PDL DRUG REVIEW

Proprietary Name: Xofluza®
Common Name: baloxavir marboxil
PDL Category: Influenza Agents

Comparable Products	Preferred Drug List Status
Tamiflu	Preferred

Summary

Pharmacology/Usage: Baloxavir marboxil, the active ingredient of Xofluza®, is an antiviral drug with activity against influenza virus. Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir, the active form that exerts anti-influenza virus activity. Baloxavir inhibits the endonuclease activity of the polymerase acidic (PA) protein, an influenza virus-specific enzyme in the viral RNA polymerase complex needed for viral gene transcription, resulting in inhibition of influenza virus replication.

Indication: 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.

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®.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. There are risks to the mother and fetus associated with influenza virus infection in pregnancy. Pregnant women are at higher risk of severe complications from influenza, which may lead to adverse pregnancy and/or fetal outcomes including maternal death, stillbirth, birth defects, preterm delivery, low birth weight and small for gestational age. The safety and efficacy of use in the pediatric population below the age of 12 years have not been established.

Dosage Forms: Film-Coated Tablets: 20mg, 40mg

Recommended Dosage: Start treatment within 48 hours of influenza symptom onset. Take as a single dose with or without food; however, 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) should be avoided.

The recommended dose is a single weight-based dose, as follows:

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

Drug Interactions: Avoid co-administration of Xofluza® with polyvalent cation-containing laxatives, antacids, or oral supplements (e.g. calcium, iron, magnesium, selenium, or zinc).

The concurrent use of Xofluza® with intranasal live attenuated influenza vaccine (LAIV) has not been evaluated. Concurrent use of antiviral drugs may inhibit viral replication of LAIV and thus decrease the effectiveness of LAIV vaccination. Interactions between inactivated influenza vaccines and Xofluza® have not been evaluated.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Xofluza®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events included diarrhea (0%), bronchitis (0%), nausea (0%), nasopharyngitis (0%), and headache (0%).

There is no evidence of efficacy of Xofluza® in any illness caused by pathogens other than influenza virus. Serious bacterial infections may begin with influenza-like symptoms, may co-exist 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.

Contraindications: History of hypersensitivity to baloxavir marboxil or any of its ingredients

Manufacturer: Genentech USA, Inc. A member of the Roche Group

Analysis: There were 2 randomized controlled double-blind studies in 2 different influenza seasons that assessed the safety and efficacy of Xofluza® in otherwise healthy subjects with acute uncomplicated influenza.

Study 1 was a placebo-controlled phase 2 dose-finding trial that included adults 20 to 64 years in Japan (N=400) who took a single dose of Xofluza® as compared with placebo. All subjects were Asian, and most were male (62%). Among subjects who received Xofluza® and had influenza virus typed, influenza A/H1N1 was the predominant strain (63%), followed by influenza B (25%), and influenza A/H3N2 (12%).

Study 2 was a phase 3 active- and placebo-controlled study that included subjects 12 to 64 years of age weighing at least 40kg in the US and Japan (N=1436). Adults 20 to 64 years of age received Xofluza® or placebo as a single oral dose on day 1 or oseltamivir BID for 5 days. Subjects in the Xofluza® and placebo groups received a placebo for the duration of the oseltamivir dosing after Xofluza® or placebo dosing. Adolescents aged 12 to less than 20 years received Xofluza® or placebo as a single oral dose. In this trial, 78% were Asian, 17% were White, and 54% were male. Among subjects who received Xofluza® and had influenza virus typed, influenza A/H3N2 was the predominant strain (90%), followed by influenza B (9%), and influenza A/H1N1 (2%).

In both trials, subjects had an axillary temperature of at least 38° C, at least one moderate or severe respiratory symptom (cough, nasal congestion, or sore throat), and at least one moderate or severe systemic symptom (headache, feverishness or chills, muscle or joint pain, or fatigue) and all were treated within 48 hours of symptoms onset. The primary efficacy population was defined as those with a positive rapid influenza diagnostic test (Study 1) or positive influenza RT-PCR (Study 2) at study entry. The primary endpoint of both trials was the time to alleviation of symptoms, defined as the time when all seven symptoms (cough, sore throat, nasal congestion, headache, feverishness, myalgia, and fatigue) had been assessed by the subject as none or mild for a duration of at least 21.5 hours.

Results suggested that in both trials, Xofluza® treatment at the recommended dose resulted in a statistically significant shorter time to alleviation of symptoms as compared with placebo in the primary efficacy population. In study 1, note that differences were statistically significant using the Gehan-Breslow's generalized Wilcoxon test ($p=0.014$), but the primary analysis using the Cox Proportional Hazards Model did not reach statistical significance ($p=0.165$). In study 2, statistical significance was seen using the Peto-Prentice's generalized Wilcoxon test ($p<0.001$). Results can be seen in the table below, which was adapted from the prescribing information.

Time to alleviation of symptoms after single dose in adults with acute uncomplicated influenza in Study 1	Xofluza® 40mg (N=100)	Placebo (N=100)
Adults (20 to 64 years of age)	50 hours	78 hours

Time to alleviation of symptoms after single dose in adults with acute uncomplicated influenza in Study 1	Xofluza® 40mg (N=100)	Placebo (N=100)
p-value (per the Gehan-Breslow's generalized Wilcoxon test)	0.014	

Time to alleviation of symptoms after single dose in subjects ≥12 years of age with acute uncomplicated influenza in Study 2	Xofluza® 40mg or 80mg (N=455)	Placebo (N=230)
Subjects (≥12 years of age)	54 hours	80 hours
p-value (per the Peto-Prentice's generalized Wilcoxon test)	<0.001	

In Study 2, there was no difference in the time to alleviation of symptoms between subjects who received Xofluza® (54 hours) and those who received oseltamivir (54 hours).

For adolescent subjects (12 to 17 years of age) in Study 2, the median time to alleviation of symptoms for subjects who received Xofluza® (N=63) was 54 hours compared to 93 hours in the placebo arm (N=27).

The number of subjects who received Xofluza® at the recommended dose and who were infected with influenza type B virus was limited, including 24 subjects in Study 1 and 38 subjects in Study 2. In the influenza B subset in Study 1, the median time to alleviation of symptoms in subjects who received 40mg Xofluza® was 63 hours compared to 83 hours in subjects who received placebo. In the influenza B subset in Study 2, the median time to alleviation of symptoms in subjects who received 40mg or 80mg Xofluza® was 93 hours compared to 77 hours in subjects who received placebo.

Place in Therapy: Xofluza® is an oral, single-dose tablet 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. Limitations of use include that 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®. (Influenza A and B viruses with treatment-emergent amino acid substitutions at positions associated with reduced susceptibility to baloxavir in cell culture were seen in clinical trials. The overall incidence of treatment-emergent amino acid substitutions associated with reduced susceptibility to baloxavir in studies 1 and 2 was 2.7% and 11%, respectively. Prescribers should consider currently available surveillance information on influenza virus drug susceptibility patterns and treatment effects when deciding whether to use Xofluza®.)

In clinical trials compared with placebo, Xofluza® resulted in statistically significant shorter time to alleviation of symptoms as compared with placebo. In one trial with oseltamivir as an active comparator, there were no differences in the time to alleviation of symptoms between subjects who received Xofluza® and those who received oseltamivir. Oseltamivir (Tamiflu®) is indicated for the treatment of acute uncomplicated illness due to influenza A and B infection in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours. When used for treatment of influenza, it must be taken twice daily for 5 days. It is also indicated for prophylaxis of influenza A and B and is available as a generic.

There is no evidence at this time to support that Xofluza® is safer or more effective than the currently available, more cost-effective medications, including oseltamivir. Oseltamivir is indicated for use as treatment in patients 2 weeks of age and older. It is therefore recommended that Xofluza® remain non-preferred and require prior authorization and be available to those who are unable to tolerate preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Xofluza [package insert]. South San Francisco, CA: Genentech USA Inc, A member of the Roche Group; 2018.
[2] Tamiflu [package insert]. South San Francisco, CA: Genentech USA Inc, A member of the Roche Group; 2018.