

Drug Class Update with New Drug Evaluation: Influenza

Date of Review: January 2019

Generic Name: baloxavir marboxil

End Date of Literature Search: 11/01/2018

Brand Name (Manufacturer): Xofluza™ (Genentech, Inc)

Dossier Received: yes

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

To evaluate new comparative evidence of the benefits and harms of antiviral agents for the treatment and prevention of influenza. In addition, evidence for baloxavir marboxil, a new antiviral for the treatment of influenza, will be reviewed.

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. Is baloxavir marboxil safe or effective for the treatment of influenza compared to other antivirals or placebo?
4. 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 no new comparative evidence assessing efficacy or safety of antivirals for treatment or prevention of influenza.
- Compared to placebo, median time to symptom improvement in adults with uncomplicated influenza was approximately 17 hours with oseltamivir and 14 hours with zanamivir (low strength evidence).¹ The clinical significance of these differences are unclear.
- In children with uncomplicated influenza, the average time to symptom improvement was statistically significant for oseltamivir (29 hours; 95% CI 12 to 47), but not zanamivir (1.08 days, 95% CI -2.23 to 0.15; low strength evidence).¹ There was no difference in time to symptom improvement for children with asthma.
- With prophylactic antiviral use, incidence of symptomatic influenza was decreased by 2-3% with oseltamivir or zanamivir compared to placebo (low strength evidence).¹
- There was insufficient evidence of no difference in rate of hospitalization or complications from influenza with oseltamivir or zanamivir compared to placebo.
- There is insufficient evidence to assess comparative harms associated with antiviral influenza treatment. Common adverse events of oseltamivir treatment include nausea, vomiting, and headache.¹

- With use of baloxavir marboxil for treatment of uncomplicated influenza, the median time to symptom improvement was 54 hours compared to 80 hours with placebo (median difference of 26.5 hours; 95% CI 17.8 to 35.8; low strength evidence).²
- There is insufficient evidence for other efficacy or safety outcomes with use of baloxavir marboxil for treatment of influenza, and applicability to patients with comorbid medical conditions or patients with severe influenza is limited. Common adverse events occurring in clinical trials were consistent with influenza disease and included diarrhea, bronchitis, nausea, nasopharyngitis, and headache. Further studies are required to assess incidence of viral resistance to baloxavir marboxil as known resistance mutations were documented in 11% of patients in clinical trials, primarily those with H3N2 infection.^{2,3}

Recommendations:

- Make baloxavir marboxil non-preferred and subject to prior authorization criteria due to lack of available evidence in high risk patients and concerns with potential resistance.
- After evaluation of comparative costs in executive session, no changes to the preferred drug list were recommended.

Summary of Prior Reviews and Current Policy

Evidence of antivirals for treatment of influenza was last evaluated in 2016. Prior reviews found insufficient direct comparative evidence between neuraminidase inhibitors to assess the comparative efficacy or safety of these drugs. Compared to placebo, the average time to symptom improvement has been documented as 14-21 hours in otherwise healthy adults if neuraminidase inhibitors 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 neuraminidase inhibitors 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. PA is required for all other oral 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.

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. It's estimated that approximately 140,000-960,000 yearly hospitalizations are associated with influenza, and 12,000 to 79,000 patients die from influenza yearly.⁴ Complications of influenza can include pneumonia, bronchitis, and otitis media.¹ 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 hemmagglutinin (H) and neuraminidase (N). In the 2017-2018 flu season, the most common circulating influenza virus subtypes included H3N2, and H1N1, and B/Yamagata lineage.⁵ 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. Trivalent vaccines for the 2018-19 season include H1N1, H3N2, and B/Victoria lineage-like viral subtypes.⁵ Quadrivalent vaccines also include a B/Yamagata lineage-like virus.⁵ Antiviral treatment may be considered in acute uncomplicated influenza infection within 48 hours of symptom onset to reduce duration of symptoms. In the 2017-18 flu season, antivirals for influenza were prescribed for over 1,000 FFS patients with the majority of use for preferred products.

The Centers for Disease Control (CDC) recommend treatment with antivirals for any patient with confirmed or suspected influenza who is hospitalized; has severe, complicated or progressive illness; or is a higher risk for influenza complications.⁶ 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 women, Native Americans, patients with BMI greater than 40, and patients residing in long-term care facilities.⁶ 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.⁶ Only oseltamivir and zanamivir are recommended 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.⁶

Currently antivirals FDA-approved for treatment of acute uncomplicated influenza include neuraminidase inhibitors (oseltamivir, zanamivir, peramivir), adamantanes (amantadine and rimantadine), and polymerase acidic protein inhibitors (baloxavir marboxil). For treatment of active influenza, oseltamivir may be considered for patients of any age, zanamivir is recommended only for 7 years and older, peramivir is recommended for those at least 2 years of age, and baloxavir marboxil is recommended for patients 12 years and older.⁶ For women who are pregnant, oseltamivir is the preferred antiviral treatment, and baloxavir marboxil is not recommended due to lack of evidence in pregnancy.⁶ Oseltamivir is also FDA-approved for prophylaxis of influenza in patients 1 year and older, and zanamivir may be considered for prophylaxis in patients at least 5 years of age without underlying airway disease.⁶ In 2017-18 flu season, resistance to antiviral neuraminidase inhibitors (oseltamivir and peramivir) was detected in only 1.0% of tested H1N1 viral infections.⁵ No viral resistance was identified for zanamivir or for oseltamivir in H3N2 infections.⁵ 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.⁵

The most common outcome evaluated in clinical trials includes 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, and serious adverse events.

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), 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. 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.

Systematic Reviews:

A 2016 systematic review funded by the National Institutes of Health evaluated regulatory and mortality data with use of oseltamivir and zanamivir for influenza.¹ The review included 46 studies comparing antiviral treatment to placebo (9,623 patients in trials for oseltamivir and 14,628 for zanamivir), and results

were based on full clinical study reports of trials provided by manufacturers and regulatory agencies such as the FDA and European Medical Agency.¹ In the majority of included trials, there was high or unclear risk of selection bias (35 trials) due to lack of reported sequence generation methods, performance and detection bias (36 trials) due to lack of reported blinding methods and lack of identical placebo comparators, attrition bias (28 trials) due to missing outcome data, and reporting bias (33 trials) due to changes in outcome definitions during the trials, protocol amendments after study completion, and inconsistent data reporting methods.¹

Symptom Improvement

Compared to treatment with placebo, oseltamivir improved the time to symptom alleviation by 16.8 hours (95% CI 8.4 to 25.1) for adults and 29 hours (95% CI 12 to 47; $I^2=0\%$) for children with uncomplicated influenza.¹ There was no change in time to symptom improvement with oseltamivir in asthmatic children (5.2 hours; 95% CI -11.1 to 21.4; $I^2=0\%$).¹ Similar improvements in time to symptom alleviation were documented with zanamivir compared to placebo for adults (14.4 hours; 0.6 days, 95% CI 0.39 to 0.81, $I^2=9\%$), but not children (1.08 days, 95% CI -2.23 to 0.15; $I^2=72\%$).¹ There was no statistical difference in symptom response upon comparison of zanamivir in patients with and without confirmed influenza or upon comparison of zanamivir to rescue medications.¹

Hospitalizations

Rate of hospitalization was not significantly different in adults or children with treatment of oseltamivir compared to placebo.¹ Hospitalizations were not reported with zanamivir treatment.¹

Complications from Influenza

Statistical differences in treatment effects for pneumonia were dependent on the method of diagnosis. For example, unverified, self-reported pneumonia in patients with influenza was slightly decreased with oseltamivir treatment compared to placebo (RD 1.0%; 95% CI 0.22% to 1.49%; NNT = 100; $I^2=0\%$), but there was no statistical difference when a more strict definition of pneumonia based on radiological confirmation was used. Incidence of pneumonia with zanamivir was not statistically different from placebo upon analysis of both unverified pneumonia and pneumonia based on more strict diagnostic criteria in patients with influenza or influenza-like symptoms.¹ Prophylactic zanamivir use in high risk populations demonstrated a slight decrease in risk of unverified pneumonia (RD 0.32%, 95% CI 0.09 to 0.41; NNT = 331; $I^2=0\%$).¹ Treatment of influenza with oseltamivir did not reduce incidence of complications (including bronchitis, sinusitis, or otitis media) in adults or incidence of otitis media in children.¹ With zanamivir treatment in adults, there was no difference in sinusitis or otitis media, but a reduced incidence of bronchitis (RD 1.8%, 95% CI 0.65 to 2.80, NNT = 56; $I^2=0\%$).¹ There was no benefit of zanamivir treatment in children for prevention of sinusitis or otitis media.¹

Prevention of Influenza

Incidence of symptomatic influenza was decreased with prophylactic oseltamivir use compared to placebo (RD 3.05%, 95% CI 1.83% to 3.88%; NNT 33; $I^2=0\%$), with no difference for other influenza outcomes including hospitalization.¹ Prophylactic zanamivir use decreased risk of symptomatic influenza for individuals (RD 1.98%, 95% CI 0.98% to 2.54%; NNT 51; $I^2=45\%$) and households (RD 14.84%, 95% CI 12.18% to 16.55%; NNT 7; $I^2=45\%$), but not when used in the setting of post-exposure prophylaxis for individuals or household contacts (RR 0.88, 95% CI 0.65 to 1.20; $I^2=0\%$).¹

Adverse Effects

There was no difference in death, serious adverse effects, or withdrawal due to adverse effects with oseltamivir or zanamivir compared to placebo in adults or children with active or prophylactic treatment of influenza.¹ Adverse effects which were more common in adults treated with oseltamivir compared to placebo included nausea (RD 3.66%, 95% CI 0.90 to 7.39; $I^2=43\%$), vomiting (RD 4.56%, 95% CI 2.39 to 7.58; $I^2=12\%$), and headache (RD 3.15%, 95% CI 0.88% to 5.78%;

NNH 32).¹ Diarrhea was less common with oseltamivir treatment compared to placebo (RD 2.33%, 95% CI 0.14% to 3.81%; NNT 43; I²=44%).¹ Cardiovascular events were slightly lower in patients treated with oseltamivir (RD 0.68%, 95% CI 0.04% to 1.00%; NNT 148; I²=0%).¹ However, cardiovascular events included both clinical outcomes and non-clinical electrocardiogram readings, and the clinical implications of this data are unclear. Psychiatric adverse events were more common during prophylactic treatment with oseltamivir (RD 1.06%, 95% CI 0.07% to 2.76%; NNH 94; I²=0%), but not with treatment of active infections (RR 0.93, 95% CI 0.43 to 2.03; I²=0%).¹ With zanamivir treatment, there was no difference in diarrhea or headache compared to placebo, but nausea and vomiting were slightly improved with treatment of active infection (RD 1.63%, 95% CI 0.24% to 2.48%; NNT 62; I²=0%).¹ No significant differences were observed for other adverse events.

After review, 6 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control) or outcome studied (e.g., non-clinical).⁷⁻¹²

New Guidelines:

High Quality Guidelines:

No new high quality guidelines identified.

Additional Guidelines for Clinical Context:

American Academy of Pediatrics Recommendations for Control of influenza in Children: 2017-2018¹³

- Antiviral medications are important for the control of influenza but are not a substitution for influenza vaccination.
- Antivirals treatment of influenza should be offered for children hospitalized with presumed influenza, hospitalized for severe, complicated or progressive illness attributed to influenza, and children at high risk of complications from influenza. Antiviral treatment may be considered for any otherwise healthy child with presumed influenza.
- For treatment of influenza, oseltamivir is the preferred drug of choice for management of influenza infections in children. Inhaled zanamivir is an option for patients without chronic respiratory disease and intravenous peramivir may be considered for children unable to tolerate oseltamivir or zanamivir.
- During an influenza outbreak, prophylactic antivirals are recommended for children with high risk of complications if they have contraindications to immunization, before optimal immunity from vaccination is achieved (~2 weeks after vaccination), or as a supplement to vaccination in children who may not achieve sufficient immune response after vaccination (e.g., immunocompromised children).
- Prophylactic antivirals may also be considered for unimmunized family members and healthcare professionals with ongoing and close contact with children at high risk. Post-exposure prophylaxis may be considered for contacts of an infected patient if they have high risk of complications from influenza.
- For prophylaxis of influenza in children, inhaled zanamivir and oral oseltamivir are the only recommended agents.

After review, 1 guideline was excluded due to methodological quality and conflicts of interest.¹⁴

New Formulations or Indications:

None identified.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts¹⁵

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Peramivir	Rapivab®	8/2016	Contraindications	Labeling revised to include anaphylaxis associated with peramivir which has been observed in post-marketing experience.
Oseltamivir	Tamiflu®	6/2016	Warnings/Precautions	Dyspepsia and diarrhea may occur in patients with hereditary fructose intolerance. One dose of 75 mg Tamiflu® contains 2 grams of sorbitol which is above the recommended limit for patients with hereditary fructose intolerance.

Randomized Controlled Trials:

A total of 82 citations were manually reviewed from the initial literature search. After further review, all 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).

NEW DRUG EVALUATION:

See **Appendix 3 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Baloxavir marboxil was FDA approved based on results from one phase 2 dose-ranging RCT and one phase 3 RCT comparing baloxavir marboxil to placebo and oseltamivir, respectively. A summary of the phase 3 trial design, baseline characteristics, inclusion criteria, and results are presented in **Table 2**. Severity of 7 influenza symptoms were each self-reported twice daily using a 4-point rating scale (0-3 corresponding to none, mild, moderate, and severe), and axillary temperature was self-evaluated four times daily for the first 4 days.² Overall health assessments were reported daily on a separate 0-10 point scale with scores of 0 corresponding to worst possible health and 10 corresponding to normal health for someone of the patient's age and condition.² The minimum clinically important differences for these scales have not been established.

The median time to symptom improvement for patients with confirmed influenza treated with baloxavir marboxil was 53.7 hours compared to 80.2 hours with placebo (median difference 26.5 hours; 95% CI 17.8 to 35.8). Similar differences were documented in the entire population of patients with influenza-like symptoms (median difference 23.2 hours; 95% CI 14.0 to 34.2). A pre-specified subgroup analysis by age demonstrated the median time to symptom improvement with treatment of baloxavir marboxil was also improved for adolescents (93 vs. 54 hours; median difference 38.6 hours) and adults (median difference of 25.6 hours) compared to placebo.^{2,3} No significant difference in time to symptom improvement was demonstrated between baloxavir marboxil and oseltamivir. Similar results were observed in the phase 2 dose ranging study with improved median time to symptom resolution (49.5 vs. 77.7 hours; median difference 28.2 hours, p=0.005) with baloxavir marboxil 40 mg compared to placebo.²

The phase 3 RCT had low risk of performance, and detection bias and high risk for reporting bias as multiple pre-specified secondary outcomes were not reported (e.g., health related quality of life, overall health assessments, and data for oseltamivir). Risk for selection bias was unclear as incidence of current smokers was lower in patients with influenza treated with baloxavir (20.6%) compared to placebo (24.2%) or oseltamivir (27.3%). Extensive exclusion criteria limit applicability to patients without comorbid medical conditions and mild to moderate severity influenza-like symptoms.² There is currently no published data available on utilization of baloxavir marboxil in patients at highest risk of complications from influenza including elderly, children less than 12 years of age, pregnant or post-partum women, or people with chronic medical conditions. A study of baloxavir marboxil in patients with influenza at high risk for complications was completed in early 2018, but full results have yet to be published.¹⁶ The majority of patients were located in Japan (72%).² On average patients located in Japan had more rapid symptom relief than patients enrolled in the United States (77.7 hours vs. 117.9 hours), but there was no difference between baloxavir marboxil and placebo upon analysis of time to treatment response based on location (median difference of 31.3 hours in Japan and 30.6 hours in the United States).²

Infectious viral load and resistance patterns were also assessed as secondary endpoints. In the phase 2 study (2015-16 flu season), 2.7% of patients had treatment-emergent viral mutations resulting in decreased susceptibility to baloxavir marboxil.³ In the phase 3 trial (2016-17 flu season), changes in viral proteins which increase resistance to baloxavir marboxil were documented in 11% of patients.³ Substitutions in amino acids known to decrease baloxavir marboxil susceptibility were particularly prevalent in patients with H3N2 infections, and 9.7% of patients treated with baloxavir marboxil in the phase 3 trial had treatment-emergent resistance mutations.² In patients with these viral amino acid substitutions, more patients treated with baloxavir marboxil had continued viral load at 5 days (91%) and longer symptom duration (63.1 hours) compared to patients without viral variants (7% and 49.6 hours, respectively).² Other viral amino acid substitutions were documented in 8% of baloxavir marboxil and placebo recipients, though the exact clinical implications of these changes is unknown.³ Although the clinical implications on susceptibility to baloxavir marboxil have yet to be fully assessed for all of these viral variants, a high rate of resistance mutations in the H3N2 virus after just one dose of baloxavir marboxil may lead to decreased susceptibility and increased viral resistance. Because baloxavir marboxil has a different mechanism of action and target protein compared to neuraminidase inhibitors, cross-resistance with other influenza antivirals is not expected, and prescribers should consider available susceptibility patterns when deciding between antiviral treatments.³

Clinical Safety:

Like other drugs to treat influenza, baloxavir marboxil contains warnings for risk of bacterial infections. Serious bacterial infections may begin with or occur concomitantly with influenza-like symptoms and prescribers should evaluate and treat secondary infections as appropriate. Baloxavir marboxil has been studied in 910 patients (92% adults and 8% adolescents) from 2 clinical trials.³ Adverse events were generally mild and were overall more common in placebo groups. Incidence of adverse events in clinical trials for baloxavir marboxil is shown in **Table 2**. Less than 1% of patients were withdrawn from the trial due to adverse events, and severe adverse events were rare (n=2).² While adverse events were infrequent in clinical trials, patients with any chronic comorbid medical conditions (including but not limited to COPD, asthma, diabetes, heart disease, kidney and liver disease) were excluded from trials. Similarly, evidence in patients with more severe influenza symptoms requiring hospitalization is lacking.

Table 2. Common adverse effects in clinical trials of baloxavir marboxil.³

Adverse Event	Baloxavir marboxil (n=710)	Placebo (n=409)
Diarrhea	3%	5%
Bronchitis	2%	4%
Nausea	1%	1%

Nasopharyngitis	1%	1%
Headache	1%	2%

Post-marketing requirements for baloxavir marboxil include ongoing clinical trials to evaluate efficacy and safety in the following populations of patients: pediatric patients from birth to 12 years of age with acute uncomplicated influenza, hospitalized patients with severe influenza, and use as post-exposure prophylaxis in household contacts of infected individuals.³ Requirements for assessment of viral resistance includes clinical trials to evaluate the impact of known viral variants on susceptibility to baloxavir marboxil, evaluate risk of transmission of viral variants with reduced susceptibility to baloxavir marboxil (including patients treated for active influenza and those treated prophylactically), and annual reports to track ongoing emergence of resistance.³

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Symptom improvement
- 2) Morbidity
- 3) Mortality
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Time to alleviation of all 7 influenza symptoms (cough, sore throat, headache, nasal congestion, fever or chills, muscle or joint pain, fatigue for at least 21.5 hours)

Table 3. Pharmacology and Pharmacokinetic Properties.³

Parameter	
Mechanism of Action	Antiviral which inhibits endonuclease activity of the polymerase acidic protein in the RNA polymerase complex inhibiting viral gene transcription and viral replication
Oral Bioavailability	Co-administration with polyvalent cation-containing products including dairy products (eg, calcium, iron, magnesium, zinc) may decrease absorption and plasma concentrations of baloxavir marboxil
Distribution and Protein Binding	Volume of distribution = 1180 L, 93% protein binding
Elimination	80% feces
Half-Life	79.1 hours
Metabolism	Metabolism primarily by UGT1A3 and CYP3A4

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Hayden, 2018. ² Product Dossier ¹⁷ Phase 3, PC, DB, double-dummy, RCT	1. Baloxavir marboxil 40 mg for <80 kg or 80 mg for ≥80 kg 2. Oseltamivir 75 mg BID 3. Placebo Adults randomized 2:2:1 Adolescents (12-19 years) were randomized 2:1 to baloxavir marboxil or placebo Duration: 22 days	<u>Demographics:</u> - Median age: 32-35 years - Weight ≤80 kg: 82% - Current smoker: Baloxavir marboxil: 20% Oseltamivir: 27% Placebo: 24% - Symptom score: 13 - Administration within 24 hours: 52% - Influenza A (H3N2): 85-88% - Influenza vaccination: 24-26% <u>Key Inclusion Criteria:</u> - Adults 12-64 years of age with influenza-like illness - Fever ≥ 38C - ≥1 systemic symptom (headache, fever, chills, muscle/joint pain, fatigue) AND ≥1 respiratory symptom (cough, sore throat, nasal congestion) of moderate severity - Symptom duration ≤48 hours <u>Key Exclusion Criteria:</u> - Severe influenza requiring inpatient treatment or residents in long-term care facilities - Underlying conditions including chronic respiratory diseases; heart disease (except uncomplicated HTN); neurodevelopmental & neurological disorders; kidney, liver or metabolic disorders; compromised immune system - Pregnant or breastfeeding - Weight <40 kg or BMI≥40 - Concurrent antivirals, antibiotics, or other pharmacotherapies for symptom relief (except APAP)	<u>ITT:</u> 1. 612 2. 514 3. 310 <u>mITT (patients with confirmed influenza):</u> 1. 456 2. 377 3. 231 <u>Attrition:</u> 1. 34 (5.5%) 2. 16 (3.1%) 3. 20 (6.5%)	<u>Primary Endpoint:</u> All endpoints reported for the mITT population; oseltamivir group includes only adults Median time to alleviation of symptoms (all symptoms rated as absent or mild for at least 21.5 hours) 1. 53.7 hours 2. 53.8 hours 3. 80.2 hours 1 vs. 3: MD 26.5 hours (95% CI 17.8-35.8); p<0.001 1 vs. 2: NS <u>Clinical Secondary Endpoints:</u> Time to resolution of fever 1. 24.5 hours 2. NR 3. 42.0 hours 1 vs. 3: 17.5 hours; p<0.001 1 vs. 2: NS Time to return to usual health 1. 129.2 hours 2. 128.5 hours ¹⁷ 3. 168.8 hours 1 vs. 3: 39.6 hours; p=0.06 1 vs. 2: MD 0.6, p=0.717 ¹⁷ Complications requiring antibiotic use 1. 3.5% 2. 2.4% 3. 4.3% 1 vs. 3: NS 1 vs. 2: NS	NA for all	<u>Serious AE</u> 1. 2 (0%) 2. 0 (0%) 3. 0 (0%) <u>DC due to AE</u> 1. 2 (<1%) 2. 4 (<1%) 3. 2 (<1%) <u>Hospitalization</u> 1. 0 (0%) 2. 1 (0%) 3. 0 (0%)	NA for all	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> UNCLEAR; interactive response system used for randomization and allocation concealment. Baseline characteristics in mITT population were similar between baloxavir and placebo except current smokers were more common with placebo (24%) and oseltamivir (27%) compared to baloxavir (21%). Oseltamivir had a higher incidence of male (58% vs. 51-52%) and Japanese (80% vs. 75-76%) patients with influenza. <u>Performance Bias:</u> LOW; patients and providers blinded with matching placebo. <u>Detection Bias:</u> LOW; patients, providers, and data analysts blinded. <u>Attrition Bias:</u> LOW; Attrition was low and similar between groups (3-6%). In patients with missing data and those without alleviation of symptoms, analysis was based on last observed data. <u>Reporting Bias:</u> HIGH. The following pre-specified secondary clinical endpoints were not reported: time to alleviation of individual systemic or respiratory symptoms, quality of life, and data for oseltamivir (e.g., time to fever resolution). <u>Other Bias:</u> UNCLEAR. Funded by Shionogi who was involved in trial design, data collection and analysis. Applicability: <u>Patient:</u> Broad exclusion criteria limits applicability to patients with comorbid medical conditions <u>Intervention:</u> Oseltamivir was not administered to adolescents due to Japanese regulatory requirements surrounding neuropsychiatric adverse events for this population. Required visits occurred on days 1, 2, 3, 5, 9, 15, and 22. <u>Comparator:</u> Placebo and active comparator appropriate for efficacy & place in therapy. <u>Outcomes:</u> Symptoms self-assessed twice daily for first 9 days, axillary temperature assessed four times daily for the first 4 days. <u>Setting:</u> United States and Japan (72%) from December 2016 to March 2017

Abbreviations [alphabetical order]: AE = adverse events;; APAP = acetaminophen; ARR = absolute risk reduction; BID = twice daily; BMI = body mass index; CI = confidence interval; DC = discontinuation DB = double blind; HTN = hypertension; ITT = intention to treat; MD = median difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; PC = placebo controlled; RCT = randomized controlled trial

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Appendix 1: Current Preferred Drug List

<u>Generic</u>	<u>Brand</u>	<u>RouteDesc</u>	<u>FormDesc</u>	<u>PDL</u>
oseltamivir phosphate	OSELTAMIVIR PHOSPHATE	ORAL	CAPSULE	Y
oseltamivir phosphate	TAMIFLU	ORAL	CAPSULE	Y
oseltamivir phosphate	OSELTAMIVIR PHOSPHATE	ORAL	SUSP RECON	Y
oseltamivir phosphate	TAMIFLU	ORAL	SUSP RECON	Y
rimantadine HCl	FLUMADINE	ORAL	TABLET	N
rimantadine HCl	RIMANTADINE HCL	ORAL	TABLET	N
zanamivir	RELENZA	INHALATION	BLST W/DEV	N
peramivir/PF	RAPIVAB	INTRAVEN	VIAL	
baloxavir marboxil	XOFLUZA	ORAL	TABLET	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1946 to October Week 3 2018

1	exp Oseltamivir/	2648
2	exp Rimantadine/	551
3	exp Zanamivir/	966
4	peramivir.mp.	327
5	baloxavir.mp.	1
6	1 or 2 or 3 or 4 or 5	3690
7	limit 6 to (english language and humans)	2665
8	limit 7 to yr="2015 -Current"	430
9	limit 8 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	82

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XOFLUZA™ (baloxavir marboxil) tablets, for oral use
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

XOFLUZA™ is a polymerase acidic (PA) endonuclease inhibitor indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. (1)
Limitations of Use: Influenza viruses change over time, and factors such as the virus type or subtype, emergence of resistance, or changes in viral virulence could diminish the clinical benefit of antiviral drugs. Consider available information on drug susceptibility patterns for circulating influenza virus strains when deciding whether to use XOFLUZA. (1)

DOSAGE AND ADMINISTRATION

Take a single dose of XOFLUZA orally within 48 hours of symptom onset with or without food. Avoid co-administration of XOFLUZA with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc). The dose of XOFLUZA depends on weight. (2)

Patient Body Weight (kg)	Recommended Oral Dose
40 kg to less than 80 kg	Single dose of 40 mg
At least 80 kg	Single dose of 80 mg

DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg and 40 mg (3)

CONTRAINDICATIONS

XOFLUZA is contraindicated in patients with a history of hypersensitivity to baloxavir marboxil or any of its ingredients. (4)

WARNINGS AND PRECAUTIONS

Risk of Bacterial Infection: Serious bacterial infections may begin with influenza-like symptoms, may coexist with, or occur as a complication of influenza. XOFLUZA has not been shown to prevent such complications. Prescribers should be alert to potential secondary bacterial infections and treat them as appropriate. (5.1)

ADVERSE REACTIONS

Adverse events reported in at least 1% of adult and adolescent subjects treated with XOFLUZA included diarrhea (3%), bronchitis (2%), nasopharyngitis (1%), headache (1%) and nausea (1%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Avoid co-administration of XOFLUZA with polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc). (7.1)
- Live attenuated influenza vaccines may be affected by antivirals. (7.2)

USE IN SPECIFIC POPULATIONS

- Safety and efficacy in patients less than 12 years of age or weighing less than 40 kg have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2018

Appendix 4: Key Inclusion Criteria

Population	Patients with or at risk for influenza
Intervention	Drugs listed in Appendix 1
Comparator	Drugs listed in Appendix 1 or placebo
Outcomes	Symptom improvement (fever, cough, sore throat, muscle pain, malaise, etc) Quality of life Morbidity Mortality
Timing	Prevention or acute treatment within 48 hours of symptom onset
Setting	Outpatient

Appendix 5: Prior Authorization 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
- Oseltamivir therapy for greater than 5 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

1. What diagnosis is being treated?

Record ICD10 code.

Approval Criteria		
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?	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 PA • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee. 	Yes: Inform prescriber of covered alternatives in class and approve for length of therapy or 5 days, whichever is less.	No: Approve based on standard FDA dosing for influenza treatment Note: baloxavir and peramivir are FDA approved as a single dose for treatment of influenza.
5. Is the antiviral prescribed oseltamivir or zanamivir?	Yes: Go to #6	No: Pass to RPh. Deny; 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; 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: 1/18 (SS); 1/16; 1/12; 9/10
 Implementation: 4/1/18; 10/13/16; 2/12/16; 1/11