Baloxavir Marboxil

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Abstract

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Keywords

Formulary Management/P & T, Infectious Diseases, Drug Information

Generic Name: Baloxavir Marboxil

Proprietary Name: *Xofluza* (Genentech)

Approval Rating: 1P

Therapeutic Class: Cap-Dependent Endonuclease Protein Inhibitors

Similar Drugs: Oseltamivir

Sound-/Look-Alike Names: *Xolair*

Indications

Baloxavir marboxil is approved by the Food and Drug Administration (FDA) 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.^{1,2}

Clinical Pharmacology

Baloxavir, derived from the prodrug baloxavir marboxil, is a cap-dependent endonuclease protein inhibitor within the polymerase acidic protein (PA) subunit of influenza A and B viruses. It blocks influenza virus replication by inhibiting the initiation of mRNA synthesis. Baloxavir is effective against influenza type A and B viruses, including oseltamivir-resistant strains and avian strains (H7N9, H5N1).²⁻⁷

Pharmacokinetics

Baloxavir marboxil is metabolized to the active form (baloxavir acid).^{7,8} Median time to peak plasma concentration (C_{max}) is 4 hours.^{2,7} Administration with food decreases

systematic exposure to baloxavir (48% decrease in C_{max} and 36% decrease in area under the curve [AUC]).²

C_{max} and AUC increase in a dose-proportional manner (dose range, 6–80 mg), and mean half-life of baloxavir acid is 79.1 hours.^{2,7,8} Baloxavir acid is highly protein bound (93%–94%). The metabolic pathways include UGT1A3 and CYP3A4. Following a single dose of radiolabeled baloxavir 40 mg in healthy participants, 80% of the drug was recovered in the feces and 15% in the urine.²

No clinically significant differences were observed based on age (adolescents vs adults), race/ethnicity, or gender. Population pharmacokinetic analysis showed no clinically meaningful effects of renal function on baloxavir pharmacokinetics in patients with creatinine clearance 50 mL/min or greater; severe renal impairment has not been evaluated. Moderate hepatic impairment (Child-Pugh class B) did not result in clinically meaningful changes, and effects of severe hepatic impairment have not been evaluated. Body weight significantly affected baloxavir exposure; increased weight was associated with decreased baloxavir exposures, leading to weight-based dosing recommendations.²

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Comparative Efficacy

Indication: Influenza

Guidelines

Guideline: Influenza antiviral medications: Summary for clinicians

Reference: Centers for Disease Control and Prevention, 2018⁹

Comments: Approved antiviral agents for the treatment of influenza include neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir) and adamantanes (amantadine and rimantadine). Neuraminidase inhibitors are effective against both influenza A and B viruses, while adamantanes are only effective against influenza A. Viral resistance can be a problem with these antivirals. Antiviral therapy, if needed, should be initiated as early as possible 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.

Studies

Drug: Baloxavir vs Oseltamivir vs Placebo

Reference: Hayden GF, et al, 2018 (CAPSTONE-1 study)^{3,10-12}

Study Design: Phase 3, randomized, double-blind, multicenter, placebo- and active-controlled study

Study Funding: Shionogi

Patients: A total of 1436 patients (12-64 years of age) with fever (axillary temperature, 38°C [100.4°F] or higher), one or more general symptoms and one or more respiratory symptoms (moderate to severe), and within 48 hours from symptom onset. Exclusion criteria included pregnancy or within 2 weeks postpartum; resident of long-term care facility (eg, welfare facility for the elderly, nursing home); chronic respiratory diseases, including bronchial asthma; neurological and neurodevelopmental disorders, including disorders of the brain, spinal cord, peripheral nerve, and muscle (eg, cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, spinal cord injury); heart disease (eg, congenital heart disease, congestive heart failure, coronary artery disease), excluding hypertension without other heart-related symptoms; American Indian and Alaskan native ethnicity; blood disorders (such as sickle cell disease); endocrine disorders (including diabetes mellitus); kidney, liver, or metabolic disorders; compromised immune system (including patients receiving immunosuppressant therapy, or those with cancer or HIV infection); and morbid obesity (body mass index [BMI] of 40 or higher) or weight less than 40 kg.

Intervention: Patients were randomized to a single oral dose of baloxavir marboxil (either 40 mg or 80 mg), oseltamivir 75 mg twice daily for 5 days, or placebo. Patients

between 12 and 19 years of age were randomized to either a single oral dose of baloxavir marboxil (40 mg or 80 mg) or placebo. Patients receiving baloxavir marboxil received oseltamivir placebo capsules on days 1 to 5, while patients receiving oseltamivir received baloxavir marboxil placebo tablets on day 1.

Results

Primary End Point(s)

- Median time to alleviation in influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, fatigue):
- Intention-to-treat (ITT)–infected cohort: 53.7 hours with baloxavir marboxil and 80.2 hours with placebo ($P < .001$); median treatment difference was 26.5 hours (95% confidence interval [CI], 17.8-35.8).
- ITT population: 65.4 hours with baloxavir marboxil and 88.6 hours with placebo ($P < .001$); median treatment difference was 23.2 hours (95% CI, 34.2-14).
- A shorter time to alleviation of symptoms was observed with baloxavir than with placebo in both adolescents (median difference, 38.6 hours; $P = .006$) and adults (median difference, 25.6 hours; $P < .001$).
- Median time to alleviation of influenza symptoms was 53.5 hours with baloxavir marboxil and 53.8 hours with oseltamivir ($P = .756$).

Secondary End Point(s)

- Difference in the time to alleviation of symptoms between the baloxavir group and the placebo group was greater in patients who initiated the trial regimen within 24 hours after symptom onset (median difference, 32.8 hours; $P < .001$) than in those who initiated it later (median difference, 13.2 hours; $P = .008$).
- Median duration of fever was 24.5 hours with baloxavir marboxil and 42 hours with placebo ($P < .001$).
- Median duration of fever was 24.4 hours with baloxavir marboxil and 24 hours with oseltamivir ($P = .9225$).
- Levels of virus in the nose and throat were reduced starting at 24 hours through 120 hours with baloxavir marboxil compared with placebo.
- Levels of virus in the nose and throat were reduced at 24 hours and 72 hours with baloxavir marboxil compared with oseltamivir.
- Median time to viral shedding was 24 hours with baloxavir marboxil ($P < .001$ vs placebo), 72 hours with oseltamivir ($P < .0001$ vs baloxavir marboxil), and 96 hours with placebo.

Comments: The study was conducted in the United States and Japan. Results are similar to those observed in a phase 2 proof-of-concept study.^{5,7}

Limitations: The efficacy evaluation was conducted over one flu season. Efficacy over several flu seasons remains to be established.

Reference: Shionogi 2018 (CAPSTONE-2 study)^{6,13,14}

Study Design: Phase 3, randomized, double-blind, multicenter study

Study Funding: Shionogi

Patients: A total of 2184 patients 12 years and older with a high risk of complication from influenza (eg, asthma, chronic lung disease, endocrine disorders, heart disease, metabolic disorders, morbid obesity, elderly). Exclusion criteria included severe influenza virus infection requiring inpatient treatment; known allergy to oseltamivir; weight of 40 kg or less; pregnancy, breastfeeding, or positive pregnancy test at the predose examination; concurrent infections at predose examination requiring systemic antimicrobial therapy; liver disease associated with hepatic impairment; cancer within the last 5 years (unless nonmelanoma skin cancer); untreated HIV infection or treated HIV infection with a CD4 count below 350 cells/mm³ in the last 6 months; immunosuppression following organ or bone marrow transplant; dose of chronic systemic corticosteroids exceeding prednisolone 20 mg or equivalent; treatment with peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir, or amantadine within 30 days prior to predose examination; use of an investigational monoclonal antibody for a viral disease in the last year; and creatinine clearance of 60 mL/min or less.

Intervention: Patients were randomized to a single oral dose of baloxavir marboxil (either 40 mg or 80 mg), oseltamivir 75 mg twice daily for 5 days, or placebo. Patients receiving baloxavir marboxil received oseltamivir placebo capsules on days 1 to 5, while patients receiving oseltamivir received baloxavir marboxil placebo tablets on day 1.

Results

Primary End Point(s)

- Median time to improvement of influenza symptoms was 73.2 hours with baloxavir marboxil ($P < .001$ vs placebo), 81 hours with oseltamivir ($P = .8347$ vs baloxavir marboxil), and 102.3 hours with placebo.
- *Secondary End Point(s)*
- Median time to viral shedding was 48 hours with baloxavir marboxil ($P < .001$ vs placebo), 96 hours with oseltamivir ($P < .001$), and 96 hours with placebo.
- Use of antibiotics for infections secondary to influenza infection was reduced with baloxavir marboxil compared with placebo (3.4% vs 7.5%; $P = .01$).
- Incidence of influenza-related complications was 2.8% with baloxavir marboxil, 4.6% with oseltamivir, and 10.4% with placebo.

Comments: Study centers were located in Australia, Belgium, Bulgaria, Germany, Hungary, Japan, the Republic of Korea, Latvia, New Zealand, the Philippines, Poland,

Romania, South Africa, Spain, Taiwan, the United Kingdom, and the United States.

Limitations: Published information is limited to press releases and an abstract.¹⁵

Contraindications, Warnings, and Precautions

Contraindications

Baloxavir marboxil is contraindicated in patients with a history of hypersensitivity to baloxavir marboxil or any of its inactive ingredients (croscarmellose sodium, hypromellose, lactose monohydrate, microcrystalline cellulose, povidone, sodium stearyl fumarate, talc, and titanium dioxide).²

Warnings and Precautions

Baloxavir marboxil is ineffective against bacterial infections. Serious bacterial infections may begin with influenza-like symptoms, or may coexist with or occur as a complication of influenza.²

There are no adequate and well-controlled studies of baloxavir marboxil in pregnant women; however, an influenza infection during pregnancy increases the risk of adverse pregnancy and/or fetal outcomes, including maternal death, stillbirth, birth defects, preterm delivery, low birth weight, and small for gestational age.²

No studies have been conducted to assess the presence of baloxavir marboxil in human milk or its effects on breastfeeding infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for baloxavir marboxil and any potential adverse effects on the breastfed infant from the drug or underlying maternal condition.²

Clinical trials of baloxavir marboxil did not include participants 65 years of age and older to determine whether they respond differently than younger participants.²

Safety and efficacy of baloxavir marboxil have not been established in pediatric patients younger than 12 years.²

Adverse Reactions

The common adverse reactions related to baloxavir marboxil therapy in clinical trials included diarrhea (3%), bronchitis (2%), nasopharyngitis (1%), headache (1%), and nausea (1%).²

Drug Interactions

Coadministration with polyvalent cation-containing products may decrease plasma concentrations of baloxavir, which may reduce baloxavir marboxil efficacy. Avoid coadministration of baloxavir marboxil with polyvalent cation-containing laxatives, antacids, or oral supplements (eg, calcium, iron, magnesium, selenium, zinc).²

The concurrent use of baloxavir marboxil with intranasal live attenuated influenza vaccine (LAIV) has not been evaluated. Coadministration of antiviral drugs may inhibit viral replication of LAIV and thereby decrease the effectiveness of LAIV vaccination. Interactions between inactivated influenza vaccines and baloxavir marboxil have not been evaluated.² The prescribing information for intranasal LAIV states that antiviral drugs active against influenza A and/or B viruses may reduce the effectiveness of LAIV if administered within 48 hours before or within 2 weeks after vaccination; if antiviral agents and LAIV are coadministered, revaccination should be considered when appropriate.¹⁶

In vitro data suggest that baloxavir marboxil in combination with oseltamivir (and other neuraminidase inhibitors) synergistically inhibits replication of influenza A/H1N1 virus; the clinical importance and utility of this possible interaction remains to be established.^{17,18}

Recommended Monitoring

Monitor for potential secondary bacterial infections.²

Dosing

Baloxavir marboxil is for oral, single-dose administration, with or without food, within 48 hours of influenza symptom onset. The recommended dosing for patients 12 years and older is weight dependent: For individuals weighing 40 kg to less than 80 kg, a single dose of 40 mg is recommended; for those weighing 80 kg or more, a single dose of 80 mg is recommended.²

Administration with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (eg, calcium, iron, magnesium, selenium, zinc) should be avoided.²

Product Availability

Baloxavir marboxil was granted priority review status by the FDA in June 2018.^{3,6} The Prescription Drug User Fee Act date was December 24, 2018.^{3,6} Baloxavir marboxil was approved by the FDA on October 24, 2018.¹

Xofluza is available as 20 mg and 40 mg tablets in blister cards. The 20 mg tablets are supplied as either two 20 mg tablets per blister card or four 20 mg tablets per blister card. The 40 mg tablets are supplied as either one 40 mg tablet per blister card or two 40 mg tablets per blister card.²

The blister card should be stored at 20°C to 25°C (68°F–77°F); excursions are permitted to 15°C to 30°C (59°F–86°F).²

Drug Safety/Risk Evaluation and Mitigation Strategy (REMS)

No REMS is required for baloxavir marboxil.¹

Conclusion

Baloxavir marboxil is FDA-approved for the treatment of acute, uncomplicated influenza in patients 12 years and older who have been symptomatic for no more than 48 hours. Baloxavir marboxil has a different mechanism of action than previously marketed drugs for the treatment of influenza. It is given as a single oral dose within 48 hours of symptom onset. Viral shedding decreases within 24 hours of administration.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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