Guidance on the use of antiviral agents for the treatment and prophylaxis of influenza, 2018-2019

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Terms of Reference of Influenza subgroup
1. To develop guidance on the use of antiviral agents for the treatment and prophylaxis of seasonal influenza based on international best practice and expert consensus opinion. The guidance will address the following:
   a) Outline risk groups in whom antivirals are indicated as treatment and/or prophylaxis
   b) Treatment of uncomplicated and complicated influenza in adults and children
   c) Treatment of oseltamivir resistant influenza
   d) Information on antiviral dosages and schedules
   e) Post exposure prophylaxis
2. Development of algorithms for the management of influenza in primary care and the Emergency Department (for both adults and children)
3. Development of guidance on the use of antivirals in pregnancy
Foreword

The influenza antiviral neuraminidase inhibitors (referred to as antivirals) are currently recommended for the treatment and prophylaxis of seasonal influenza by a number of organisations worldwide including the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC) USA, the European Centre for Disease Prevention and Control (ECDC) and Public Health England (PHE).

This guidance summarises the current Irish recommendations for the use of antiviral agents in the treatment and prophylaxis (prevention) of seasonal influenza. It draws on guidance already issued by Public Health England (PHE), the European Centre for Disease Prevention and Control (ECDC), US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). It applies to the management of the currently circulating seasonal influenza viruses, influenza A (H1N1) pdm09, influenza A (H3N2) and influenza B.

In keeping with the international guidance cited above, this guidance recommends the targeted use of antiviral medicines for the treatment of uncomplicated influenza for specific at-risk groups in the population who are at increased risk of severe illness and death due to influenza. These groups include persons aged 65 years and older, pregnant women, residents of residential care facilities for the elderly and others e.g. those with intellectual disabilities, those who are immunosuppressed and persons with chronic medical conditions. The guidance recommends antiviral treatment for patients with complicated influenza regardless of whether or not they belong to one of the at-risk groups above or have underlying risk conditions. The targeted use of antivirals for post-exposure prophylaxis is recommended for those in at-risk groups.

Antiviral medicines may be prescribed at any time in the secondary care setting for patients with suspected or confirmed influenza. However, it is recommended that prescribing of antivirals in primary care only occurs when the Health Protection Surveillance Centre (HPSC) issues an alert that influenza is circulating in the community.

Due to the complex nature of influenza management, clinicians with enquiries about individual patients may wish to seek specialist advice about the use of antiviral medicines from local consultant medical microbiologists and consultant medical virologists. Early specialist advice is recommended for the management of all patients with complicated influenza. Local Departments of Public Health should be notified of all local influenza/acute respiratory outbreaks. Separate guidance on management of influenza outbreaks in residential care facilities is available on the HPSC website.

As influenza management is a complex and evolving area, this guidance document may be updated during the season.

Clinicians may be aware of the Cochrane review on the efficacy of antivirals which was published in 2014. (1) In Ireland, recommendations for antiviral medications remain unchanged as per CDC (USA), the Infectious Disease Society of America (ISDA), Public Health England (PHE) and the European Centre for Disease Prevention and Control. (2-6)
Introduction

Influenza antiviral neuraminidase inhibitors (NAI) can be used to treat or to prevent influenza. Antiviral medications are an important adjunct to vaccination and infection prevention and control in the control of influenza. Influenza vaccination and infection prevention and control practices are of utmost importance in the prevention of influenza and are universally preferred over the administration of chemoprophylaxis. There is separate guidance of the management of influenza in residential care facilities which is available at [http://www.hpsc.ie/A-Z/Respiratory/Influenza/SeasonalInfluenza/Guidance/ResidentialCareFacilitiesGuidance/](http://www.hpsc.ie/A-Z/Respiratory/Influenza/SeasonalInfluenza/Guidance/ResidentialCareFacilitiesGuidance/)

Two antiviral medications are recommended for use in Ireland during the 2018-2019 influenza season: Oseltamivir (Tamiflu) and Zanamivir (Relenza). They are both antiviral neuraminidase inhibitors which have activity against seasonal influenza A and B.

Early antiviral treatment can reduce the risk of complications from influenza e.g. otitis media in young children, pneumonia and respiratory failure, shorten duration of illness among acutely ill patients and reduce morbidity including hospitalisation and mortality among patients with severe infection. Antiviral treatment is recommended as early as possible for any patient with suspected or confirmed influenza who:

1. Is hospitalised
2. Has severe complications or progressive illness
3. Is at higher risk from influenza complications (see risk groups for antivirals for influenza in Definitions section, P. 5 of this document)

Antiviral treatment can also be considered for any previously healthy symptomatic outpatient (not at high risk) with suspected or confirmed influenza on the basis of clinical judgement. Ideally, treatment should be initiated early, within 48 hours of illness onset if Oseltamivir is being used and 36 hours if Zanamivir is being used. (8)

Clinical judgement on the basis of the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since symptom onset is important when considering the initiation of antiviral therapy for high risk outpatients. The greatest benefit is achieved when antiviral therapy is commenced within 36 or 48 hours of illness onset depending on which NAI is being used for treatment. However, antiviral therapy may still be beneficial in patients with severe complicated or progressive illness and in hospitalised patients when administered after 48 hours of illness onset. (10, 11)

Empiric antiviral treatment is often necessary and providers should not delay commencement of treatment while awaiting confirmatory diagnostic test results or if specimens are not obtained. Patients with suspected influenza should complete antiviral treatment for a full treatment course regardless of negative initial test results unless an alternative diagnosis can be established and clinical judgement suggests that influenza is an unlikely diagnosis. (8)
Definitions

**Uncomplicated influenza:** Influenza presenting with fever, cough, sore throat, coryza, generalised symptoms (headache, malaise, myalgia, arthralgia), and sometimes gastrointestinal symptoms, but without any complications of influenza e.g. pneumonia, acute respiratory distress syndrome (ARDS).

**Complicated influenza:** Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, lung infiltrate), central nervous system involvement and/or a significant exacerbation of an underlying medical condition.

**Risk factors for complicated influenza:**
- a) Age 65 years and over
- b) Pregnancy (including up to two weeks post-partum)
- c) Children aged <2 years of age
- d) Chronic respiratory disease including those on medication for asthma
- e) Chronic heart, kidney, liver or neurological disease
- f) Diabetes mellitus
- g) Haemoglobinopathies
- h) Immunosuppression (whether due to treatment or disease e.g. HIV)
- i) Morbid obesity (BMI ≥40)
- j) Those with any condition that can compromise respiratory function (e.g. cognitive dysfunction, spinal cord injury, seizure disorder, or other neuromuscular disorder), especially those attending special schools/day centres.
- k) Those with Down Syndrome
- l) Children with moderate to severe neurodevelopmental disorders such as cerebral palsy and intellectual disability
- m) Residents of nursing homes or other residential care facilities.

**Severe immunosuppression:**
Examples of severe immunosuppression relevant to this guidance are outlined below. Degrees of immunosuppression are difficult to quantify and individual variation exists, therefore this list is not comprehensive.

- a) Severe primary immunodeficiency
- b) Current or recent (within six months) chemotherapy or radiotherapy for malignancy
- c) Solid organ transplant recipients on immunosuppressive therapy
- d) Bone marrow transplant recipients currently receiving immunosuppressive treatment, or who received it within the last 12 months
- e) Patients with current graft-versus-host disease
- f) Patients currently receiving high dose systemic corticosteroids (See Chapter 3 Immunisation Guidelines for Ireland 2013 (updated July 2018) - available on the [HSE website](http://www.hse.ie/)
- g) Patients currently or recently (within six months) on other types of immunosuppressive therapy or where the patient’s consultant regards them as severely immunocompromised.
- h) HIV infected patients with severe immunosuppression (CD4 <200/ l or <15% of total lymphocytes in adult or child over five years; CD4 <500/ l or <15% of total lymphocytes in a child aged one to five; expert clinical opinion in a child aged under one year).
Section 1: Treatment of persons with suspected or confirmed influenza

Figure 1: Selection of antiviral therapy for the treatment of influenza

Please refer to the definitions provided on Page 5 when using Figure 1.

Suspected or confirmed influenza

UNCOMPPLICATED

Previously healthy

At risk group

Severely immunosuppressed?

NO:

No treatment

OR

oseltamivir PO

if physician feels patient is at serious risk of developing complications

YES:

oseltamivir PO within 48 hours of onset or later at clinical discretion

OR

zanamivir INH (Diskhaler) and clinical follow up

COMPLICATED

Severe immunosuppression?

NO:

First line:

oseltamivir PO/NG within 48 hours of onset or later at clinical discretion

2nd line:

zanamivir INH, NEB IV and clinical follow-up

YES:

First line:

oseltamivir PO/NG within 48 hours of onset or later at clinical discretion

2nd line:

zanamivir INH, NEB OR IV and clinical follow-up

1. For treatment of suspected or confirmed oseltamivir resistant influenza, see section 1.3.1
2. Rapid emergence of oseltamivir resistance on treatment has been described in these patients (see footnote1). Resistance to oseltamivir has been described in infections from influenza A (H1N1)pdm09 subtype but not in those from influenza A (H3N2) to date (personal communication with NVRL). Clinicians may consider the use of zanamivir as first line therapy in immunosuppressed patients with suspected or confirmed influenza A (H1N1)pdm09 based on clinical judgement. In immunosuppressed patients, if no clinical improvement is seen within 5 days, test for antiviral resistance (at NVRL).

1 Oseltamivir resistance sometimes within one week of treatment initiation has been reported particularly among immunocompromised patients with influenza A (H1N1)pdm09. Infection control measures are especially important for patients who are immunocompromised in order to reduce the transmission of oseltamivir-resistant viruses.
3. Inhaled zanamivir via Diskhaler may not be an effective delivery route in some patients, including those unable to administer the Diskhaler and patients with severe underlying respiratory disease. It is not licensed for use in children less than five years of age (see footnote 2). The powder preparation for the Diskhaler should NEVER be made into nebuliser solution or administered to a mechanically ventilated patient.

4. For treatment of complicated influenza, see section 1.2.

5. Zanamivir solution for IV or nebulised administration is an unlicensed medication and is available only on a compassionate use basis for named patients in Ireland. **There is limited experience with the use of nebulised aqueous solution of zanamivir in critical care.** The use of nebulised or IV zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if the patient is being treated in critical care). Where possible, patients who have good respiratory function despite their illness and who can use the Diskhaler should receive inhaled zanamivir rather than nebulised or IV zanamivir unless there is multiorgan failure.

6. Zanamivir is available for inhalation (Diskhaler device) or as unlicensed aqueous solution for nebulised or intravenous use.

In general, influenza A (H1N1) pdm09 is considered to be at higher risk for the development of oseltamivir resistance while influenza A (H3N2) and influenza B are considered lower risk. This list is not exhaustive of all possible subtypes causing human infection and further advice on the risk of individual subtypes can be obtained from a consultant medical microbiologist or consultant medical virologist.

The risk of resistance is highest in people who are severely immunosuppressed. The selection of first line drugs in severely immunosuppressed individuals should take into account the subtype of influenza causing infection or if not yet known, the dominant strain of influenza that is circulating during the influenza season. The dominant circulating strain of influenza can be obtained from the HPSC weekly influenza reports available at [http://www.hpsc.ie/A-Z/Respiratory/Influenza/SeasonalInfluenza/Surveillance/InfluenzaSurveillanceReports/](http://www.hpsc.ie/A-Z/Respiratory/Influenza/SeasonalInfluenza/Surveillance/InfluenzaSurveillanceReports/)

**Section 1.1: Treatment of adults and children in the community/Emergency Departments with uncomplicated influenza**

All patients should be advised of the symptoms of complicated influenza and told to seek medical help should their condition worsen.

1. **Previously healthy people (excluding pregnant women):** No antiviral treatment (symptomatic treatment only) OR oseltamivir (PO) if the clinician feels the patient is at serious risk of developing complications from influenza. Commence therapy within 48 hours of onset (or later at clinical discretion). See Table 1, section 1.3 for dosage.

2. **At risk population including pregnant women (but excluding severely immunosuppressed patients):** Oseltamivir (PO) (See Table 1, section 1.3 for dosage). Do not wait for laboratory confirmation. Treatment should be started as soon as possible, ideally within 48 hours of onset. There is evidence that treatment may reduce the risk of mortality up to five days after onset. Treatment after 48 hours is an off-label use of oseltamivir and clinical judgement should be used.

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2 Please note that this guidance describes the use of unlicensed medications for which there is limited safety and efficacy data. Specialist advice should always be obtained before using these products. This guidance represents the views of the HPSC influenza expert subgroup and not that of any manufacturer of medicines.
3. **Severely immunosuppressed patients:** Oseltamivir (PO) (See Table 1, section 1.3 for dosage). Treatment should start as soon as possible and ideally within 48 hours of symptom onset (or later at clinical discretion). Rapid emergence of oseltamivir resistance on treatment has been described in these patients and they should be monitored closely (see footnote 3). Resistance to oseltamivir has been described in infections from influenza A (H1N1) pdm09 subtype but not in those from influenza A (H3N2) or influenza B to date (personal communication with NVRL). Clinicians may consider the use of zanamivir (inhaler) as first line therapy (ideally within 36 hours of symptom onset) in immunosuppressed patients with suspected or confirmed influenza A (H1N1) pdm09 based on clinical judgement (see Table 1, section 1.3 for dosage). In immunosuppressed patients, if no clinical improvement is seen within 5 days, test for antiviral resistance (at NVRL).

4. **Suspected or confirmed oseltamivir resistant influenza in a patient who requires treatment:** Zanamivir (inhaler). Treatment should be started as soon as possible and ideally within 36 hours of symptom onset.

5. **Management of patients for whom zanamivir is indicated, who are unable to administer inhaled zanamivir:**

Some patients who would normally receive inhaled zanamivir are unable to use it, either due to underlying severe respiratory disease or inability to effectively administer the Diskhaler (including children less than 5 years of age for whom zanamivir is unlicensed).

   a. Patients who are severely immunosuppressed and cannot take inhaled zanamivir should receive oseltamivir PO. As they are at increased risk of developing oseltamivir resistant influenza, they should be reviewed clinically to assess response to therapy.

   b. Patients who have suspected or confirmed oseltamivir resistant infection and cannot take inhaled zanamivir should be considered for nebulised aqueous zanamivir. This decision will always be based on clinical judgement. This is an unlicensed medication and the dose is provided on the manufacturer’s guidance, supplied with the drug.

   c. The use of nebulised zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if the patient is being treated in critical care).

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3 Oseltamivir resistance sometimes within one week of treatment initiation has been reported, particularly among immunocompromised patients with influenza A (H1N1) pdm09 [13, 15]. Infection control measures are especially important for patients who are immunocompromised in order to reduce the transmission of oseltamivir-resistant viruses.
**Peramivir (IV) (Alpivab)** *(16)*

In 2018, the European Medicines Agency (EMA) approved the antiviral medication peramivir injection (Alpivab) for intravenous use for the treatment of acute uncomplicated influenza in adults and children aged over 2 years old. At the time of writing, it is unclear when peramivir will be marketed for use in Ireland. In this context, background information is provided on this medicine but it has not been included in the main recommendations for use in this document at this time. This will be kept under review.

It is a neuraminidase inhibitor similar to oseltamivir and zanamivir. Peramivir works on the neuraminidases of both influenza A and influenza B viruses. However evidence of efficacy of the 600 mg dose is limited to mainly influenza A infection and there is no evidence for the drug’s routine use in treating serious influenza requiring hospitalisation. There is no evidence for improved outcomes in combination therapy with oseltamivir though there are recent case reports and retrospective cohort series of survival when used as salvage therapy. *(5)*

Peramivir (Alpivab) is administered as a single intravenous infusion (within 48 hours of onset of acute influenza symptoms) and is given as an infusion lasting 15 to 30 minutes. The dose depends on age and body weight, and should be reduced in adults and adolescents over 13 years of age with reduced kidney function. It is given once only, within 48 hours of symptoms onset. It is shown to reduce the length of time symptoms lasted in patients with influenza. See [http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004299/WC500247881.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004299/WC500247881.pdf) and [https://www.ema.europa.eu/medicines/human/EPAR/alpivab](https://www.ema.europa.eu/medicines/human/EPAR/alpivab)

Several neuraminidase mutations, including the H275Y amino acid substitution, confer reduced susceptibility or resistance to peramivir in addition to oseltamivir. Peramivir should not be used in patients with known oseltamivir resistance unless susceptibility to peramivir has been demonstrated by reference laboratory tests. *(5)*

There is no information available in terms of safety of use in pregnancy or in breastfeeding. Peramivir is renally excreted and a dose adjustment in renal impairment is required as described in the manufacturer’s prescribing information.

**Section 1.2: Treatment of adults and children with complicated influenza**

All patients with complicated influenza should receive treatment, usually in hospital. Rapid testing for respiratory viruses including influenza virus is recommended for all patients fulfilling the clinical criteria for complicated infection. Treatment should be started as early as possible. Do not wait for laboratory confirmation of influenza virus infection.

**Note:**

1. Ensure that appropriate infection prevention and control precautions are applied to all patients. See [http://www.hpsc.ie/a-z/respiratory/influenza/seasonallinfluenza/infectioncontroladvice/](http://www.hpsc.ie/a-z/respiratory/influenza/seasonallinfluenza/infectioncontroladvice/)
2. Previous influenza immunisation does not exclude influenza as a possible diagnosis
3. The duration of therapy depends on the clinical response
4. Test for antiviral resistance in patients who do not respond after five days of treatment
5. Peramivir is not licensed for the treatment of complicated influenza
The following recommendations include the use of IV antivirals and nebulised aqueous zanamivir which are unlicensed medications.

**First line treatment:** Oseltamivir PO or NG (see exceptions below). There is evidence that PO/NG oseltamivir is adequately absorbed in critical illness at standard doses.\(^{(17)}\)

**Second line treatment:** If there is a poor clinical response to first line treatment or if there is poor gastrointestinal absorption, use zanamivir. Some patients who are considered to have good respiratory function despite their illness may be able to use inhaled zanamivir (Diskhaler). Those who cannot use a zanamivir Diskhaler should be considered for nebulised aqueous zanamivir. There is limited experience with the use of nebulised aqueous solution of zanamivir in critical care. The use of nebulised zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if patient is being treated in critical care).

The following patients may be considered for IV zanamivir:
1. Patients who have already failed to respond to nebulised zanamivir
2. Patients who have developed respiratory conditions affecting nebuliser delivery (e.g. airways disease, pulmonary oedema)
3. Patients who have multi-organ involvement, or
4. Patients who require intensive care

**Exceptions:**

**Severely immunosuppressed patients:**
1. **First line treatment:** Oseltamivir PO or NG. Treatment should be started as soon as possible. Arrange influenza A subtype testing by the NVRL and monitor clinical condition closely.
2. Rapid emergence of oseltamivir resistance on treatment has been described in these patients and they should be monitored closely (see footnote 4). Resistance to oseltamivir has been described in infections from influenza A (H1N1) pdm09 but not in those from influenza A (H3) or influenza B to date (personal communication with NVRL). **Clinicians may consider the use of zanamivir as first line therapy in immunosuppressed patients with suspected or confirmed influenza A (H1N1) pdm09 based on clinical judgement.** In immunosuppressed patients, if no clinical improvement is seen within 5 days, test for antiviral resistance.
3. **Second line treatment:** If there is a poor clinical response to first line treatment, consider use of zanamivir and test for oseltamivir resistance. Ensure that appropriate infection prevention and control precautions are applied to these patients see [http://www.hpsc.ie/A-Z/Respiratory/Influenza/SeasonalInfluenza/Infectioncontroladvice/](http://www.hpsc.ie/A-Z/Respiratory/Influenza/SeasonalInfluenza/Infectioncontroladvice/)
4. Some patients who are considered to have good respiratory function despite their illness may be able to use inhaled zanamivir (Diskhaler). Those who cannot should be

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\(^{4}\) Oseltamivir resistance sometimes within one week of treatment initiation has been reported particularly among immunocompromised patients with influenza A (H1N1) pdm09. \(^{(15)}\) Infection control measures are especially important for patients who are immunocompromised in order to reduce the transmission of oseltamivir-resistant viruses
considered for nebulised aqueous zanamivir (unlicensed). There is limited experience with the use of nebulised aqueous solution of zanamivir in critical care.

5. IV zanamivir (unlicensed) based on clinician's judgment may be considered for patients who: (a) are not responding to nebulised zanamivir, (b) who have developed respiratory conditions affecting nebuliser delivery (e.g. airways disease, pulmonary oedema), (c) who have multi-organ involvement, or (d) who require intensive care.

6. The use of nebulised or IV zanamivir should be supervised by an infection expert (consultant clinical microbiologist/virologist or infectious diseases consultant) and a consultant in intensive care medicine (if the patient is being treated in critical care).

**Suspected or confirmed oseltamivir resistance (e.g. contact of known oseltamivir resistant case (see footnote 5):**

1) **Do not use oseltamivir.**
2) Some patients who are considered to have good respiratory function despite their illness may be able to use inhaled zanamivir (Diskhaler). Those who cannot should be considered for nebulised aqueous zanamivir (unlicensed).
3) IV zanamivir (unlicensed) based on the clinician’s judgement may be considered for (a) patients who are not responding to nebulised zanamivir, (b) who have respiratory conditions affecting nebuliser delivery, (c) who have multi-organ involvement, or (d) require intensive care.

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5 Sporadic oseltamivir resistant influenza A (H1N1) pdm09 has been identified including rare episodes of limited transmission; however the public health impact has been limited to date. (13, 15)
**Section 1.3: Antiviral dosage and schedules**

The recommended duration of antiviral treatment is 5 days. \(^{(18)}\) Longer treatment regimens based on clinical judgement may be necessary in severely ill hospitalised patients or patients with immunosuppression.

**Table 1: Antiviral treatment dosages and schedules for treatment**

| Treatment                  | Premature (less than 36 weeks post conceptual age) | 0-12 months (36 weeks post conceptual age or greater) | >1-12 years: Dose according to weight below: | Adults (≥ 13 years)
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<td></td>
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<td>≤15kg</td>
<td>&gt;15-23 kg</td>
<td>&gt;23-40 kg</td>
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<tr>
<td>Oseltamivir (treatment course: 5 days)</td>
<td>1mg/kg/dose bd Unlicensed (see footnote 6)</td>
<td>30mg bd</td>
<td>45mg bd</td>
<td>60mg bd</td>
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<tr>
<td>Zanamivir (see footnote 7) inhaled (treatment course: 5 days)</td>
<td>Not licensed for use in children aged &lt; 5 years old. For children aged ≥ 5 years of age, Dose: 10mg (two 5mg inhalations) bd</td>
<td>10mg (Two 5mg inhalations ) bd</td>
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\(^{1}\) If a person in this age group weighs 40kg or less, it is suggested that the >23-40kg dose for those aged >1-12 years is used.

Product information for Oseltamivir is available at [https://www.hpra.ie/homepage/site-tools/search?query=oseltamivir](https://www.hpra.ie/homepage/site-tools/search?query=oseltamivir)

Product information for Zanamivir is available at [https://www.hpra.ie/homepage/site-tools/search?query=relenza](https://www.hpra.ie/homepage/site-tools/search?query=relenza)

**Oseltamivir**

Oseltamivir oral suspension should be used only for children less than one year of age. It is available as Tamiflu oral suspension (Roche 6 mg/mL oral suspension reconstituted from powder). The pack includes an oral dispenser which is marked in millilitres (mLs), since prescriptions for Tamiflu 6 mg in 1 mL powder for oral suspension should state the dose in millilitres. This is an off-label use of oseltamivir but is supported by the British National Formulary (BNF) for children. Children aged over one year and adults with swallowing

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\(^{6}\) This is an unlicensed use of oseltamivir and is based on evidence from literature and expert opinion.\(^{(19 - 21)}\)

\(^{7}\) Zanamivir is manufactured by GlaxoSmithKline. Zanamivir is approved for the treatment of persons aged ≥5 years in Ireland.
difficulties and those receiving nasogastric oseltamivir should use capsules that are opened and mixed into an appropriate sugary liquid as oseltamivir has a very bitter taste. If the powder for suspension is used in children aged over one year of age and/or adults there may not be adequate quantities of the powder for suspension to meet demands for the under one year age group. It is important that powder for suspension is reserved for those under than one year of age.

Zanamivir
Aqueous zanamivir solution for nebulised or IV administration is an unlicensed medicine. Dosing information is supplied by the manufacturer on the physician’s guidance document that accompanies the medicine when issued. Recommendations for when to use nebulised or intravenous delivery are included in section 1.2 above.

Note that the powder preparation should NOT be used to make nebuliser solution

For the use of oseltamivir and zanamivir in pregnancy, breastfeeding, or renal or hepatic dysfunction, see Appendix A.

Note on dosing for extremes of weight:
Oseltamivir: no dose adjustment is needed in obese patients. (22 - 24)
Inhaled or nebulised zanamivir: no dose adjustment is needed in obese patients. (25)
IV Zanamivir: For adult patients (and adolescents with actual body weight 50kg or greater) the dose is not weight adjusted.

In adolescents with actual body weight less than 50kg and in children, the dose is weight adjusted. For specific dosing information please refer to the physician’s guidance document supplied by GSK. (25)

Section 1.3.1: Treatment of oseltamivir resistant influenza
The same criteria as for non-resistant influenza infection apply in deciding whom to treat.
1. Previously healthy people with uncomplicated disease, or those who have recovered with or without oseltamivir, do not require treatment
2. Those who require treatment should have zanamivir
3. Those with uncomplicated influenza should receive inhaled zanamivir via Diskhaler (or nebulised aqueous zanamivir if the inhaled Diskhaler route is unsuitable)
4. Those with complicated influenza may receive inhaled, nebulised or intravenous zanamivir as is appropriate to their clinical condition (see section 1.2).
5. In the event of changes in the epidemiology or clinical aspects of drug resistant influenza during the season, HPSC will alert clinicians and provide updated advice.
**Section 1.3.2: Management of influenza in critical care**

The principles are the same as for complicated influenza.

1) The first line therapy remains PO/NG oseltamivir and there is evidence that standard dose oseltamivir PO or NG is adequately absorbed even in critical illness. Increasing the dosage is no longer recommended in patients who are severely ill with influenza A due to lack of evidence that it is any more effective. Specialist advice should be sought for dosage of patients critically ill with influenza B.

2) Zanamivir should be used when there is suspected poor gastrointestinal absorption or failure to respond to oseltamivir.

3) In intensive care, zanamivir may be given intravenously based on the clinician’s judgement for situations such as multi-organ failure. The use of nebulised or IV zanamivir should be supervised by a consultant in intensive care medicine.

**Section 2: Post exposure prophylaxis**

Influenza vaccination and infection prevention and control practices are of utmost importance in the prevention of influenza, and are universally preferred over the administration of chemoprophylaxis. Antiviral medications with activity against influenza viruses are an important adjunct to these measures in the control of influenza. In randomised placebo controlled trials, both oseltamivir and zanamivir were efficacious in the prevention of influenza illness among persons administered chemoprophylaxis after exposure to a household member or other close contact who had laboratory-confirmed influenza (zanamivir: 72-82%; oseltamivir: 68-89%). Both are recommended for antiviral chemoprophylaxis of influenza A and B.

Chemoprophylaxis should be reserved for those in at risk groups (see P. 5 of this guidance) who have had recent close contact (see footnote 8) with a person with influenza or influenza-like illness in the same household or residential setting. Previous influenza vaccination does not preclude the use of post exposure prophylaxis, in particular where localised outbreaks occur in residential care facilities. (see footnote 9)

**An emphasis on early treatment and monitoring is an alternative to chemoprophylaxis after a suspected exposure in some persons.** Clinical judgement should be exercised in individual cases. If a high risk contact becomes symptomatic, ensure early commencement of antiviral treatment. Patients receiving chemoprophylaxis should be encouraged to seek medical evaluation as soon as they develop any signs of illness suggestive of influenza.

Decisions on whether to administer antivirals for chemoprophylaxis should take into account:

1. The exposed person’s risk for influenza complications
2. The type and duration of contact
3. Clinical judgement

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8 Close contact is defined as having cared for or lived with a person who has confirmed, probable or suspect influenza or having been in a setting where there is a high likelihood of contact with respiratory droplets and/or body fluids of such a person, including having talked face-to-face with them.

Previous influenza vaccination does not preclude the use of post exposure prophylaxis. Per UK National Institute of Clinical Excellence (NICE) guidance, prophylaxis should be issued if the contact is not adequately protected by vaccination that is in the situations outlined below:

- The vaccine is not well matched to the circulating strain (Refer to HPSC weekly influenza reports available at http://www.hpsc.ie/A-Z/Respiratory/Influenza/SeasonalInfluenza/Surveillance/InfluenzaSurveillanceReports/)
- There have been fewer than 14 days between vaccination and symptom onset

Use of post exposure prophylaxis may also be considered where:

- The individual has been exposed as part of a localised outbreak (such as in a residential care facility) regardless of vaccination status as seasonal influenza vaccination may be less effective in older persons or the immunosuppressed (5,31)

Generally, post exposure chemoprophylaxis should be commenced within 48 hours of the most recent exposure for oseltamivir and within 36 hours for zanamivir and is administered for 10 days after the most recent known exposure to a close contact known to have influenza. Commencement of the administration of chemoprophylaxis >48 hours for oseltamivir and >36 hours for zanamivir should be based on specialist advice only.
Table 3: Selection of antivirals for post-exposure chemoprophylaxis

<table>
<thead>
<tr>
<th>Previously healthy (excluding pregnant women)</th>
<th>If identified strain in index case or dominant circulating strain is at lower risk of oseltamivir resistance e.g. influenza A (H3), influenza B</th>
<th>If identified strain in index case or dominant circulating influenza strain is at higher risk for oseltamivir resistance e.g. influenza A (H1N1) pdm09</th>
<th>Exposed to suspected or confirmed oseltamivir resistant influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prophylaxis</td>
<td>No prophylaxis</td>
<td>No prophylaxis</td>
<td>No prophylaxis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At risk of complicated influenza (including pregnant women, but excluding severely immunosuppressed patients and excluding children aged &lt; 5 years old)</th>
<th>Oseltamivir PO once daily for 10 days if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only</th>
<th>Oseltamivir PO once daily for 10 days if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only</th>
<th>Zanamivir INH once daily for 10 days if therapy can be started within 36 hours of last contact; or after 36 hours on specialist advice only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir PO once daily for 10 days if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only</td>
<td>Zanamivir INH once daily for 10 days if therapy can be started within 36 hours of last contact; or after 36 hours on specialist advice only</td>
<td>If unable to administer zanamivir INH, Oseltamivir PO once daily for 10 days if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only; If unable to administer zanamivir INH, discuss with specialist and consider nebulised aqueous zanamivir (unlicensed) after individual risk assessment.</td>
<td></td>
</tr>
</tbody>
</table>

| Severely immunosuppressed patients (excluding children aged < 5 years old) | Zanamivir INH once daily for 10 days if therapy can be started within 36 hours of last contact; or after 36 hours on specialist advice only | Discuss with specialist. Consider nebulised aqueous zanamivir (unlicensed) after individual risk assessment. |

| Children aged < 5 years in at risk group including severely immunocompromised children | Oseltamivir PO once daily for 10 days if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only | Oseltamivir PO once daily for 10 days if therapy can be started within 48 hours of last contact; or after 48 hours on specialist advice only | Discuss with specialist. Consider nebulised aqueous zanamivir (unlicensed) after individual risk assessment. |
Table 4: Antiviral dosage and schedules for chemoprophylaxis

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Premature (&lt; 36 weeks post conceptual age)</th>
<th>0-12 months (36 weeks post conceptual age or greater)</th>
<th>&gt;1-12 years: Dose according to weight below</th>
<th>Adults (≥13 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>≤15kg</td>
<td>&gt;23-40kg</td>
</tr>
<tr>
<td>Oseltamivir PO</td>
<td>See below (see footnote 10)</td>
<td>3 mg/kg od</td>
<td>30 mg od</td>
<td>75 mg</td>
</tr>
<tr>
<td>(prophylaxis course: 10 days)</td>
<td></td>
<td></td>
<td>45 mg od</td>
<td>75 mg od</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60 mg od</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zanamivir INH</td>
<td>Not licensed in children aged &lt;5 years old</td>
<td>Children aged ≥5 years: 10 mg (2 inhalations) od</td>
<td></td>
<td>10 mg (two 5 mg inhalations) od</td>
</tr>
<tr>
<td>(prophylaxis course: 10 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 If a person in this age group weighs 40 kg or less, it is suggested that the >23-40 kg dose for those aged >1-12 years is used.

Oseltamivir
Oseltamivir oral suspension should be used only for children less than one year of age. It is available as Tamiflu oral suspension (Roche 6 mg/mL oral suspension reconstituted from powder). The pack includes an oral dispenser which is marked in millilitres (mLs), since prescriptions for Tamiflu 6 mg in 1 mL powder for oral suspension should state the dose in millilitres. This is an off-label use of oseltamivir but is supported by the BNF for children. Children aged over one year and adults with swallowing difficulties and those receiving nasogastric oseltamivir should use capsules that are opened and mixed into an appropriate sugary liquid as oseltamivir has a very bitter taste. If the powder for suspension is used in children aged over one year of age and/or adults there may not be adequate quantities of the powder for suspension to meet demands for the under one year age group. It is important that powder for suspension is reserved for those under than one year of age.

Zanamivir
Inhaled zanamivir is not licensed for children less than five years of age and is unlikely to be an effective delivery route in this age group. In addition patients with severe underlying respiratory disease may also be unable to use the Diskhaler effectively.

Severely immunosuppressed children under five years of age and all other severely immunosuppressed patients who cannot use the zanamivir Diskhaler and require prophylaxis after exposure to currently circulating antiviral sensitive strains of influenza should receive oral oseltamivir with advice to seek medical attention if they become unwell (Table 3).

Chemoprophylaxis (discuss with local public health) for both residents and staff may be considered appropriate in some residential settings such as nursing homes and intellectual...
disability residential centres. Specialist advice should be sought regarding prophylaxis in these situations. See guidance on the management of influenza in residential care facilities available on the HPSC website.

Post-exposure antiviral chemoprophylaxis can be considered for pregnant women and women who are up to two weeks postpartum who have had close contact (see footnote11) with someone likely to have been infectious with influenza. Clinical judgement may be exercised in individual cases to determine if the benefit outweighs the risk. Pregnant women and women who are up to two weeks postpartum who are given post-exposure chemoprophylaxis should be informed that the chemoprophylaxis lowers but does not eliminate the risk of influenza and that protection stops when the medication course is stopped. See http://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/guidance/pregnancyguidance/

An alternative approach for pregnant women who have had close contact with a patient with laboratory proven influenza is to provide information on the early signs and symptoms of influenza, and advise them to contact their doctor immediately for evaluation and possible early treatment if clinical signs or symptoms develop following a risk assessment.

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11 Close contact is defined as having cared for or lived with a person who has confirmed, probable or suspect influenza or having been in a setting where there is a high likelihood of contact with respiratory droplets and/or body fluids of such a person, including having talked face-to-face with them.
Appendix A: Use of antivirals in pregnancy, breastfeeding, hepatic or renal dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Liver dysfunction</th>
<th>Renal dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oseltamivir</strong></td>
<td>Standard dosing</td>
<td>See product information for oseltamivir available <a href="http://www.hpra.ie/homepage/site-tools/search?query=oseltamivir">http://www.hpra.ie/homepage/site-tools/search?query=oseltamivir</a></td>
</tr>
<tr>
<td>PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zanamivir</strong></td>
<td>Standard dosing</td>
<td>See product information for zanamivir available at <a href="https://www.hpra.ie/homepage/site-tools/search?query=relenza&amp;page=1&amp;tab=tabwebsite">https://www.hpra.ie/homepage/site-tools/search?query=relenza&amp;page=1&amp;tab=tabwebsite</a></td>
</tr>
<tr>
<td>INH (Diskhaler)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zanamivir solution</strong></td>
<td>Refer to the physician’s guidance document supplied by the manufacturer with the medication.</td>
<td>This information is provided by the manufacturer when IV zanamivir is supplied. See manufacturer’s guidance. (22)</td>
</tr>
<tr>
<td>IV/NEB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Use in Pregnant women

Antivirals have been recommended for pregnant women due to the adverse clinical outcomes that have been observed for influenza infection in this group.

Oseltamivir remains the first line option for the vast majority of pregnant women with influenza, including during seasons that are dominated by influenza A (H1N1) pdm09.

For pregnant women who meet additional criteria for requiring zanamivir first line, further assessment (i.e. rapid diagnostics) and antiviral treatment should be discussed with a local infection specialist.

Oseltamivir is generally well tolerated in patients with influenza, but side effects can occur. There are no data suggesting tolerability differs between pregnant and non-pregnant adults.

Recent studies suggest there is no evidence of harm in pregnant women treated with oseltamivir or zanamivir. (32, 33)

The Summary of Product Characteristics (SPC) for Tamiflu® (oseltamivir) states the following: “While no controlled clinical studies have been conducted on the use of oseltamivir in pregnant women data on use in pregnancy has been collected from postmarketing and observational studies… These data in conjunction with animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development…Pregnant women may receive Tamiflu® after considering the available safety information, the pathogenicity of the circulating influenza virus strain, and the underlying condition of the pregnant woman.” (34)

The Summary of Product Characteristics (SPC) for Relenza® (zanamivir) states the following: “The safe use of zanamivir during pregnancy has not been established. In rats and rabbits zanamivir has been shown to cross the placenta. High doses of zanamivir were not associated
with malformations in rats or rabbits and only minor alterations were reported. The potential risk for humans is unknown. Zanamivir should not be used in pregnancy unless the expected benefit to the mother is thought to outweigh any possible risk to the foetus”. (35)

**Use during breastfeeding**

The UK Drugs in Lactation Advisory Service (UK DILAS) has published advice on the use of oseltamivir and zanamivir while breastfeeding:  
https://www.sps.nhs.uk/articles/oseltamivir-or-zanamivir-can-mothers-breastfeed-after-treatment-for-influenza-2/
References


4. Infectious Disease Society of America. (April 2014). Statement by the Infectious Disease Society of America (IDSA) on the recent publication on "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children". https://www.healio.com/pediatrics/influenza/news/online/%7Ba0c96499-e0c3-409a-9d59-538131ed73c0%7D/controversy-surrounds-recent-papers-on-use-of-neuraminidase-inhibitors-for-influenza


