IMMUNISATION COALITION

2024 ANTIVIRAL TREATMENTS FOR INFLUENZA GUIDE

FOR HEALTHCARE PROFESSIONALS

ABOUT INFLUENZA ANTIVIRALS

Vaccination remains the first line of defence against influenza. However, vaccination does not always guarantee full protection against the disease and its symptoms. In this case, it may be an option to use antiviral therapy to reduce the impact of the disease.

Specific antiviral medications active against influenza viruses have been available on prescription in Australia for over two decades, but they have not been widely used here except during the 2009 pandemic. This may reflect a lack of familiarity with their use, uncertainty about which patients have influenza, and an uncertainty about which patients will derive the greatest benefit.

As with all prescription medications, the treating practitioner makes a decision about the appropriateness of antiviral therapy for their patient. The decision should take into account the likelihood that they have influenza (based on influenza activity, exposure risk, and their vaccination status), the severity of the acute illness, underlying medical conditions that predispose the patient to more severe influenza, the time since the onset of symptoms and the likelihood of spreading it to nearby high-risk individuals.

This guide has been prepared to assist medical practitioners with making treatment decisions for patients presenting with influenza-like illness, particularly those most vulnerable to severe disease, and for short-term prophylaxis.

WHICH ANTIVIRAL TREATMENTS ARE AVAILABLE IN AUSTRALIA?

Currently there are 4 specific antiviral medicines active against influenza viruses registered for use in Australia:

Oseltamivir, an oral capsule formulation (marketed as *Tamiflu*)

Zanamivir, an inhaled formulation (marketed as *Relenza*)

Peramivir, an intravenous infusion (marketed as *Rapivab*)

Baloxavir Marboxil, an oral capsule formulation (marketed as *Xofluza*)

HOW DO INFLUENZA ANTIVIRAL MEDICINES WORK?

There are a few mechanisms that antiviral medications can use.

Oseltamivir, *Zanamivir*, and *Peramivir* are neuraminidase inhibitors. Neuraminidase inhibitors block the activity of the neuraminidase enzyme which in turn stops the release of virus from infected cells and restricts further progression within the body.

Baloxavir Marboxil is a cap-dependent endonuclease inhibitor. This mechanism works by blocking the cap-dependent endonuclease (CEN) enzyme which is involved in the viral replication process. Specifically, this enzyme is critical for the "cap-snatching" mechanism that influenza viruses use to hijack the host's mRNA processing machinery. By inhibiting this enzyme, Xofluza effectively halts viral replication early in the process.[1]

WHEN TO USE INFLUENZA ANTIVIRALS

NEURAMINIDASE INHIBITORS

The neuraminidase inhibitors (NIs) are antiviral agents recommended for the treatment of influenza and some can also be used in prophylaxis.

3 NIs are currently registered in Australia:

- *Oseltamivir* (oral formulations)
- *Zanamivir* (inhaled presentation)
- *Peramivir* (Intravenous infusion)

NOTE: Amantadine from the Adamantanes group has been used in the past for treatment and prevention of influenza A but it is no longer recommended for use due to high levels of resistance.

BALOXAVIR MARBOXIL

Baloxavir Marboxil is indicated for the treatment of uncomplicated influenza in patients aged 12 years and older who have been symptomatic for no more than 48 hours, and who are otherwise healthy, or at high risk of developing influenza complications.[2]

TREATMENT WITH INFLUENZA ANTIVIRALS

NEURAMINIDASE INHIBITORS

Treatment with NIs is recommended for patients with confirmed or suspected influenza who require hospitalisation or are at risk of complications, including:

- Children <5 years
- Adults>=65 years
- During pregnancy
- Immunosuppressed patients or significant comorbidities
- Those who have a severe, complicated or progressive disease

Treatment should commence within 48 hours of the onset of illness, and should not be delayed while awaiting laboratory test results[*]. Recommended duration of treatment is 5 days for both Oseltamivir and Zanamivir whereas Peramivir is a single dose infusion. Longer daily dosing (oral Oseltamivir or intravenous Peramivir) can be considered for hospitalised patients with influenza who remain severely ill after 5 days of treatment.[3]

For mild/moderate illness, treatment commenced beyond 48 hours is unlikely to be effective. However, for patients hospitalised with more severe respiratory tract infections, treatment can be commenced up to 4–5 days after onset and reduces the risk of progression of disease.[3][16] During the 2009 H1N1 pandemic a number of studies showed that early treatment of hospitalised patients reduced progression of the disease, and probably reduced mortality.[4][5][6]

** Conventional laboratory tests usually do not provide results quickly enough to inform decisions about treatment. Point-of-care (POC) tests can be performed in the surgery/clinic or in the nearby laboratory, though negative results should be treated with caution due to the low sensitivity of the antigen tests.[7] Hospitalised patients with suspected influenza should be tested using molecular assays with high sensitivity and specificity (e.g. RT-PCR) to confirm the need to pursue antiviral therapy or change the treatment therapy.[8]*

BALOXAVIR MARBOXIL

Baloxavir Marboxil (Xofluza) is recommended for the treatment of uncomplicated influenza in patients aged 12 years and older who have been symptomatic for no more than 48 hours.[9] It is indicated for use in individuals who are otherwise healthy or at high risk of developing influenza-related complications. The recommended dosage is a single oral dose, with the specific dose based on the patient's body weight: The recommended dosage is a single oral dose, with the specific dose based on the patient's body weight:

- Patients weighing 40–80 kg: 40 mg
- Patients weighing 80 kg or more: 80 mg

Clinical trials have demonstrated that Baloxavir Marboxil is effective in reducing the time to alleviation of symptoms in patients with influenza. For patients with an influenza B virus infection, Baloxavir Marboxil significantly reduced the median time to improvement of symptoms compared to Oseltamivir by more than 24 hours.[3]

For patients with mild to moderate influenza, treatment should commence within 48 hours of the onset of illness for maximum efficacy. For those hospitalised with more severe respiratory tract infections, treatment initiation can extend up to 4–5 days after symptom onset as it may reduce the risk of disease progression. Baloxavir Marboxil is effective for uncomplicated influenza, but there is limited data on its use during pregnancy, immunocompromised individuals, and those with severe influenza who are not hospitalised.[3]

PROPHYLAXIS WITH INFLUENZA ANTIVIRALS

NEURAMINIDASE INHIBITORS

Prophylaxis with NIs should be considered for contacts of a suspected or confirmed influenza case when at high risk of influenza complications. This is most relevant for control of institutional outbreaks, especially in high-risk settings such as long-term residential care facilities. It can also be used for the prevention of illness in high-risk individuals who lack vaccine-induced protection.[10] This includes those within two weeks of vaccination, severely immunosuppressed patients, and people who have contraindications to vaccination. *Oseltamivir* and *Zanamivir* are both approved for prophylaxis as they can effectively prevent symptomatic influenza.

Antiviral prophylaxis is most effective when given within 48 hours of the first exposure to a person with influenza, and should be taken for at least 10 days.

Pregnancy can increase the risk of serious influenza illness and *Oseltamivir* is considered the safest option for treatment and prophylactic use based on the studies currently available.

BALOXAVIR MARBOXIL

Baloxavir Marboxil is indicated for the post-exposure prophylaxis of influenza in patients aged 12 years and older following contact with an individual who has confirmed influenza.[11]

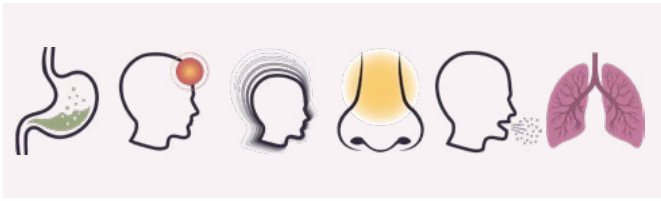
SIDE EFFECTS

NEURAMINIDASE INHIBITORS

Side effects of NIs are limited and generally mild. *Oseltamivir* may cause nausea, vomiting, headache and pain.[12]

Healthcare professionals are encouraged to report any suspected adverse reactions to the Therapeutic Goods Administration (TGA) to enable continued monitoring of the benefit-risk balance of *Baloxavir Marboxil*.[9]

Zanamivir may cause gastrointestinal disturbances (diarrhoea, nausea), headache, dizziness, and because it is inhalational it may also cause upper airways congestion, sinusitis, bronchitis and a cough.[13]



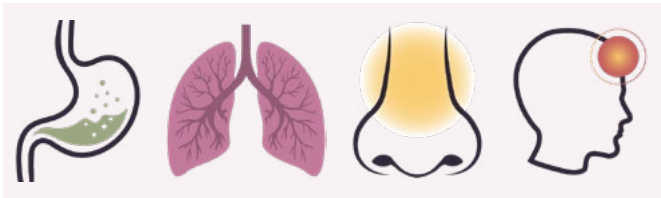
Peramivir may cause diarrhoea in adults, and vomiting, fever and tympanic membrane erythema in paediatric patients.[14]

There have been post-marketing reports of **rare transient neuropsychiatric events in children and adolescents** for both *Oseltamivir* and *Peramivir*.

BALOXAVIR MARBOXIL

The overall safety profile of Baloxavir Marboxil is based on data from 18 clinical trials involving 2483 subjects. In clinical trials for the treatment of influenza, no adverse drug reactions were identified based on pooled data from 3 placebo-controlled studies (studies 1518T0821, CAPSTONE-1, and CAPSTONE-2).[9]

The most common adverse events reported in at least 1% of adult and adolescent subjects who received Baloxavir Marboxil included diarrhoea, bronchitis, nausea, sinusitis, and headache.



For prophylaxis, treatment-emergent adverse events were reported in a similar proportion of subjects in both the Baloxavir Marboxil and placebo groups, with nasopharyngitis being the most frequently reported adverse event. [9]

Post-marketing surveillance has identified hypersensitivity reactions, including anaphylaxis, facial/throat swelling, skin eruptions, and urticaria. Gastrointestinal disorders such as vomiting, bloody diarrhoea, and ischemic colitis have also been reported.

HOW EFFECTIVE ARE INFLUENZA ANTIVIRALS?

NEURAMINIDASE INHIBITORS

If the NIs are commenced within 48 hours of the onset of illness, they can reduce the duration of fever due to influenza by 1 day.[3][17]

The NIs are active against all known influenza virus types and subtypes, including the A/H5N1 and A/H7N9 avian influenza viruses, but not against any other respiratory viruses.

Resistance to Oseltamivir is very low, but resistant strains do occasionally emerge and circulate within the community, though they are not sufficiently common to lead to a change in vaccine strain recommendations. Oseltamivir-resistant viruses usually only cause significant disease in immunocompromised patients. **Resistance to Zanamivir and Peramivir is extremely rare.**

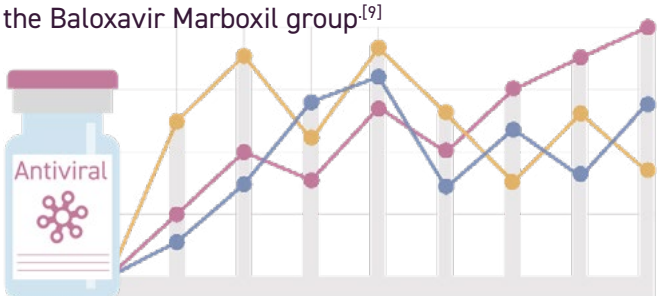
BALOXAVIR MARBOXIL

Baloxavir Marboxil has demonstrated efficacy in the treatment of uncomplicated influenza in patients aged 12 years and older who have been symptomatic for no more than 48 hours.

In the CAPSTONE-1 trial, a randomised, double-blind, placebo- and active-controlled study, Baloxavir Marboxil significantly reduced the median time to alleviation of symptoms compared to placebo (53.7 hours vs. 80.2 hours). The drug was also comparable to Oseltamivir in time to alleviation of symptoms.[9]

In high-risk patients, the CAPSTONE-2 trial showed that Baloxavir Marboxil reduced the median time to improvement of influenza symptoms compared to placebo (73.2 hours vs. 102.3 hours). Additionally, Baloxavir Marboxil was effective in reducing the duration of fever and the time to cessation of viral shedding.[9]

The BLOCKSTONE study demonstrated that Baloxavir Marboxil significantly reduced the risk of developing influenza among household contacts of infected individuals, with a reduction in symptomatic influenza infection from 13.6% in the placebo group to 1.9% in the Baloxavir Marboxil group.[9]



GENERAL RECOMMENDATIONS

Antiviral treatment for seasonal influenza should be considered where the patient has clinical illness suggestive of influenza and a reasonable risk of exposure, i.e. either:

- During the local influenza season (noting that the influenza season in northern Australia often begins in January and local epidemics may occur during the summer months)
- They have recently travelled in areas with influenza activity
- They have had exposure to a known or likely influenza-infected person, e.g. during an institutional or travel-related outbreak.

If so, treatment with a neuraminidase inhibitor is:

- **Recommended** for persons with mild/moderate illness at the time of consultation but who are at higher risk of influenza complications (as defined by Australian Department of Health)[15], and who are within 48 hours of onset of illness. Clinical judgement on the basis of the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms is important when making antiviral treatment decisions for high-risk outpatients. Prior vaccination does not preclude the use of antivirals.
- **Strongly recommended** for patients with severe illness that is known or suspected to be due to influenza, up to 5 days after onset of illness. This includes anyone requiring hospitalisation and anyone who has progressive, severe or complicated illness. This decision should be independent of whether they have been vaccinated against influenza or their prior state of health. Only *Oseltamivir* is recommended in these patients.
- **To be considered** for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza if treatment can be initiated within 48 hours of illness onset. This should be based on clinical judgement of the likely benefits.
- **Recommended** for prophylaxis of close contacts, particularly in household settings and institutional influenza outbreaks.

Always consult a GP or physician before giving antiviral treatment.

TREATMENT WITH BALOXAVIR MARBOXIL:

While *Baloxavir Marboxil* has been shown to reduce the duration of symptoms and may offer a more convenient single-dose option compared to other antivirals, it is not part of the broader public health recommendations made by ATAGI or included in the Australian Immunisation Handbook; therefore its use should be considered in the context of individual patient needs and in consultation with clinical guidelines.

CURRENT AUSTRALIAN LICENSED INDICATIONS

All 3 NIs are indicated for the treatment of infections due to Influenza A and B viruses. While Oseltamivir and Zanamivir can be used for both treatment and prophylaxis, Peramivir is limited to treatment only

While Baloxavir Marboxil is not included in ATAGI recommendations, it is approved by the TGA for the treatment of uncomplicated influenza in patients aged 12 years and older who have been symptomatic for no more than 48 hours and who are[9]:

- Otherwise healthy, or
- At high risk of developing influenza complications.

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