Brand Name: Xofluza

Generic Name: Baloxavir marboxil

Manufacturer[1]: Genetech USA, INC

Drug Class[2,3,4,5]: Anti-infective agent; Antiviral Agent; Endonuclease inhibitor

Uses:

Labeled Uses[1,2,3,4,5]: Treats acute uncomplicated influenza in patients ≥ 12-years-old who have been symptomatic for less than 48 hours

Unlabeled Uses: N/A

Mechanism of Action[1,2,3,4,5]:

Baloxavir marboxil is an oral prodrug that is converted to baloxavir, which is the active compound. Baloxavir inhibits endonuclease activity of polymerase acidic protein. This protein plays a prominent role in influenza virus replication; inhibiting the protein suppresses viral replication of influenza.

Pharmacokinetics[1,3,4,5]:

Absorption:

T_{max}	4 hrs
V_d	1,180 L
$t_{½}$	79.1 hrs
Clearance	10.3 L/hr
Protein binding	~93-94%
Bioavailability	N/A

Metabolism: Baloxavir marboxil is converted to the active metabolite, baloxavir, via UGT1A3 (major) and CYP3A4 (minor).

Elimination: Urine (14.7%, 3.3% (Baloxavir)); Feces (80.1%)

Efficacy:

Koshimichi H, Ishibashi T, Kawaguchi N, Sato C, Kawasaki A, Wajima T. Safety, Tolerability, and Pharmacokinetics of the Novel Anti-influenza Agent Baloxavir Marboxil in Healthy Adults: Phase I Study Findings. Clin Drug Investig. 2018 Dec;38(12):1189-1196.

Study Design: Randomized, placebo-controlled, double-blind single center study

Description of Study:

Methods: Forty healthy male participants were randomized to receive a single dose of baloxavir marboxil (either 6, 20, 40, 60, or 80 mg) or placebo in the form of a 20 mL oral suspension after fasting for greater than or equal to 10 hours. There were six participants for each dose given (6 mg [n=6], 20 mg [n=6], 40 mg [n=6], 60 mg [n=6], 80 mg [n=6]). Ten participants were in the placebo group. Participants were administered the study drug (day 1) and then were observed at the study center for 3 additional days before discharged (day 4). Participants received post-treatment observation (day 6) and a follow-up visit (day 8). Those who received 60 mg or 80 mg of baloxavir marboxil would receive an additional follow-up visit (day 15). Adverse events were monitored for all participants throughout the study.

Outcome Results: One participant in the 6-mg dose group reported experiencing a headache that was mild in severity and resolved without any treatment. Plasma baloxavir marboxil concentrations were very low (maximum 0.363 ng/mL, quantification limit <0.100 ng/mL) and baloxavir marboxil was rapidly eliminated from the plasma in all of the participants. Plasma baloxavir acid concentrations increased with increasing the dose of baloxavir marboxil. Baloxavir acid exposure measures essentially showed a dose-proportional increases in the fasted state, with C_{max} generally attained within 3.5 hours after dosing. The half-life ranged from 49-91 hours, while renal excretion was minimal.

Limitations: All of the participants were Japanese males, within the normal BMI range of 20-25, and were within a 23-30 age range. The demographics of the twelve individuals who participated in the study lacked diversity thus lacking the ability to extrapolate the results to the general population. Additionally, the sample size was small. The study was performed at a single study center, which also shows the lack of diversity. In addition, it was unclear how investigators treated patients or what participants were able to do while under observation, which could potentially lead to some bias.

Conclusion: The results of this study showed that based on the limited adverse effects of baloxavir marboxil – only one patient experienced a headache in the 6 mg dose group – that all doses of baloxavir marboxil were tolerable in the patients. Pharmacokinetic studies revealed dose-proportional increases in plasma concentrations, the Cmax was 3.5 hours, and the half-life was 49-91 hours. The long half-life supports single oral dosing. Further studies should be performed in a larger group of participants to evaluate the safety and efficacy in the use of baloxavir marboxil.

Koshimichi H, Ishibashi T, Kawaguchi N, Sato C, Kawasaki A, Wajima T. Safety, Tolerability, and Pharmacokinetics of the Novel Anti-influenza Agent Baloxavir Marboxil in Healthy Adults: Phase I Study Findings. Clin Drug Investig. 2018 Dec;38(12):1189-1196.

Study Design: Randomized, three-dosing sequence, three-period crossover

Description of Study:

Methods: Fifteen Japanese participants were randomized to receive a single-dose of oral baloxavir marboxil 20 mg in tablet form. Participants were administered this dose in the fasted (≥ 10 hours), fed (30 minutes after eating), or before-meal state (after a fast of ≥ 10 hours and before initiation of a meal) at the same testing center as the previous study. Five patients were randomized to each cohort. There was a washout period of at least 21 days between periods, where no doses of baloxavir marboxil were administered. Meals that were administered by investigators had approximately 400-500 kcal, of which approximately 150 kcal was derived from fat. Initial screening lasted for 28 days prior to admission to the study center. Participants reported to the study center for admission two days prior to the treatment being given. Baloxavir marboxil was administered on day 1 and patients were observed for three days before discharge on day 4. Participants were observed on day 6. There were three follow-up visits, which were on day 8, day 15, and day 22. The follow-up on day 22 was for period 3 only. Period 3 is the last dose of baloxavir marboxil that participants received during the crossover study.

Outcome Results: Of the fifteen participants who were enrolled in the study, twelve completed the study. Three participants who received baloxavir marboxil in the fed state withdrew from the study due to treatment-emergent adverse effects. One participant from the fed group experienced increased aspartate aminotransferase (46IU/L) and alanine transferase (ALT, 48 IU/L) levels that were assumed to be associated with infectious mononucleosis. Out of the other two participants, one reported moderate tonsillitis and the other reported rash. Within the fasted group, patients experienced headaches and an increase in ALT, eosinophil count, and white blood cell count. None of these adverse effects were considered to be associated with the study drug. Plasma baloxavir acid concentrations tended to be lower in the fed or before-meal states than in the fasted state. Exposure was decreased and apparent total clearance (CL/F) increased in the fed and before-meal states compared with the fasted state. In the fed state, C_{max}, AUC_{last}, and AUC_{∞} were decreased by 47%, 37%, and 37%, respectively, compared with the fasted state. In the before-meal state, C_{max}, AUC extrapolated from time zero to the time of the last quantifiable concentration after dosing (AUC_{last}), and AUC_{∞} were decreased by 48%, 40%, and 39%, respectively, compared with the fasted state.

Limitations: All of the participants were Japanese males, within the normal BMI range of 20-25, and were within a 23-30 age range. The demographics of the fifteen individuals who participated in the study lacked diversity thus lacking the ability to extrapolate the results of the study to the general population. Also, there was a small sample size. The study was performed at a single testing center, which also shows the lack of diversity. In addition, it was unclear how investigators treated patients or what participants were able to do while under observation, which could potentially lead to some bias.

Conclusion: The results showed that the participants experienced side effects. These side effects could be due to how certain participants had additional illnesses (e.g., infectious mononucleosis) or could possibly be due to baloxoavir marboxil. Pharmacokinetic studies found that the AUC of baloxavir acid decreased with food intake. This will be an important counselling point for patients when using this medication in clinical practice.

Further studies should be performed in a larger group of participants to evaluate the safety and efficacy in the use of baloxavir marboxil.

Hayden FG, Sugaya N, Hirotsu N, Lee N, de Jong MD, Hurt AC, Ishida T, Sekino H, Yamada K, Portsmouth S, Kawaguchi K, Shishido T, Arai M, Tsuchiya K, Uehara T, Watanabe A; Baloxavir Marboxil Investigators Group. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl J Med. 2018 Sep 6;379(10):913-923.

Study Design: Double-blind, placebo-controlled, dose-ranging, randomized trial

Description of Study:

Methods: The phase 2 trial enrolled 400 Japanese adults 20 to 64 years of age with acute influenza. The participants were randomized in a 1:1:1:1 ratio to receive single doses of baloxavir (10, 20, or 40 mg) or placebo. There were 100 patients in each group who received 10 mg, 20 mg, 40 mg, or placebo. Of the 400 patients who were randomized, there were 389 patients who completed the study. Patients assessed the severity of their influenza symptoms on a 4-point scale survey (with 0 indicating no symptoms, 1-mild symptoms, 2-moderate symptoms, and 3-severe symptoms) daily. Patients then assessed their overall health status on a scale of 0 (worst possible) to 10 (normal) each evening through day 14. Safety laboratory tests (hematologic tests, blood chemical test, and urinalysis) were performed and serum for influenza neutralizing antibody testing was obtained. The primary efficacy endpoint was the time to alleviation of symptoms. Secondary endpoints were the time to resolution of fever, the time to a return to usual health, and newly occurring complications leading to antibiotic use.

Outcome Results: The median time to alleviation of symptoms decreased depending on increasing doses of baloxavir marboxil, which was statistically significant. Adverse events were reported in 23-27% of patients in the three baloxavir groups and 29% of patients in the placebo group. The following adverse events occurred: diarrhea, seasonal allergy, nasopharyngitis, vertigo, stomatitis, headache, gastritis, ALT increased, AST increased, white blood cell count decreased, blood bilirubin increased, and abnormal liver function test. There were no adverse events leading to withdrawal from the trial and no serious adverse events.

Limitations: Results may not extrapolate well to the general public considering the main ethnicity included was those of Asian descent. In addition,elderly patients (>65 years of age) were not studied, and smokers were included which could have increased the metabolism of the medication. Acetaminophen was allowed, but it does not state how often patients were taking acetaminophen. Patients taking more acetaminophen could potentially have scored lower on the survey assessing for symptomatic relief.

Conclusion: These results support the use of baloxavir marboxil in patients with acute influenza due to the efficacy of the medication in addition to the tolerable adverse effects. Increasing doses correlated to faster alleviation of symptoms. Future studies could be

performed to assess the highest dose of baloxavir marboxil that would result in the fastest alleviation of symptoms. Prior studies have established that 60-mg and 80-mg doses were safe in humans, so specifically, these doses could be investigated. Also, further studies could be performed to investigate the efficacy of baloxavir marboxil compared to other medications used to treat influenza (e.g., oseltamivir).

Hayden FG, Sugaya N, Hirotsu N, Lee N, de Jong MD, Hurt AC, Ishida T, Sekino H, Yamada K, Portsmouth S, Kawaguchi K, Shishido T, Arai M, Tsuchiya K, Uehara T, Watanabe A; Baloxavir Marboxil Investigators Group. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl J Med. 2018 Sep 6;379(10):913-923.

Study Design: Double-blind, placebo- and oseltamivir-controlled, randomized trial

Description of Study:

Methods: The phase 3 (CAPSTONE-1) trial enrolled outpatients 12 to 64 years of age with influenza-like illness in the United States and Japan. Patients 20 to 64 years of age were randomly assigned in a 2:2:1 ratio, to receive a single oral dose of baloxavir (40 mg for patients weighing <80 kg or an 80 mg dose for those weighing ≥ 80 kg), oseltamivir at a dose of 75 mg twice daily for 5 days, or matching placebos. Patients 12 to 19 years of age were randomly assigned, in a 2:1 ratio, to receive either baloxavir or placebo (on day 1 only). One-thousand-three-hundred-sixty-six patients out of the 1436 patients who underwent randomization completed the trial. Of these 1366 patients, 1064 were included in the intention-to-treat infected population. For all patients, the first dose was administered under direct observation. Patients assessed the severity of their influenza symptoms on a 4-point scale survey (with 0 indicating no symptoms, 1-mild symptoms, 2-moderate symptoms, and 3-severe symptoms) and assessed their overall health status on a scale of 0 (worst possible) to 10 (normal) each evening through day 14. Safety laboratory tests (hematologic tests, blood chemical test, and urinalysis) and serum was obtained to test for influenza neutralizing antibodies. The primary efficacy endpoint was the time to alleviation of symptoms. Secondary endpoints were the time to resolution of fever, the time to a return to usual health, and newly occurring complications leading to antibiotic use.

Outcome Results: The median time to alleviation of symptoms (TTAS) was shorter in the baloxavir group than in the placebo group in both the intention-to-treat infected population (53.7 hours vs. 80.2 hours, P<0.001) and intention-to-treat population (65.4 hours vs. 88.6 hours, P<0.001), corresponding to median differences of 26.5 hours (95% confidence interval [CI], 17.8 to 35.8) and 23.2 hours (95% CI, 34.2 to 14.0), respectively. The median TTAS was 53.5 hours (95% CI: 48.0, 58.5) in the baloxavir group compared with 53.8 hours (95% CI: 50.2, 56.4) in the oseltamivir group. It was evident that by day two there was more rapid alleviation of symptoms with baloxavir than with placebo. Baloxavir was associated with more rapid declines in infectious viral load than placebo or oseltamivir; by one day after initiation of the trial regimen, the median

reductions in viral load from baseline were 4.8, 2.8, and 1.3 $\log_{10}$ $TCID_{50}$/mL in the baloxavir, oseltamivir, and placebo groups, respectively.

Adverse events were reported in 20.7% of baloxavir recipients, 24.6% of placebo recipients, and 24.8% of osteltamivir recipients. The adverse events experienced by the patients in the baloxavir marboxil groups included diarrhea, bronchitis, nasopharyngitis, nausea, sinusitis, increase in ALT level, headaches, vomiting, and dizziness. There were two serious adverse events noted in baloxavir recipients (incarcerated inguinal hernia and aseptic meningitis), but neither were considered to be related to the trial regimen by investigators. Adverse events that were associated with cessation of the trial regimen occurred in 0.3 to 0.4% of patients across all treatment groups.

Limitations: Elderly patients (>65 years of age) were not studied, and smokers were included which could have increased the metabolism of the medication. Also, there were significantly more Japanese patients, 294 (78.2%) in the baloxavir group and 303 (80.4%) in the oseltamivir group, than United States patients, 82 (21.8%) in the baloxavir group and 74 (19.6%) in the oseltamivir group. This study will not extrapolate well to individuals in the population who are greater than 65 years old and/or are other ethnicities than Japanese individuals. Acetaminophen was allowed, but it does not state how often patients were taking acetaminophen. Patients taking more acetaminophen could potentially have scored lower on the survey assessing for symptomatic relief.

Conclusion: The results from this study support that single-dose baloxavir was associated with clinical benefit and antiviral activity in patients with uncomplicated influenza. There were no apparent safety concerns due to the lack of serious adverse effects. Future clinical trials could involve patients specifically at high risk for influenza complications or patients with complicated influenza.

Contraindications[1,2,3,4,5]:

Hypersensitivity to baloxavir marboxil or any of its ingredients

Precautions[1,2,3,4,5]:

Risk of bacterial infections: Serious bacterial infections may begin with influenza-like symptoms and may occur simultaneously with influenza infections. There is no evidence of efficacy of baloxavir marboxil in infections caused by pathogens other than influenza viruses. Monitor for potential secondary bacterial infections during treatment and manage appropriately.

Adverse Effects[1,2,3,4,5]:

Occurring in >1% or <10% of patients

Gastrointestinal

- Diarrhea (3%)
- Nausea (1%)

Neurologic

Headache (1%)

Respiratory

Bronchitis (2%)

Nasopharyngitis (1%)

Drug Interactions[1,3,5]:

Antacids: May decrease the serum concentration of baloxavir marboxil

Calcium Salts: May decrease the serum concentration of baloxavir marboxil

Influenza Virus Vaccine (Live/Attenuated): May diminish the therapeutic effect of the Influenza Virus Vaccine

Management: Avoid anti-influenza antivirals during the period beginning 48 hours prior to and ending 2 weeks after liver influenza virus vaccine administration

Iron Salts: May decrease the serum concentration of baloxavir marboxil

Magnesium Salts: May decrease the serum concentration of baloxavir marboxil

Multivitamins/Minerals (with ADEK, Folate, Iron): May decrease the serum concentration of baloxavir marboxil

Multivitamins/Minerals (with AE, No Iron): May decrease the serum concentration of baloxavir marboxil

Selenium: May decrease the serum concentration of baloxavir marboxil

Zinc Salts: May decrease the serum concentration of baloxavir marboxil

Dosing/Administration[1,2,3,4,5]:

Adult Dosing

40 to <80 kg: 40 mg as a single dose within 48 hours of onset of influenza symptoms

≥80 kg: 80 mg as a single dose within 48 hours of onset of influenza symptoms

Renal impairment

Creatinine clearance (CrCl) 50 mL/min and above: A population pharmacokinetic analysis did not identify a clinically meaningful effect of renal function on the pharmacokinetics of baloxavir in patients with this CrCl range.

Creatinine clearance (CrCl) lower than 50 mL/min: Clinical trials did not include patients with severe renal impairment.

Hepatic impairment

Mild impairment (Child-Pugh class A): There are no dosage adjustments provided in the manufacturer's labeling.

Moderate impairment (Child-Pugh class B): There are no dosage adjustments provided in the manufacturer's labeling, however moderate hepatic impairment had no clinically important effect on baloxavir (the active metabolite) pharmacokinetics.
Severe impairment (Child-Pugh class C): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Use in Special Populations[1,3,4,5]:

Pediatrics:

>12 years of age and older

40 to <80 kg: 40 mg as a single dose within 48 hours of onset of influenza symptoms

≥80 kg: 80 mg as a single dose within 48 hours of onset of influenza symptoms

<12 years of age

Safety and efficacy have not been established

Elderly:

There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Pregnancy:

There are no available data in the use of baloxavir marboxil in pregnant female humans. However, in animal reproduction studies, no adverse developmental effects were observed within pregnant rats or pregnant rabbits with oral administration of baloxavir marboxil at exposures 5 (rats) and 7 (rabbits) times the systemic baloxavir exposure at the maximum recommended human dose (MRHD). There are risks of severe complications from influenza within pregnant women, which may result in adverse events to the fetus and complications to the mother. The CDC states that the benefits of treatment against influenza virus likely outweigh the theoretical use; however, there are safer alternatives to administer to pregnant females and females up to 2 weeks postpartum.

Lactation:

There are no available clinical trials within the human population in the use of baloxavir marboxil for lactation, the effects on the breastfed infant, or the effects on milk production. However, in animal studies, it was noted that baloxavir and its related metabolites were present in the milk of rats who were administered 1 mg/kg of baloxavir marboxil. On postpartum/lactation day 11, there was a peak milk concentration approximately 5 times that of maternal plasma concentrations occurring 2 hours post-dose. There were no effects of baloxavir marboxil on growth and postnatal development observed in nursing pups at the highest test dose tested in rats. Healthcare providers are encouraged to consider the benefits of breast-feeding, the risk of the potential infant drug exposure, and the risk of an untreated condition before recommending baloxavir marboxil in this patient population.

Overdosage[1]:

Currently, there have not been any overdoses of baloxavir marboxil reported. In the situation of an overdose, treatment should consist of general supportive measures. It is important to note that baloxavir is unlikely to be significantly removed by dialysis because it is 93-94% protein bound within the body.

Conclusion:

According to the CDC, over the past eight years there have been between 9.3 million - 49.0 million cases of illnesses, 140,000-960,000 hospitalizations, and 12,000-79,000 deaths related to influenza annually.[6] Currently, there are not many medication regimens indicated for treating the influenza virus. Baloxavir, if administered within 48 hours of symptom onset, will prevent the virus from replicating. Baloxavir has a novel mechanism and works quicker than alternative medications (e.g., oseltamivir), thus supporting its use. However, use after 48 hours of symptom onset does not provide the same clinical benefit. Based off the average wholesale price, the cost for a treatment course of baloxavir marboxil is $90, while the cost for a treatment course of oseltamivir phosphate is $182.26 (7). Due to the minimal drug interactions, effectiveness in influenza treatment, quicker onset of action, and cheaper cost of baloxavir marboxil, this medication appears to be a more useful agent compared to oseltamivir phosphate.

Recommended References:

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