high risk of developing influenza complications during periods of influenza activity when influenza vaccination is contraindicated or unavailable and these high-risk persons are unable to take antiviral chemoprophylaxis (C-III).

Postexposure prophylaxis can be considered in certain non-institutionalized, asymptomatic patients detailed below. Postexposure chemoprophylaxis should begin as soon as possible after exposure, and ideally no later than 48 hours after exposure (A-III), and should last for 7 days in a non-outbreak setting (A-I/II).

After 48 hours once-daily chemoprophylaxis should not be started, but symptomatic patients should receive treatment (A-III).1

• Asymptomatic adults and children aged ≥ 3 months who are at very high risk of developing complications from influenza (e.g., severely immunocompromised persons) and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness, after household exposure to influenza (C-II).
• With prompt administration of influenza vaccination for adults and children aged ≥ 3 months who are unvaccinated and are household contacts of a person at very high risk of complications from influenza (e.g., severely immunocompromised persons), after exposure to influenza (C-II).

Additional Guidelines for Clinical Context:
Recommendations for Prevention and Control of Influenza in Children 2021-2022

The AAP issued a technical report in 2022. Recommendations are not graded and do not include a systematic review methodology. The report focuses heavily on vaccination recommendations.

AAP defines people at high risk of influenza complications as:23
• Children < 5 years, and especially those < 2 years, regardless of the presence of underlying medical conditions
• Adults ≥ 50 years, and especially those ≥ 65 years
• Children and adults with chronic pulmonary disease (including asthma and cystic fibrosis); hemodynamically significant cardiovascular disease (except hypertension alone); or renal, hepatic, hematologic (including sickle cell disease and other hemoglobinopathies), or metabolic disorders (including diabetes mellitus)
• Children and adults with immunosuppression attributable to any cause, including that caused by medications or by HIV infection
• Children and adults with neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy, stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
• Children and adults with conditions that compromise respiratory function or handling of secretions (including tracheostomy and mechanical ventilation)
• Women who are pregnant or postpartum during the influenza season
• Children and adolescents < 19 years who are receiving long-term aspirin therapy or salicylate-containing medications (including those with Kawasaki disease and rheumatologic conditions) because of increased risk of Reye syndrome
- American Indian/Alaska Native people
- Children and adults with obesity (i.e., BMI ≥ 40 for adults and based on age for children)
- Residents of chronic care facilities and nursing homes

This report included dosing recommendations for adults, children, infants, and preterm infants (oseltamivir only for preterm infants). Preterm infant dosing has not been evaluated by the FDA, though with available pharmacokinetic and safety data the CDC and AAP recommend use in term and preterm infants as benefits of use in neonatal influenza likely outweigh risks.\textsuperscript{1,10} Patients at higher risk of complications should be offered treatment.

Oseltamivir remains the agent of choice for treatment while inhaled zanamivir is an alternative in those who do not have chronic respiratory disease. Oseltamivir, inhaled zanamivir, and baloxavir all have indications for use as chemoprophylaxis in certain ages. Decisions regarding prophylaxis should weigh risk of complications for exposed patient, vaccination status, type and duration of contract, public health recommendations in local area, and clinical judgment, and should begin within 48 hours of exposure.\textsuperscript{23}

Resistance to antivirals can emerge, though testing of the 2019-2020 circulating viruses showed almost no resistance to NAIs and none to baloxavir. Baloxavir resistance has been reported in Japan where it is more widely used. Amantadine and rimantadine resistance to influenza A continues to persist and they are not currently recommended for use.\textsuperscript{23}

After review, no guidelines were excluded due to poor quality.

**New Formulations or Indications:**

- Peramivir (RAPIVAB)\textsuperscript{6}:
  - Expanded indication for treatment of acute uncomplicated influenza in patients \textbf{6 months} of age and older who have been symptomatic for no more than two days. (January 2021)

- Baloxavir marboxil (XOFLUZA)\textsuperscript{7}:
  - Expanded indication for treatment of acute uncomplicated influenza in patients who have been symptomatic for no more than 48 hours who are otherwise healthy expanded to include pediatric patients \textbf{5 years of age} and older. (August 2022)
  - Expanded indication for post-exposure prophylaxis of influenza in patients \textbf{5 years of age} and older following contact with an individual who has influenza. (August 2022)
  - Expanded indication for \textbf{post-exposure prophylaxis} of influenza in patients 12 years of age and older following contact with an individual who has influenza. (November 2020)
  - \textbf{Suspension formulation} approved in for treatment of flu in ages 12 years and older and post-exposure prophylaxis in patients 12 years of age and older (November 2020)
  - Indication updated from “treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours” to “acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours and \textbf{who are otherwise healthy, or at high risk of developing influenza-related complications}”. (October 2019)
New FDA Safety Alerts:

Table 2. Description of new FDA Safety Alerts

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Month / Year of Change</th>
<th>Location of Change (Boxed Warning, Warnings, CI)</th>
<th>Addition or Change and Mitigation Principles (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baloxavir marboxil?</td>
<td>XOFLUZA</td>
<td>October 2019</td>
<td>Warnings and Precautions</td>
<td>Hypersensitivity subsection added</td>
</tr>
</tbody>
</table>

Randomized Controlled Trials:
A total of 69 citations were manually reviewed from the initial literature search. After further review, 66 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in Appendix 2.

Table 3. Description of Randomized Comparative Clinical Trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Notes/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker et al.</td>
<td>1. baloxavir -oral -Wt-based single dose ranging from 2mg/kg to 40 mg N=117</td>
<td>-children 1 to 11 years -Clinical influenza diagnosis, but otherwise healthy -2018/2019 Northern Hemisphere influenza season -symptom onset &lt;= 48 h -excluded if hospitalization required or other antiviral use</td>
<td>Safety</td>
<td>AE incidence</td>
<td>--sites in US, South America, and Europe</td>
</tr>
<tr>
<td>MiniSTONE-2</td>
<td>2. oseltamivir -oral -wt-based BID doses for 5 d ranging from 30 mg to 75 mg per dose -wt based N=59</td>
<td>-2:1 randomization -Stratification by age -1 to &lt;5 years -5 to &lt;12 years Followed x 29 d</td>
<td>-AE related to study drug</td>
<td>1. 2.6% 2. 8.6%</td>
<td>-Predominant strains: -Influenza A H3N2 65.5% -Influenza A H1N1pdm09 24.1% -Influenza B 6%</td>
</tr>
<tr>
<td>MC, DB, DD, RCT</td>
<td></td>
<td></td>
<td>Safety</td>
<td>Most common AE Gastrointestinal 1. 10.4% 2. 17.2%</td>
<td>Withdrawal d/t AE 1. 2 -accidental OD of oseltamivir placebo -grade 2 rash on day 4 2. 0</td>
</tr>
<tr>
<td>Ison et al.</td>
<td>1. baloxavir wt-based x 1 dose -outpatients 12 years and olderILI</td>
<td>TTIIS in mITT Time from start of treatment to patient-</td>
<td>Efficacy</td>
<td>Median mITT 1. 73.2 h</td>
<td>-551 sites in 17 countries and territories -Influenza A H3N2 48%</td>
</tr>
<tr>
<td>CAPSTONE-2</td>
<td></td>
<td></td>
<td>Safety</td>
<td>-</td>
<td></td>
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<tr>
<td><strong>MC, DB, DD, RCT</strong></td>
<td><strong>Kato et al.</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td><strong>Efficacy</strong></td>
<td><strong>Safety</strong></td>
<td><strong>Frequency and severity of AEs</strong></td>
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</table>
| 2. oseltamivir 75 mg BID x 5 d 3. placebo  
N= 2184  
mITT N=1163  
1:1:1 randomization  
Stratified by:  
- baseline symptom score  
- pre-existing or worsening symptoms at onset of illness compared to pre-influenza  
- region  
- weight | 1. IV peramivir 600 mg daily x 2 d 2. IV peramivir 300 mg x 1 dose 3. oseltamivir 75 mg BID x 5 d  
N = 214  
1:1:1 randomization | reported improvement in all 7 influenza associated symptoms  
7 influenza symptoms:  
- cough  
- sore throat  
- headache  
- nasal congestion  
- feverishness or chills  
- muscle or joint pain  
- fatigue  
Frequency and severity of AEs | Any AE  
1. 183 (25%)  
2. 202 (28%)  
3. 216 (30%)  
TRAE leading to study withdrawal  
1. 2 (<1%)  
2. 3 (<1%)  
3. 2 (<1%)  
Serious AE (excluding death)  
1. 0  
2. 2 (<1%)  
3. 2 (<1%)  
Death  
1. 0  
2. 0  
3. 0 | 1 vs. 2  
Median difference 7.7 h  
95% CI -7.9 to 22.7 h  
Safety  
1. 183 (25%)  
2. 202 (28%)  
3. 216 (30%)  
Est difference -78.36  
95% CI -215.69 to 58.96  
P=0.0416  
Est difference -145.07  
95% CI -284.57 to -5.56  
P=0.0416 |

- ≥ one risk factor for influenza-associated complications  
- symptom onset ≤ 48 h  
- age 16 to 70 years  
- inpatient or outpatient  
- confirmed influenza A or B  
- preexisting chronic respiratory diseases (bronchial asthma, COPD, or pulmonary fibrosis)  
- symptom onset ≤ 48 h  
CATVS in ITT  
Expressed as index value for AUC of total score of cough, sore throat, nasal congestion from start of study drug administration to 2 wk post-administration  
Efficacy  
Mean (SD)  
1. 782.78 (487.17)  
2. 717.35 (347.55)  
3. 856.34 (404.99)  
1 vs 3  
Est difference -78.36  
95% CI -215.69 to 58.96  
2 vs 3  
Est difference -145.07  
95% CI -284.57 to -5.56  
P=0.0416  
- Influenza B 42%  
- Influenza A H1N1 7%  
- “high-risk” for complications adapted from CDC definition  
- mITT population included those with paired baseline and f/u samples confirmed influenza + by RT-PCR and received at least one dose of study drug  
- missing data not imputed  
- sponsor involved in study design, data collection, data analysis, and manuscript preparation. Data compiled by sponsor and analyzed by sponsor-employed statistician.  
- non-standard endpoint metric  
- FDA approved peramivir dose 600 mg IV x 1 dose  
- inpatient status ranged from 2.8% (oseltamivir) to 10.4% (peramivir 300mg)  
- preexisting chronic respiratory disease was bronchial asthma in >90% of patients  
- 50 sites, all in Japan
<table>
<thead>
<tr>
<th>-excluded if on mechanical ventilator</th>
<th>Safety TEAE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. 25.7%</td>
</tr>
<tr>
<td></td>
<td>2. 13.4%</td>
</tr>
<tr>
<td></td>
<td>3. 13.9%</td>
</tr>
<tr>
<td></td>
<td>Severe AE</td>
</tr>
<tr>
<td></td>
<td>1. 2 (vomiting, pneumonia)</td>
</tr>
<tr>
<td></td>
<td>2. 1 (pneumococcal pneumonia)</td>
</tr>
<tr>
<td></td>
<td>3. 0</td>
</tr>
</tbody>
</table>

Abbreviations: AE = adverse events; AUC = area under the curve; BID = twice daily; d = days; CDC = Centers for Disease Control and Prevention; CI = confidence interval; CATVS = cumulative area of time vs symptoms; COPD = chronic obstructive pulmonary disorder; DB = double-blind; DD = double-dummy; h= hours; f/u = follow-up; ILI = influenza-like illness; ITT = intent-to-treat; ITTi = intent-to-treat influenza-infected; IV =intravenous; MC = multicenter; mITT = modified intention-to-treat; OD = overdose; OL = open-label; RCT = randomized clinical trial, RT-PCR = reverse transcription-polymerase chain reaction molecular assay; TEAE = treatment-emergent adverse events; TRAE = treatment-related adverse event; TTIIS = time to improvement of influenza symptoms; US = United States; wk = week; wt = weight.
References:


Author: Fletcher  December 2022


**Appendix 1: Current Preferred Drug List**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Route</th>
<th>Form</th>
<th>PDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>zanamivir</td>
<td>RELENZA</td>
<td>INHALATION</td>
<td>BLST W/DEV</td>
<td>N</td>
</tr>
<tr>
<td>oseltamivir</td>
<td>OSELTAMIVIR PHOSPHATE</td>
<td>ORAL</td>
<td>CAPSULE</td>
<td>Y</td>
</tr>
<tr>
<td>oseltamivir</td>
<td>TAMIFLU</td>
<td>ORAL</td>
<td>CAPSULE</td>
<td>Y</td>
</tr>
<tr>
<td>oseltamivir</td>
<td>OSELTAMIVIR PHOSPHATE</td>
<td>ORAL</td>
<td>SUSP RECON</td>
<td>Y</td>
</tr>
<tr>
<td>oseltamivir</td>
<td>TAMIFLU</td>
<td>ORAL</td>
<td>SUSP RECON</td>
<td>Y</td>
</tr>
<tr>
<td>rimantadine HCl</td>
<td>FLUMADINE</td>
<td>ORAL</td>
<td>TABLET</td>
<td>N</td>
</tr>
<tr>
<td>rimantadine HCl</td>
<td>RIMANTADINE HCL</td>
<td>ORAL</td>
<td>TABLET</td>
<td>N</td>
</tr>
<tr>
<td>baloxavir marboxil</td>
<td>XOFLUZA</td>
<td>ORAL</td>
<td>TABLET</td>
<td>N</td>
</tr>
<tr>
<td>peramivir/PF</td>
<td>RAPIVAB</td>
<td>INTRAVEN</td>
<td>VIAL</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2: Abstracts of Comparative Clinical Trials


BACKGROUND: Baloxavir marboxil (baloxavir) is a novel, cap-dependent endonuclease inhibitor that has previously demonstrated efficacy in the treatment of influenza in adults and adolescents. We assessed the safety and efficacy of baloxavir in otherwise healthy children with acute influenza.

METHODS: MiniSTONE-2 (Clinicaltrials.gov: NCT03629184) was a double-blind, randomized, active controlled trial enrolling children 1-<12 years old with a clinical diagnosis of influenza. Children were randomized 2:1 to receive either a single dose of oral baloxavir or oral oseltamivir twice daily for 5 days. The primary endpoint was incidence, severity and timing of adverse events (AEs); efficacy was a secondary endpoint.

RESULTS: In total, 173 children were randomized and dosed, 115 to the baloxavir group and 58 to the oseltamivir group. Characteristics of participants were similar between treatment groups. Overall, 122 AEs were reported in 84 (48.6%) children. Incidence of AEs was similar between baloxavir and oseltamivir groups (46.1% vs. 53.4%, respectively). The most common AEs were gastrointestinal (vomiting/diarrhea) in both groups [baloxavir: 12 children (10.4%); oseltamivir: 10 children (17.2%)]. No deaths, serious AEs or hospitalizations were reported. Median time (95% confidence interval) to alleviation of signs and symptoms of influenza was similar between groups: 138.1 (116.6-163.2) hours with baloxavir versus 150.0 (115.0-165.7) hours with oseltamivir.

CONCLUSIONS: Oral baloxavir is well tolerated and effective at alleviating symptoms in otherwise healthy children with acute influenza. Baloxavir provides a new therapeutic option with a simple oral dosing regimen.


Background Baloxavir marboxil (hereafter baloxavir), a selective inhibitor of influenza cap-dependent endonuclease, was approved in 2018 in the USA and Japan for the treatment of uncomplicated influenza in otherwise healthy individuals aged 12 years and older. We aimed to study the efficacy of baloxavir in outpatients at high risk of developing influenza-associated complications.

Methods We did a double-blind, placebo-controlled and oseltamivir-controlled trial in outpatients aged 12 years and older in 551 sites in 17 countries and territories. Eligible patients had clinically diagnosed influenza-like illness, at least one risk factor for influenza-associated complications (eg, age older than 65 years), and a symptom duration of less than 48 h. Patients were stratified by baseline symptom score (≤14 vs ≥15), pre-existing and worsened symptoms at onset of illness compared with pre-influenza (yes or no), region (Asia, North America and Europe, or southern hemisphere), and weight (<80 kg vs ≥80 kg), and randomly assigned (1:1:1) via an interactive web-response system to either a single weight-based dose of baloxavir (40 mg for patients weighing <80 kg and 80 mg for patients weighing ≥80 kg; baloxavir group), oseltamivir 75 mg twice daily for 5 days (oseltamivir group), or matching placebo (placebo group). All patients, investigators, study personnel, and data analysts were masked to treatment assignment until database lock. The primary endpoint was time to improvement of influenza symptoms (TTIIS) in the modified intention-to-treat population, which included all patients who received at least one dose of study drug and had RT-PCR-confirmed influenza virus infection. Safety was assessed in all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT02949011.

Findings 2184 patients were enrolled from Jan 11, 2017, to March 30, 2018, and randomly assigned to receive baloxavir (n=730), placebo (n=729), or oseltamivir (n=725). The modified intention-to-treat population included 1163 patients: 388 in the baloxavir group, 386 in the placebo group, and 389 in the oseltamivir group. 557 (48%) of 1163 patients had influenza A H3N2, 484 (42%) had influenza B, 80 (7%) had influenza A H1N1, 14 patients had a mixed infection, and 28 had infections with non-typable viruses. The median TTIIS was shorter in the baloxavir group (73.2 h [95% CI 67.2 to 85.1]) than in the placebo group (102.3 h [92.7
to 113·1]; difference 29·1 h [95% CI 14·6 to 42·8]; p<0·0001). The median TTIIS in the oseltamivir group was 81·0 h (95% CI 69·4 to 91·5), with a difference from the baloxavir group of 7·7 h (–7·9 to 22·7). Adverse events were reported in 183 (25%) of 730 patients in the baloxavir group, 216 (30%) of 727 in the placebo group, and 202 (28%) of 721 in the oseltamivir group. Serious adverse events were noted in five patients in the baloxavir group, nine patients in the placebo group, and eight patients in the oseltamivir group; one case each of hypertension and nausea in the placebo group and two cases of transaminase elevation in the oseltamivir group were considered to be treatment related. Polymerase acidic protein variants with Ile38Thr, Ile38Met, or Ile38Asn substitutions conferring reduced baloxavir susceptibility emerged in 15 (5%) of 290 baloxavir recipients assessed for amino acid substitutions in the virus.

**Interpretation** Single-dose baloxavir has superior efficacy to placebo and similar efficacy to oseltamivir for ameliorating influenza symptoms in high-risk outpatients. The safety of baloxavir was comparable to placebo. This study supports early therapy for patients at high risk of complications of influenza to speed clinical recovery and reduce complications.


**BACKGROUND:** The efficacy of neuraminidase inhibitors on improvement of respiratory symptoms triggered by influenza in patients with pre-existing chronic respiratory diseases is unknown. **METHODS:** This 2-week, randomized, open-label study evaluated intravenous peramivir 600 mg on two consecutive days (peramivir-repeat), peramivir 300 mg single dose (peramivir-single), and oral oseltamivir 75 mg twice daily for 5 days in patients with confirmed influenza and chronic respiratory diseases. Patients recorded symptom scores daily. The primary endpoint of cumulative area of time vs symptoms (CATVS) was expressed as an index value of area under the curve vs time of the total score of cough, sore throat, and nasal congestion from baseline to 2 weeks. **RESULTS:** Of 214 randomized patients, 209 (56% female, 77% aged <65 years, 94% outpatients, 91% bronchial asthma, 62% influenza A) received >/=1 dose of study drug. Mean (standard deviation) CATVS was similar for peramivir-repeat (782.78 [487.17]) vs peramivir-single (717.35 [347.55]; P = .4371), and for peramivir-repeat vs oseltamivir (856.34 [404.99]; P = 1.00). However, CATVS was significantly shorter for peramivir-single vs oseltamivir, with an estimated treatment difference (TD) of -145.07 (95% confidence interval: -284.57, -5.56; P = .0416). In subgroup analyses, CATVS was significantly shorter for peramivir-single vs oseltamivir among patients with influenza A (TD: -206.31 [-383.86, -28.76]; P = .0231), bronchial asthma (TD: -156.57 [-300.22, -12.92]; P = .0328), baseline respiratory severity score <5 (TD: -265.32 [-470.42, -60.21]; P = .0120), and age <65 (TD: -184.30 [-345.08, -23.52]; P = .0249). **CONCLUSIONS:** In patients with chronic respiratory diseases, peramivir-single was not significantly different from peramivir-repeat and was more effective than oseltamivir at alleviating respiratory symptoms.
Appendix 3: Medline Search Strategy

*Ovid MEDLINE(R) without Revisions, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 1, 2018 to Oct 7th, 2022*

<table>
<thead>
<tr>
<th>Search Term</th>
<th>Results</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zanamivirae, tu [Adverse Effects, Therapeutic Use]</td>
<td>361</td>
<td>Advanced</td>
</tr>
<tr>
<td>Oseltamivirae, tu [Adverse Effects, Therapeutic Use]</td>
<td>1806</td>
<td>Advanced</td>
</tr>
<tr>
<td>Rimantadine/ae, tu [Adverse Effects, Therapeutic Use]</td>
<td>281</td>
<td>Advanced</td>
</tr>
<tr>
<td>baloxavir.mp.</td>
<td>288</td>
<td>Advanced</td>
</tr>
<tr>
<td>peramivir.mp.</td>
<td>506</td>
<td>Advanced</td>
</tr>
<tr>
<td>1 or 2 or 3 or 4 or 5</td>
<td>2565</td>
<td>Advanced</td>
</tr>
<tr>
<td>limit 6 to (english language and humans and yr=&quot;2018 -Current&quot;) and (clinical trial. phase iii or clinical trial. phase iv or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or &quot;systematic review&quot;)</td>
<td>94</td>
<td>Advanced</td>
</tr>
</tbody>
</table>

Appendix 4: Key Inclusion Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with or at risk for influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Drugs in Appendix 1</td>
</tr>
<tr>
<td>Comparator</td>
<td>Drugs listed in Appendix 1</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Symptom Improvement (fever, cough, sore throat, muscle pain, malaise, etc)</td>
</tr>
<tr>
<td></td>
<td>Quality of Life, Morbidity, Mortality</td>
</tr>
<tr>
<td>Timing</td>
<td>Prevention</td>
</tr>
<tr>
<td></td>
<td>Acute treatment within 48 hours of symptom onset</td>
</tr>
<tr>
<td>Setting</td>
<td>Outpatient</td>
</tr>
</tbody>
</table>
Appendix 5: Prior Authorization and Quantity Limit Criteria

**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 drugs for point of sale (POS) or provider administered drugs (PAD).
- Oseltamivir therapy for greater than 75 days

**Covered Alternatives:**
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

### Approval Criteria

<table>
<thead>
<tr>
<th>Step</th>
<th>Question</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>What diagnosis is being treated?</td>
<td>Record ICD10 code.</td>
</tr>
<tr>
<td>2.</td>
<td>Is this an OHP-funded diagnosis?</td>
<td>Yes: Go to #3</td>
</tr>
<tr>
<td>3.</td>
<td>Is the antiviral agent to be used to treat a current influenza infection?</td>
<td>Yes: Go to #4</td>
</tr>
<tr>
<td>Approval Criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Will the prescriber consider a change to a preferred product?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Message:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Preferred products do not require PA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy &amp; Therapeutics Committee.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yes:</strong> Inform prescriber of covered alternatives in class and approve for length of therapy or 5 days, whichever is less.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No:</strong> Approve based on standard FDA or compendia-supported dosing for influenza treatment.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Note: baloxavir and peramivir are FDA approved as a single dose for treatment of influenza.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Is the antiviral prescribed oseltamivir, zanamivir, or baloxavir?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yes:</strong> Go to #6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No:</strong> Pass to RPh. Deny; medical appropriateness.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approval Criteria</td>
<td>Yes:</td>
<td>No:</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>6. <strong>Is the request for post-exposure chemoprophylaxis AND does the patient have any of the following CDC and IDSA criteria that may place them at increased risk for complications requiring chemoprophylaxis?</strong></td>
<td>Approve for duration of prophylaxis or 30 days, whichever is less.</td>
<td>Pass to RPh. Deny; medical appropriateness. Go to #7</td>
</tr>
<tr>
<td>• 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).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Persons at high risk for complications from influenza who cannot receive influenza vaccine after exposure to an infectious person.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Residents of institutions, such as long-term care facilities, during influenza outbreaks in the institution.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pregnancy and women up to 2 weeks postpartum (including after pregnancy loss) who have been in close contact with someone suspected or confirmed of having influenza.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Approval Criteria

7. Is the request for pre-exposure prophylaxis with oseltamivir or zanamivir AND does the patient meet IDSA\(^2\) criteria that would qualify for prophylaxis for duration of season?

- Adults and children aged ≥3 months who are at very high risk of developing complications from influenza and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (eg, persons who are severely immunocompromised).
- Adults and children aged ≥3 months who have the highest risk of influenza-associated complications, such as recipients of haematopoietic stem cell transplant in the first 6–12 months posttransplant and lung transplant recipients.

| Yes: Approve for duration of prophylaxis or 9 months, whichever is less. |
| No: Pass to RPh. Deny; medical appropriateness. |

### References


### P&T/DUR Review

| 12/22 (SF): 1/19 (SS); 1/16; 1/12; 9/10 |

### Implementation

| TBD: 3/1/19; 4/1/18; 10/13/16; 2/12/16; 1/11 |