# BALOXAVIR

## Introduction

**Baloxavir marboxil** (trade name **"**Xofluza") is an orally active, **selective inhibitor,** of **influenza cap-dependent endonuclease** of **influenza A** and **influenza B viruses.**

It is the first anti-influenza drug with a **novel** mechanism to be developed since the *neuraminidase inhibitors.*

Baloxavir has shown therapeutic activity in preclinical models of **influenza A** and **B** virus infections, *including* **strains resistant to current antiviral agents**.

**Baloxavir marboxil** is a **prodrug** that is converted in the body to the active compound **baloxavir acid.**

Like the neuraminidase inhibitors baloxavir should be commenced within **48 hours**.

Time to clinical improvement is similar to oseltamivir

Clinical advantages include:

1. **Because of its novel mechanism of action, it has the potential to be effective against strains which have developed resistance to *neuraminidase inhibitors*.**

2. Owing to its *long half-life*, a **single** baloxavir dose provides the advantage of avoiding adherence concerns with treatment with twice daily oseltamivir for 5 days.

## History

For many years, antiviral treatment of influenza has primarily consisted of monotherapy with a **neuraminidase inhibitor**.

The Food and Drug Administration (FDA) approval for the neuraminidase inhibitors:

- Oseltamivir (oral administration) in 1999
- Zanamivir (oral inhalation) in 1999
- Peramivir (intravenous administration) in 2014.

**Baloxavir marboxil** is the first anti-influenza drug with a **novel** mechanism to be developed since the *neuraminidase inhibitors.*

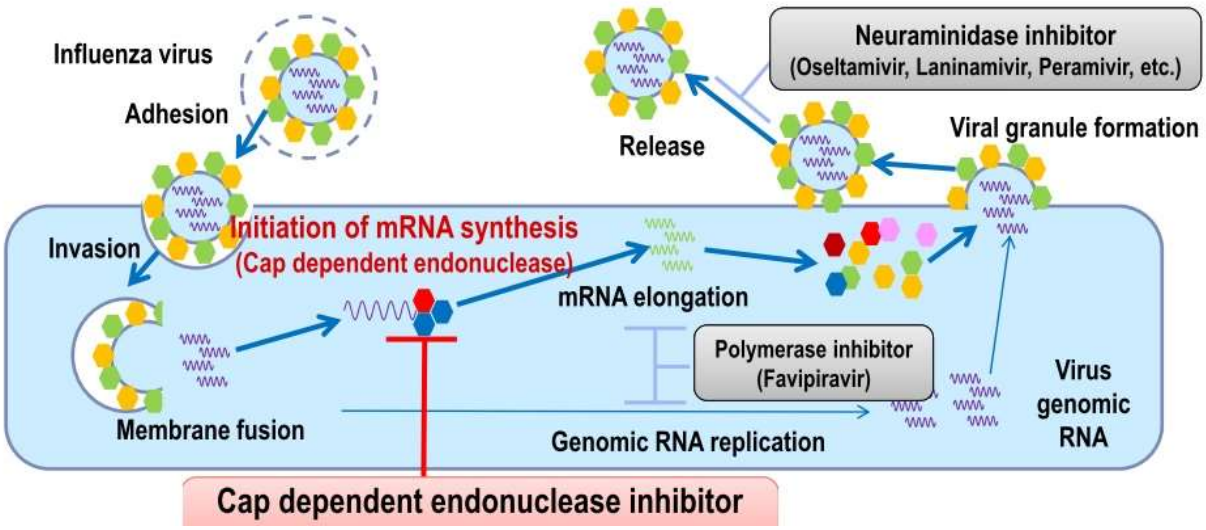
Baloxavir marboxil was first introduced into clinical practice in Japan in February 2018.

It was approved by the FDA for clinical use in October 2018.

## Chemistry

**Baloxavir marboxil** is a **prodrug** that is converted in the body to the active compound **baloxavir acid.**

## Pathophysiology




## Classification

Anti-Influenza virus agents include:

1. Neuraminidase inhibitors:
    - Oseltamivir (oral)
    - Zanamivir (inhaled or IV)
    - Peramivir (IV)
2. Endonuclease inhibitors
    - **Baloxavir (oral)**

## Preparations

Baloxavir marboxil as:

Tablets:

- 40 mg
- 80 mg

## Mechanism of Action

**Influenza viral polymerase** is a hetero-trimer composed of three subunits:

- PA
- PB1
- PB2

It is responsible for the replication and transcription of the eight separate segments of the influenza RNA genome within the nuclei of infected cells.

"**Cap snatching**" is a mechanism used by viruses to hijack the host mRNA transcription system to allow synthesis of viral RNAs.

The first step of transcription for some RNA viruses is cap snatching, in which the first 10-20 residues of a host cell RNA is removed (snatched) and used as the 5' cap (an initiator of RNA production) of the nascent viral RNA.

In the influenza virus, the cap snatching endonuclease function is contained in the PA subunit of the RNA polymerase.

Baloxavir selectively inhibits the function of **endonuclease** within the **(PA) protein subunit** of influenza viral polymerase, thereby inhibiting the **initiation of influenza mRNA synthesis.**

The neuraminidase inhibitors such as oseltamivir (Tamiflu) and zanamivir (Relenza) have different mechanism of action. They inhibit the liberation of viruses from the infected cell surface.

## Pharmacodynamics

Single-dose baloxavir is superior to placebo in alleviating influenza symptoms.

It is superior to both **oseltamivir** and placebo in reducing the viral load 1 day after initiation of the trial regimen in patients with uncomplicated influenza.

Baloxavir time to clinical symptom alleviation is similar to that of oseltamivir

Evidence for the development of decreased susceptibility to baloxavir after treatment has been observed.

Owing to its longer half-life, a single baloxavir dose provides the advantage of avoiding adherence concerns with treatment with 5 days of twice-daily oseltamivir.

The greatest clinical benefit is when antiviral treatment is started soon after the onset of influenza, preferably within 48 hours.

## Pharmacokinetics

*Absorption:*

- Baloxavir marboxil is administered orally.

  Baloxavir marboxil is a prodrug that is converted in the body to the active compound baloxavir acid.

  Baloxavir marboxil → baloxavir acid

*Distribution*

- Protein bounding is around 94 %
- Vd is 1180 L

*Metabolism and excretion:*

- Baloxavir marboxil is a prodrug and is almost completely converted to baloxavir acid (active metabolite)

  Baloxavir is metabolized by:

  - ♥ UGT1A3 (the major pathway)
  - ♥ CYP3A4 (the minor pathway)

- Elimination half-life is around 79 hours

## Indications

Baloxavir is indicated to treat acute uncomplicated influenza in patients who have been symptomatic for < **48 hours**.

If a single dose is successful in reducing influenza virus transmission, baloxavir **could** be a very useful agent for seasonal and pandemic influenza **prophylaxis**.

**Note that, as for all antivirals, the prevalence of viral resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.**

## Contra-indications/precautions

1. Known allergy to baloxavir

2. Baloxavir (active metabolite) may form a chelate with **polyvalent cations,** such as calcium, aluminium, or magnesium, in food or medications

   Avoid coadministration with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, magnesium, iron, selenium, zinc)

3. Safety and efficacy have not been established for children < 12 years of age.

### *Pregnancy*

Unknown

### *Breast feeding*

Unknown

## Adverse Effects

GIT upset:

- Nausea / diarrhea

## Dosing

Usual dosing is:

- 40 - < 80 kg:
  - ♥ 40 mg as a single oral dose.
- ≥ 80 kg:
  - ♥ 80 mg as a single oral dose.

*References*


1. Frederick G. Hayden et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl J Med 2018; 379: 913-23.

    - DOI: 10.1056/NEJMoa1716197

2. XOFLUZA PI, Genentech, Inc. 2018


Dr J. Hayes
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