**Baloxavir Marboxil (Xofluza™; Genentech USA, Inc.)**

**Description**

Baloxavir is a polymerase acidic (PA) endonuclease inhibitor with antiviral activity against influenza virus A and B. Baloxavir inhibits the endonuclease activity of the polymerase acidic (PA) protein, an influenza virus-specific enzyme in the viral RNA polymerase complex required for viral gene transcription, resulting in inhibition of influenza virus replication.

**Indications for Use**

Baloxavir is an oral, single-dose regimen that is FDA-labeled for acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

Limitations of Use: The clinical benefit of antiviral drugs could be diminished due to factors such as the type of virus, emergence of resistance, or changes in viral virulence.

**Pharmacokinetics**

Baloxavir marboxil is a prodrug that is almost completely converted to its active metabolite, baloxavir, following oral administration.

Published pharmacokinetic parameters are based on Phase 3 trials.

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| **Doses** | **Cmax** | **AUC0-inf** |
| 40 mg | 96.4 ng/mL (45.9%)a | 6160 ng$∙$hr/mL (39.2%) a |
| 80 mg | 107 ng/mL (47.2%) a | 8009 ng·hr/mL (42.4%) a |

aGeometric mean (geometric CV%)

Absorption

* Tmax: 4 hours

Distribution

* Plasma protein binding: 92.9-93.9%
* Volume of Distribution: 1180 L

Elimination

* Major route of elimination: Metabolism
* Metabolic pathways: Primarily by UGT1A3 with minor contribution from CYP3A4
* Clearance (L/hr): 10.3 L/hr
* Elimination t/12: 79.1 hours
* Excretion: Urine (14.7%); Feces (80.1%)

**Contraindications**

History of hypersensitivity to baloxavir or any of its ingredients

**Warnings/Precautions**

Risk of bacterial infections

* No evidence for the efficacy of baloxavir in any illness other than influenza
* Serious bacterial infections can begin with influenza-like symptoms or coexist with/ occur as a complication of influenza; baloxavir has not been shown to prevent these complications
* Prescribers should be alert to possible secondary bacterial infections and treat appropriately

**Adverse Reactions**

The most common adverse reaction is diarrhea (~3%). Other adverse events reported in at least 1% of adult and adolescent subjects included: bronchitis (2%), nasopharyngitis (1%), headache (1%), and nausea (1%).

**Drug Interactions**

* Polyvalent cation-containing products: Co-administration with baloxavir may decrease plasma concentrations and reduce efficacy of baloxavir. Avoid co-administration of baloxavir with polyvalent cation containing antacids, laxatives, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc).
* Live attenuated influenza vaccine (LAIV): Concurrent use with baloxavir has not been evaluated. However, concurrent administration with antiviral medications may inhibit viral replication of LAIV and therefore decrease effectiveness of vaccination.

**Medication Safety**

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| **REMS (Risk Evaluation Mitigation Strategy) Requirement** | None |
| **Black Box Warning** | None |
| **ISMP Medication Safety Concerns** | None identified to date |
| **Hazardous Risk Assessment** | Not hazardous  |
| **Electronic Health Record Safety Assessment** | Inclusion of criteria for use/approval by ID.Caution with use in CrCl <50 mL/min; the effects of severe renal impairment have not been evaluated  |
| **Miscellaneous Safety Concerns** | None identified |

**Study Results - Table 1.**

Overall, studies demonstrate that baloxavir and safe and effective in the management of uncomplicated acute influenza. Baloxavir was found to have a shorter median time to alleviation of symptoms when compared to placebo and a similar time when compared to oseltamivir. Baloxavir was associated with significantly more rapid decline in infectious viral load, greater reduction in viral RNA loads, and shorter median duration of infectious virus detection than oseltamivir or placebo. An additional benefit of baloxavir is the single-dose regimen. However, these trials were performed exclusively in otherwise healthy outpatients with acute uncomplicated influenza. To date, studies do not support its routine use in serious infections requiring hospitalization. The potential role of baloxavir is in cases of neuraminidase (NA) inhibitor-resistant Influenza strains.

**Resistance**

* Amino acid substitutions 138T/M/F in the polyermase acidic (PA) protein of the viral RNA polymerase complex conferred decrease antiviral activity of baloxavir.
* Variant viruses with138T/M/F substitutions were detected in 2.2% of baloxavir recipients in the phase 2 trial (all with the influenza A(H1N1) pdm09 infection) and 9.7% of recipients in the phase 3 trial all with the influenza A(H3N2) infection). These substitutions were “sometimes in association withrebounds in viral titers and possibly prolongation of symptoms”.
	+ Infectious influenza virus detection
		- 7% (22 of 295) of baloxavir recipients without PA substitutions had infectious virus detected on day 5
			* 2% (5 of 288) had infectious virus detected on day 9
		- 91% (29 of 32) of baloxavir recipients with I38T/M substitutions had infectious virus detected on day 5
			* 17% (6 of 26) had infectious virus detected on day 9
		- 31% (27 of 87 patients) of placebo patients had had infectious virus detected on day 5
			* 6% (5 of 90) had infectious virus detected on day 9
	+ The median time to alleviation of symptoms was longer in baloxavir recipients with 138 T/M substitutions than those without variants (63.1 hours vs. 49.6 hours)
* Cross resistance between baloxavir and neuraminidase inhibitors (ie., oseltamivir) is not expected because these drugs target different viral proteins. Influenza virus may carry amino acid substitutions in PA that reduce susceptibility to baloxavir and at the same time carry resistance-associated substitutions for NA inhibitors, however, the clinical relevance of phenotypic cross-resistance evaluations has not been established.

**Dosage Forms and Strengths**

* Dosage form: tablet
* Dosage strengths: 20 mg and 40 mg

**Dosage and Administration**

* Administer within 2 days of influenza symptom onset
* Dosage (for patients >12 years of age with acute uncomplicated influenza):

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| **Patient Body Weight (kg)** | **Recommended Oral Dose** |
| 40 kg to <80 kg | Single dose of 40 mg |
| >80 kg | Single dose of 80 mg |

* Dosage adjustments:
* Renal impairment: no adjustment provided (has not been studied in creatinine clearance <50 mL/minute),
	+ Although not studied in CrCl <50 ml/min, only 14.7% of baloxavir is excreted through the urine and this is only a one-time dose. Therefore, no dosage adjustment would be recommended among patients with significant renal impairment.
* Hepatic impairment: no adjustment provided (has not been studied in severe impairment)
* Body weight: has a significant effect on the pharmacokinetics of baloxavir (as body weight increases, baloxavir exposure decreases). No clinically significant difference in exposure was observed between body weight groups when dosed according to the recommended weight-based dosing.
* Race/ethnicity: based on population pharmacokinetic analysis, baloxavir AUC exposure is approximately 35% lower in non-Asians when compared to Asians; however, this difference is not considered clinically significant
* Pregnancy:
* No available data on baloxavir use in pregnancy
* Pregnant women are at higher risk of severe complications from influenza
* Animal data: In animal reproduction studies, no adverse developmental effects were

observed in rats or rabbits with oral administration of baloxavir marboxil at exposures approximately 5 (rats)

and 7 (rabbits) times the systemic baloxavir exposure at the maximum recommended human dose

* Although not preferred, if benefit outweighs the risk of using baloxavir in pregnancy, use may be considered.
* Nursing mothers:
* No data on the presence of baloxavir in human milk, the effects on the breastfed infant, or the effects on milk production
* Animal data: In a lactation study, baloxavir and its related metabolites were excreted in the milk of lactating rats administered baloxavir with peak milk concentration approximately 5 times that of maternal plasma concentrations occurring 2 hours post-dose. No effects of baloxavir on growth and postnatal development were observed in nursing pups at the highest oral dose tested in rats. Maternal systemic exposure was approximately 5 times the baloxavir exposure in humans at the maximum recommended human dose.
* Although not preferred, if benefit outweighs the risk of using baloxavir in nursing mothers, use may be considered.
* Pediatric use:
* Safety and effectiveness of baloxavir for the treatment of influenza have been established in pediatric patients >12 years of age weighing >40 kg
* Adverse reactions reported in adolescents were similar to those reported in adults
* Geriatric use:
* Clinical trials did not include patients >65 years
* Administration:
* PO as a single dose without regard for food
* Avoid co-administration with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc)
	+ Due to lack of specific instructions in the package insert, we recommend administering baloxavir 2 hours before or 4 hours after administration of polyvalent cations, which is aligned with other medications with similar drug interactions.

**Availability and Cost**

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|  | Usual Dose\* | UMHS Cost/Unit | UMHS Cost/Day | UMHS Cost\*/Course | AWP Cost/Unit | AWP Cost/Day | AWP Cost/Course |
| Baloxavir 40 mg tablet | 40 mg if <80 kg80 mg if >80 kg | $68.98 a$137.96 b | $68.98 a$137.96 b | $68.98 a$137.96b | $90 a$180b | $90 a$180b | $90 a$180b |
| Oseltamivir 75 mg capsule | 75 mg po bid x 5 days | $9.38 | $18.76 | $93.80 | $10.20 | $20.40 | $102.01  |
| Peramivir 200 mg vial | 600 mg x 1 (uncomplicated) | $311.92 | $935.76 | $935.76 | $380.00 | $1140 | $1140 |
| Zanamavir inhaler | 10 mg INH daily x10 days | $54.27 | $54.27 | $54.27 | $59.00 | $59.00 | $59.00 |

a price for 40 mg tablet

b price for two 40 mg tablets (total 80 mg dose)

**Summary**

* Baloxavir is a convenient single-dose regimen for the treatment of uncomplicated influenza which costs $68.98 for a treatment course for patients weighing <80 kg and $137.96 for a treatment course for patients weighing >80 kg.
* Baloxavir demonstrated similar efficacy with regard to time to alleviation of symptoms and had a similar tolerability profile compared to oseltamivir.
* Baloxavir has only been studied for uncomplicated influenza in the outpatient setting, and has not been studied in the inpatient setting or among critically-ill patients.
* Baloxavir may be administered with or without food, however, co-administration with polyvalent cations should be avoided due to the formation of a chelate which can significantly decrease baloxavir exposure. There is no information provided to determine whether or not baloxavir can be crushed.
* The emergence of polyermase acidic protein variants with138T/M/F substitutions conferring reduced susceptibility to baloxavir were detected in 2.2% of baloxavir recipients in the phase 2 trial and 9.7% of recipients in the phase 3 trial. These substitutions were sometimes associated withrebounds in viral titers and prolongation of symptoms.
* In terms of neuraminidase inhibitor resistance, based on CDC data for the 2017-2018 influenza season, the majority of the tested influenza viruses showed susceptibility to the neuraminidase inhibitors (i.e., oseltamivir, zanamivir, or peramivir). 11 (1.0%) A(H1N1)pdm09 viruses were resistant to both oseltamivir and peramivir, but were sensitive to zanamivir.

**Recommendation**

Baloxavir marboxil should be approved for formulary use, however, it should be reserved only for patients with the following use criteria due to concern for the development of resistance seen in phase 2 and 3 clinical trials and lack of clinical efficacy data in hospitalized and critically ill patients in the ICU with influenza.

**Criteria for use:**

**Inpatients**

* Patients > 12 years of age who have been symptomatic for < 48 hours with neuraminidase inhibitor-resistant strains.
* ID consult is required prior to use and will be added as a restricted Tier 1 antimicrobial agent.

**Outpatients and Emergency Department**

* Oseltamivir is preferred for the treatment of influenza A and B. Zanamavir is the preferred alternative to oseltamivir.
* Baloxavir should be reserved for patients > 12 years of age who have been symptomatic for < 48 hours with intolerance to oseltamivir (i.e. neuropsychiatric adverse events) or significant compliance concerns with oseltamivir, but should not be routinely used due to low barrier to resistance.

**References**

1. Baloxavir [package insert]. Osaka, Japan: Shionogi & Co., Ltd. 2018.
2. Oseltamivir [package insert]. San Francisco, CA: Genentech, Inc. 1999.
3. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. *N Engl J Med*. 2018;379(10):913-923.
4. Centers for Disease Control and Prevention. (2018). Influenza Antiviral Drug Resistance. Retrieved from https://www.cdc.gov/flu/about/qa/antiviralresistance.htm

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**Table 1: Clinical Studies of Baloxavir for the Treatment of Influenza Virus Infection**

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|  | **CAPSTONE-1 Phase 2 Trial** | **CAPSTONE-1 Phase 3 Trial** |
| **Design** | Phase 2, double-blind, placebo-controlled, dose-ranging,randomized trial | Phase 3, double-blind, placebo- and oseltamivir-controlled,randomized trial |
| **Drug and Comparator** | Baloxavir vs. Placebo | Baloxavir vs. Oseltamivir vs. Placebo |
| **Population** | * Treatment of acute uncomplicated influenza in otherwise healthy outpatients (Japanese adults 20-64 years of age)
* Intervention:
* Baloxavir (n=400)
* 10 mg (n=100)
* 20 mg (n=100)
* 40 mg (n=100)
* Placebo (n=100)
* Total treatment duration: single dose
* Median age: 36-38 years
* Male gender: 58-68%
* Race: Asian 99-100%
* Inclusion criteria: fever (temperature ≥38.0°C), ≥1 systemic symptom and ≥1 respiratory symptom of at least moderate severity, symptom duration <48 hours, and a positive rapid antigen test
 | * Treatment of acute uncomplicated influenza in otherwise healthy outpatients (patients in the United States and Japan 12-64 years of age)
* Intervention:
* Baloxavir (n=456)
* 40 mg for patients weighing <80 kg
* 80 mg for patients weighing ≥80 kg
* Oseltamivir 75 mg PO BID (n=377)
* Placebo (n=231)
* Treatment duration: 5 days (baloxavir group received a single dose, followed by placebo)
* Median age: 32-35 years
* Weight < 80 kg: 81.2-81.4%
* Male gender: 50-58%
* Regions: Japan (75-81%), United States (19-25%)
* Inclusion criteria: fever (temperature ≥38.0°C), ≥1 systemic symptom and ≥1 respiratory symptom of at least moderate severity, symptom duration <48 hours
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| **Endpoints** | * **Primary efficacy endpoint:** time to alleviation of symptoms (defined as the time from the start of the trial regimen to the time when all influenza-related symptoms were rated by the patient as absent/mild for ≥21.5 hours)
* **Secondary endpoints:** time to resolution of fever, return to usual health, and newly occurring complications leading to antibiotic use
* **Virologic endpoints:** changes from baseline in infectious virus and viral RNA titers, duration of virus detection, and frequency of emergence of amino acid changes associated with reduced susceptibility to baloxavir
* **Safety endpoints:** frequency and severity of adverse events
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| **Results** |

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| **Group** | **Time (Hours)** | **P-value** |
| Baloxavir 10 mg 20 mg 40 mg | 54.25149.5 | 0.0090.020.005 |
| Placebo | 77.7 |

* **Primary endpoint:** Median Time to Alleviation of Symptoms
* **Viral endpoints**:
	+ All baloxavir groups had significantly greater reductions in influenza virus titers on days 2 and 3 when compared to the placebo group
	+ Amino acid substitutions: 4/182 baloxavir recipients (2.2%) had post-treatment viruses with amino acid substitutions that confer reductions in susceptibility to baloxavir
* **Safety endpoints**: Adverse events
* Reported in 23-27% of patients in the baloxavir groups and 29% in the placebo group, with no important differences in rates of specific events
* No adverse events leading to withdrawal from the trial and no serious adverse events occurred
 | * **Primary endpoint**: Median time to alleviation of symptoms
* Baloxavir: 53.5 hours (95% CI: 48.0, 58.5)
* Oseltamivir: 53.8 hours (95% CI: 50.2, 56.4)
* Placebo: 80.2 hours
* Difference in time was greater in patients who initiated the regimen within 24 hours after symptom onset (median difference, 32.8 hours; P<0.001) than those who initiated it later (median difference, 13.2 hours; P=0.008)
* **Secondary endpoints** (baloxavir vs. placebo)
	+ Median time to resolution of fever was shorter with baloxavir than with placebo (24.5 hours vs. 42.0 hours, P<0.001)
	+ Median time to return to usual health was 129.2 hours in the baloxavir group and 168.8 hours in the placebo group (P=0.06)
	+ The frequency of complications that resulted in antibiotic treatment was low (3.5% with baloxavir, 4.3% with placebo, and 2.4% with oseltamivir)
* **Viral endpoints**:
	+ Baloxavir was associated with significantly more rapid decline in infectious viral load, greater reduction in viral RNA loads, and shorter median duration of infectious virus detection than oseltamivir or placebo
	+ Amino acid substitutions: detected after initiation of the trial regimen in 9.7% of baloxavir recipients
* **Safety endpoints**: Adverse events
* Reported in 20.7% of baloxavir recipients, 24.6% of placebo recipients, and 24.8% of oseltamivir recipients
* Adverse events associated with cessation of the trial regimen occurred in 0.3-0.4% of patients across the groups
* Two serious adverse events occurred in baloxavir recipients (incarcerated inguinal hernia and aseptic meningitis) but neither considered to be related to trial regimen
* No deaths occurred during the trial, but there was one hospitalization (in the oseltamivir group)
 |