Guidance on the use of antiviral agents for the treatment and prophylaxis of influenza, 2019-2020

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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
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Foreword

The influenza antiviral neuraminidase inhibitors (referred to herein as antivirals) are currently recommended for the treatment and prophylaxis (prevention) 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 antivirals in the treatment and prophylaxis of seasonal influenza. It draws on guidance already issued by PHE, ECDC, CDC and the 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 antivirals 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 (RCF) 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 an at-risk group. The targeted use of antivirals for post-exposure prophylaxis is recommended for those in at-risk groups.

Antivirals 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 antivirals from local consultant medical microbiologists and 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 RCF 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 (IDSA), ECDC and PHE. (2-6)

What has changed since the last version?

Changes from version 1.7 (2018-2019) include:

- Information on the recommended dosing for renal dysfunction in adults and children for treatment (Section 1.3.1) and chemoprophylaxis (Section 2.3.1)
- Additional information on chemoprophylaxis in neonates exposed to mothers who develop seasonal influenza in the peripartum period (Section 2.1)
- Updated information on the use of antivirals in pregnancy and breastfeeding (Section 2.1 and Appendix A)
- Updated information on Peramivir (Section 1.1) and antiviral medications that are currently unlicensed in Ireland including Baloxavir Marboxil (Appendix B)
- Addition of frequently asked questions (FAQs) (Appendix C)
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 RCF.  

**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 February 2019) - 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/μl or <15% of total lymphocytes in adult or child over five years; CD4 <500/μl or <15% of total lymphocytes in a child aged one to five; expert clinical opinion in a child aged under one year).
Introduction

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

Two antiviral medications are recommended for use in Ireland during the 2019-2020 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. \(^{7-9}\)

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 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 symptom onset if Oseltamivir is being used and within 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 symptom onset depending on which NAI is used. However, antiviral therapy may still be beneficial in patients with severe complicated or progressive illness and in hospitalised patients when administered more than 48 hours after symptom 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 a full course of antiviral treatment regardless of negative initial test results unless an alternative diagnosis can be established and clinical judgement suggests that influenza is an unlikely diagnosis. \(^{8}\)

This guidance should be used by clinicians in conjunction with the summary of product characteristics (SPC) for these medicines, particularly with reference to the contraindications, interactions and adverse events.
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

UNCOMPLICATED

Previously healthy

At risk group

Severely immunosuppressed?

NO:
First line:
oseltamivir PO/NG within 48 hours of onset or later at clinical discretion
2nd line:
zanamivir INH or IV and clinical follow-up

YES:
ooseltamivir PO
within 48 hours of onset or later at clinical discretion
OR
zanamivir INH (Diskhaler) 2 and clinical follow-up

COMPLICATED

Severe immunosuppression?

NO:
ooseltamivir PO/NG within 48 hours of onset or later at clinical discretion
2nd line:
zanamivir INH or IV and clinical follow-up

YES:
ooseltamivir PO
within 48 hours of onset or later at clinical discretion
OR
zanamivir INH (Diskhaler) 3 and clinical follow-up

1. For treatment of suspected or confirmed oseltamivir resistant influenza, see section 1.3.2.
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.

Footnote 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.
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).

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 administration is an unlicensed medication and is available only on a compassionate use basis for named patients in Ireland. The use of 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 IV zanamivir unless there is multiorgan failure.

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

In general, influenza A(H1N1)pdm09 is considered to be 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 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/

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 symptom onset. (9, 10, 14) Treatment after 48 hours is an off-label use of oseltamivir and clinical judgement should be used.

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

2 Footnote 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 Footnote 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.
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 IV zanamivir. This decision will always be based on clinical judgement. This is an unlicensed medication and dosage is as per the manufacturer’s guidance supplied with the drug. The use of 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).

**Peramivir (IV) (Alpivab)**

In 2018, the European Medicines Agency (EMA) approved the antiviral medication peramivir (IV) (Alpivab) for IV use for the treatment of acute uncomplicated influenza in adults and children aged over 2 years. 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.

Peramivir 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 IV infusion lasting 15 to 30 minutes (administered within 48 hours of onset of acute influenza symptoms). The dose depends on age and body weight, and should be reduced in adults and adolescents over 13 years of age with impaired renal function. It is shown to reduce duration of symptoms in patients with influenza.


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 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/seasonalinfluenza/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 zanamivir which is an unlicensed use.

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 may be considered for IV zanamivir. The use of 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).

The following patients may be considered for IV zanamivir:
1. Patients who have multi-organ involvement
2. 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

4 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
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 may be considered for IV zanamivir (unlicensed). IV zanamivir (unlicensed) based on clinician’s judgment may be considered for patients who: (a) have multi-organ involvement, or (b) require intensive care. The use of 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 may be considered for IV zanamivir (unlicensed). IV zanamivir (unlicensed) based on the clinician’s judgement may be considered for patients who have multi-organ involvement or require intensive care.

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**Footnote 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 for treatment

The recommended duration of antiviral treatment is 5 days. However, longer treatment regimens based on clinical judgement may be necessary in severely ill hospitalised patients or patients with immunosuppression. The optimal duration of treatment for hospitalised patients with influenza is not clear. Persistent detection of viral ribonucleic acid (RNA) and 'rebound' of previously undetectable viral RNA have been described in patients with severe influenza who completed 5 or 7 day courses of oseltamivir.

Extending the duration of treatment to at least 10 days may be appropriate in patients with severe influenza (e.g. critically ill patients) and in severely immunosuppressed patients. The manufacturer of oseltamivir recommends a longer treatment course of 75mg PO twice daily for 10 days for immunosuppressed patients. Prolonged treatment can be associated with development of antiviral resistance, particularly in immunosuppressed patients, and antiviral resistance monitoring is recommended. Use of oseltamivir as treatment for longer than 5 days is an off-label use.

Table 1: Antiviral treatment dosages and schedules for treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Premature (less than 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)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir PO</td>
<td>1mg/kg/dose bd Unlicensed (see footnote 6)</td>
<td>3mg/kg/dose bd</td>
<td>30mg bd</td>
<td>75mg bd</td>
</tr>
<tr>
<td>(treatment course: 5 days)</td>
<td></td>
<td></td>
<td>45mg bd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60mg bd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75mg bd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75mg bd</td>
<td></td>
</tr>
<tr>
<td>Zanamivir</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>
<td></td>
<td></td>
</tr>
<tr>
<td>(see footnote 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(inhaled treatment course: 5 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 an unlicensed use of oseltamivir and is based on evidence from literature and expert opinion [19-21]. Zanamivir is manufactured by GlaxoSmithKline. Zanamivir is approved for the treatment of persons aged ≥5 years in Ireland.

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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.
supported by the British National Formulary (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
Aqueous zanamivir solution for IV administration is currently 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 IV zanamivir are included in section 1.2 above.

For the use of oseltamivir and zanamivir in pregnancy and breastfeeding see Appendix A. For dosing in renal dysfunction, see Section 1.3.1.

Note on dosing for extremes of weight:
Oseltamivir: no dose adjustment is needed in obese patients. (22 - 24)
Inhaled 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: Dosing in patients with renal dysfunction (5)

The information provided here on dosing in renal impairment and renal failure is intended specifically for consideration when patients have an existing history of chronic kidney disease (CKD) and renal failure results have been previously documented for the purpose of managing CKD. As with other groups, it is essential to initiate treatment as soon as possible.

The choice of dose in renal failure is complicated by the different measures available to describe degree of renal impairment, as well as a lack of specific data in some circumstances. Creatinine Clearance (CrCl) is used in this document as it is a more accurate measure upon which to make dosing recommendations and is congruent with the manufacturers prescribing information for both oseltamivir and zanamivir. The limitations for using eGFR are described in the British National Formulary (‘Prescribing in renal impairment’). CrCl can be estimated in adults by utilising the Cockcroft and Gault equation. Both eGFR and CrCl (using Cockcroft and Gault) assume the patient’s renal function is stable. Clinical judgement will be required where renal function is unstable (i.e. in acute renal failure).

It is recognised that eGFR may be more readily available at the outset of therapy. If this is the only value available then do not delay therapy and prescribe a dose according to eGFR (substituting eGFR for the CrCl figure in Table 2). Some patients may receive a larger oseltamivir dose as a result, but this is unlikely to be harmful as clinical experience reveals a wide margin of safety. The use of IV zanamivir is anticipated to only occur in hospitals, and as such all the data necessary to make a CrCl calculation will be available; do not use eGFR in this setting.
Table 2: Recommended oseltamivir treatment dosing in renal dysfunction (adults and those aged 13 years and over) (5)

<table>
<thead>
<tr>
<th>CrCL (ml/min)</th>
<th>Osealtamivir PO Treatment for 5 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60mL/min*</td>
<td>75mg BD</td>
</tr>
<tr>
<td>31-60 mL/min*</td>
<td>30mg BD</td>
</tr>
<tr>
<td>11-30mL/min*</td>
<td>30mg OD</td>
</tr>
<tr>
<td>≤10mL/min++</td>
<td>30mg ONCE</td>
</tr>
<tr>
<td>Haemo-dialysis (HD)*</td>
<td>30mg ONCE and then 30mg after every HD session</td>
</tr>
<tr>
<td>Peritoneal dialysis'</td>
<td>30mg ONCE</td>
</tr>
<tr>
<td>Haemo(dia)filtration++</td>
<td>30mg OD</td>
</tr>
<tr>
<td>1.1.8L/hr exchange rate</td>
<td></td>
</tr>
<tr>
<td>Haemo(dia)filtration++</td>
<td>30mg BD</td>
</tr>
<tr>
<td>1.9 – 3.6L/hr exchange rate</td>
<td></td>
</tr>
<tr>
<td>Haemo(dia)filtration++</td>
<td>75mg BD</td>
</tr>
<tr>
<td>&gt; 3.6L/hr exchange rate</td>
<td></td>
</tr>
</tbody>
</table>

Source: Summary of Product Characteristics (SPC) updated Jan 2017 (*). The recommendations for haemo(dia)filtration and established renal failure are based on expert opinion (++).

Note: It is acknowledged that some of the advice for dosing in renal impairment presented in Table 2 may differ to the renal drug handbook; however, the dosage information presented above is consistent with the summary of product characteristics provided by the manufacturer at the time of writing.

Section 1.3.2: 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.
4. Those with complicated influenza may receive inhaled or IV 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 1.3.3: 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 IV zanamivir should be supervised by a consultant in intensive care medicine.

Section 2: Post exposure prophylaxis

Key points:

- Chemoprophylaxis (oseltamivir/ zanamivir) may be considered for people in at risk groups who have had recent close contact with a person with influenza or influenza like illnes (ILI) in the same household or residential setting when influenza is circulating in the community.
- Chemoprophylaxis may be considered if the contact is not adequately protected by vaccination OR where the person has been exposed in the context of a local outbreak, regardless of vaccination status.
- 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.

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 when influenza is circulating in the community. Previous influenza vaccination does not preclude the use of post exposure prophylaxis, in particular where localised outbreaks occur in residential care facilities (RCF). (see footnote 9)

As 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...)

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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. (30)

9 See guidance re the management of influenza/ILI outbreaks in residential care facilities at http://www.hpsc.ie/A-Z/Respiratory/Influenza/SeasonalInfluenza/Guidance/ResidentialCareFacilitiesGuidance/
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.\(^\text{(5, 31)}\)

Chemoprophylaxis is not routinely considered in at-risk groups who have been vaccinated against seasonal influenza at least 14 days prior to exposure, with the above exceptions.

**An alternative to chemoprophylaxis in some clinical settings may be to monitor persons exposed to an influenza case and commence antiviral treatment promptly if symptoms of influenza arise.**\(^\text{(5)}\)

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 be made on a case-by-case basis, taking into account:

1. the exposed person’s risk of developing influenza complications
2. the type and duration of contact
3. clinical judgement\(^\text{(8)}\)

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 is an off-label use and should be based on specialist advice only.

**Section 2.1: Chemoprophylaxis in specific settings/ risk groups**

- **Residential care facilities (RCF):**

  Specialist advice should be sought regarding chemoprophylaxis in these situations. See guidance on the management of influenza in residential care facilities available on the HPSC website.

- **Pregnant and postpartum women:**

  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 footnote10) with someone likely to have been infectious with influenza. Clinical judgement should 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.\(^\text{(30)}\)

  See http://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/guidance/pregnancyguidance/

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10 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.\(^\text{(30)}\)
An alternative approach for pregnant women who have had close contact with a patient with laboratory confirmed 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 antiviral treatment if clinical signs or symptoms develop following a risk assessment.

- **Neonates exposed to mothers who develop seasonal influenza in the peripartum period:**

As pregnancy confers increased risk of complicated influenza, antiviral treatment of a pregnant woman with seasonal influenza should be strongly considered, commensurate with recommendations outlined earlier in this guidance document. A particular clinical challenge arises with regard to the neonate if a pregnant woman develops laboratory confirmed seasonal influenza shortly before the onset of labour. The potential mode of transmission to the neonate in such a scenario is via direct contact with the infected respiratory secretions of the mother rather than via breastmilk.

There are limited data regarding seasonal influenza infection in neonates. The Influenza Clinical Information network (Flu-CIN) study reported severe outcomes in 9.3% of children aged less than 12 months in the UK who were hospitalised with influenza A(H1N1)pdm09 during the 2009-2010 pandemic.

The Summary of Product Characteristics (SPC) for Tamiflu® (oseltamivir) oral suspension states that the medicine can be used for post-exposure prevention of influenza in infants aged over 1 year; therefore oseltamivir prophylaxis for infants aged less than 1 year is an off-label use. Treatment of seasonal influenza in children, including full term neonates, is however, specified in the SPC for capsules and Tamiflu® (oseltamivir) 6mg/ml Powder for Oral suspension. Relenza® (zanamivir) inhalation powder is not licensed for treatment or prophylaxis in children less than 5 years of age.

There are three potential options which may be considered by mothers and clinicians in relation to neonates:

1. Oseltamivir oral suspension for post-exposure prophylaxis in the neonate, as an off-label use.
   As prophylaxis reduces but does not eliminate the risk of infection, infants should be closely monitored for signs and symptoms of Influenza. The mother should be advised of measures to reduce risk of transmission including respiratory hygiene and cough etiquette, use of a facemask during close contact and handwashing with soap and water, particularly before breast feeding or touching any other item that the neonate may come in contact with. If expressing breast milk using a pump, this should be cleaned as per the manufacturer's instructions.

2. Physical separation of the symptomatic mother and asymptomatic neonate until 5 days after symptom onset.
   Disadvantages for the neonate would include not being able to benefit from breastfeeding-related transfer of immune factors and nutrients. These considerations should be included in the discussion with the mother. Women should be encouraged to express breastmilk so that the neonate can receive the benefits of breastmilk, and to maintain the mother's milk supply in order that breastfeeding can continue once mother and baby are reunited.

3. No prophylaxis for the neonate and no separation of neonate and mother.
   This will require careful monitoring for symptoms of influenza, a discussion in advance with the mother about prompt antiviral treatment of the neonate, and advance arrangements for rapidly accessing oseltamivir oral suspension if required (as this is more readily available via hospital pharmacies than community pharmacies). There should also be consideration of laboratory testing of a symptomatic neonate, as per existing local arrangements. In this situation, the mother should be advised of measures to reduce risk of transmission, including respiratory hygiene and cough etiquette, use of personal protective equipment such as a facemasks, and handwashing with soap and water, particularly before breast feeding or touching any other item that the neonate may come in contact with. If expressing breast milk using a pump, this should be cleaned as per the manufacturer's instructions.
Decisions regarding the most appropriate course of action should be made on a case-by-case basis and are likely to involve detailed discussion between the mother and physician regarding the relative advantages and disadvantages of each potential option. This advice does not constitute a specific endorsement of the routine use of oseltamivir oral suspension for prophylaxis in neonates, but recognises that this may occur as an off-label use in specific circumstances. Such clinical scenarios highlight the importance of seasonal influenza vaccination of pregnant women; previous research has shown that this was 71% effective in preventing influenza infection in infants aged less than 6 months in England.\(^{(41,42)}\)

### Section 2.2: Selection of antivirals for post exposure chemoprophylaxis

#### Table 3: Selection of antivirals for post-exposure chemoprophylaxis

<table>
<thead>
<tr>
<th></th>
<th>Exposed to influenza A or B</th>
<th>Exposed to suspected or confirmed oseltamivir resistant influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously healthy (excluding pregnant women)</td>
<td>No prophylaxis.</td>
<td>No prophylaxis</td>
</tr>
<tr>
<td>At risk of complicated influenza (including pregnant women, but excluding severely immunosuppressed patients and excluding children aged &lt; 5 years old)</td>
<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>
</tr>
<tr>
<td>Severeley immunosuppressed patients (excluding children aged &lt; 5 years old)</td>
<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. If unable to administer zanamivir INH monitor closely and begin treatment promptly if ILI symptoms develop.</td>
</tr>
<tr>
<td>Children aged &lt; 5 years in at risk group including severely immunocompromised children</td>
<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>Discuss with specialist. Consider IV zanamivir (unlicensed) after individual risk assessment.</td>
</tr>
</tbody>
</table>
Section 2.3: Antiviral dosage and schedules for post exposure chemoprophylaxis

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) (^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤15kg</td>
<td>&gt;15-23kg</td>
<td>&gt;23-40kg</td>
</tr>
<tr>
<td>Oseltamivir PO (prophylaxis course: 10 days)</td>
<td>See below (see footnote 11)</td>
<td>3 mg/kg od</td>
<td>30 mg od</td>
<td>45 mg od</td>
</tr>
<tr>
<td>Zanamivir INH (prophylaxis course: 10 days)</td>
<td>Not licensed in children aged &lt;5 years old</td>
<td>Children aged ≥5 years : 10 mg (2 inhalations) od</td>
<td>10 mg (two 5 mg inhalations) od</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 less 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 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).

\(^1\) Although it may be possible to provide half the treatment frequency each day for 10 days there is currently no publicly available dosing information for oseltamivir prophylaxis in pre-term infants so it is outside the product licence.
Section 2.3.1: Dosing in patients with renal dysfunction

General considerations about prescribing for renal impairment discussed in the treatment section (section 1.3.1) may also be applicable when prescribing for prophylaxis, except that the dosage of oseltamivir in Table 5 should be used.

Table 5: Recommended oseltamivir prophylaxis dosing in renal impairment (adults and those aged 13 years or over)

<table>
<thead>
<tr>
<th>CrCL (ml/min)</th>
<th>Oseltamivir PO prophylaxis for 10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60mL/min*</td>
<td>75mg OD</td>
</tr>
<tr>
<td>31-60 mL/min*</td>
<td>30mg OD</td>
</tr>
<tr>
<td>11-30mL/min*</td>
<td>30mg every 48 hours</td>
</tr>
<tr>
<td>≤10mL/min**</td>
<td>30mg ONCE, repeated after 7 days</td>
</tr>
<tr>
<td>Haemo-dialysis (HD)*</td>
<td>30mg ONCE and then 30mg after every second HD session</td>
</tr>
<tr>
<td>Peritoneal dialysis*</td>
<td>30mg ONCE, repeated after 7 days</td>
</tr>
<tr>
<td>Haemo(dia)filtration**</td>
<td></td>
</tr>
<tr>
<td>1-1.8L/hr exchange rate</td>
<td>30mg every 48 hours</td>
</tr>
<tr>
<td>Haemo(dia)filtration**</td>
<td>30mg OD</td>
</tr>
<tr>
<td>1.9-3.6L/hr exchange rate</td>
<td></td>
</tr>
<tr>
<td>Haemo(dia)filtration**</td>
<td>75mg OD</td>
</tr>
<tr>
<td>&gt;3.6L/hr exchange rate</td>
<td></td>
</tr>
</tbody>
</table>

Source: Summary of Product Characteristics updated Jan 2017 (*). The recommendations for haemo(dia)filtration and established renal failure are based on expert opinion (++)

Note: It is acknowledged that some of the advice for dosing in renal impairment presented here may differ to the renal drug handbook; however, the dosage information presented above is consistent with the summary of product characteristics provided by the manufacturer, at the time of writing.

No difference in prophylaxis dosing for high flu and low flux intermittent haemodialysis (HD) is recommended due to a lack of published clinical data on oseltamivir carboxylate levels in highflux intermittent HD patients; this advice is expert opinion based on information on pore size, OC molecule size and likely length of HD sessions.

For children aged less than 13 years, adjust the Oseltamivir dose as per the Oseltamivir chapter in the BNF for children: https://bnfc.nice.org.uk/drug/oseltamivir.html#renalImpairment
Appendix A: Use of antivirals in pregnancy, breastfeeding, hepatic dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Liver dysfunction</th>
<th>Renal dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>Standard dosing</td>
<td>See product information for oseltamivir available <a href="http://www.hpra.ie/homepage/site-tools/search?query=oseltamivir">here</a></td>
</tr>
<tr>
<td>INH (Diskhaler)</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">here</a></td>
</tr>
<tr>
<td>Zanamivir solution IV</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>
</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:

“Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations, including congenital heart defects. A large amount of data on oseltamivir exposure of pregnant women from post-marketing reports and observational studies (more than 1000 exposed outcomes during the first trimester) indicate no malformative or feto/neonatal toxicity by oseltamivir. However, in one observational study, while the overall malformation risk was not increased, the results for major congenital heart defects diagnosed within 12 months of birth were not conclusive. In this study, the rate of major congenital heart defects following oseltamivir exposure during the first trimester was 1.76% (7 infants out of 397 pregnancies) compared to 1.01% in unexposed pregnancies from the general population (Odds Ratio 1.75, 95% Confidence Interval 0.51 to 5.98). The clinical significance of this finding is not clear, as the study had limited power. Additionally, this study was too small to reliably assess individual types of major malformations; moreover women exposed to oseltamivir and women unexposed could not be made fully comparable, in particular whether or not they had influenza. Animal studies do not indicate reproductive toxicity.” (34)

“The use of Tamiflu may be considered during pregnancy if necessary and after considering the available safety and benefit information and the pathogenicity of the circulating influenza virus strain.” (34)

The Summary of Product Characteristics (SPC) for Relenza® (zanamivir) states the following:

“Systemic exposure to zanamivir is low following administration by inhalation; however, there is no
information on placental transfer of zanamivir in humans. There is a limited amount of data (less than 300 pregnancy outcomes) from the use of zanamivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Relenza during pregnancy, unless the clinical condition of the woman is such that the potential benefit to the mother significantly outweighs the possible risk to the foetus.” (33)

**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/](https://www.sps.nhs.uk/articles/oseltamivir-or-zanamivir-can-mothers-breastfeed-after-treatment-for-influenza-2/)
Appendix B: Unlicensed antiviral medications

All of the following influenza treatments are unlicensed. The prescription of unlicensed medication is the clinical responsibility of the prescribing physician. It is essential that the prescribing physician return the case data requested by the manufacturer – this is an important component of safety monitoring. Specialist advice should always be sought prior to initiating unlicensed treatment for influenza.

- **Zanamivir aqueous solution**: Zanamivir aqueous solution for IV administration is currently an unlicensed medication and is available only on a compassionate use basis for named patients in Ireland. The use of 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 IV zanamivir unless there is multiorgan failure.

- **Baloxavir marboxil (PO)** is a novel, single dose, oral antiviral agent that demonstrates antiviral activity against influenza A and B. It is a cap-dependent endonuclease inhibitor and, as such, has a different mechanism of action from the neuraminidase inhibitors. Baloxavir received regulatory approval in Japan in 2018 and was approved by the US Food and Drug Administration in October 2018 for the treatment of acute uncomplicated influenza in patients aged 12 years and older who have been symptomatic for no more than 48 hours. Baloxavir is unlicensed in Europe. Phase III trials have been completed in uncomplicated influenza and in high-risk groups for complications of influenza. The results of further phase III trials in paediatric and hospitalised patients with severe influenza are awaited. Resistance is a potential concern, as the development of reduced susceptibility to Baloxavir following treatment has been observed in clinical trials. (36)

The following antivirals are unlicensed for the treatment of influenza in Europe and should only be used in the context of an approved research protocol:

- **Ribavirin (IV)** is unlicensed for the treatment of influenza and should only be used in the context of an approved research protocol. It should never be used for influenza treatment of chemoprophylaxis in pregnant women.

- **Favipiravir (PO)** is a novel antiviral medication which inhibits viral RNA-dependent RNA polymerase. Favipiravir is approved for use in Japan under strictly defined circumstances – i.e. in patients infected with novel or re-emerging influenza viruses (i.e. in the event of a pandemic), and only when the virus is resistant to other antiviral agents. Favipiravir is unlicensed for use in Ireland and should only be used in the context of an approved research protocol. Animal studies have generated concerns in relation to teratogenicity.

- **Laninamivir (INH)** is a neuraminidase inhibitor that has been licensed in Japan for influenza treatment and chemoprophylaxis. Recent data demonstrate that Laninamivir may be useful for Post Exposure Prophylaxis (PEP). Laninamivir is unlicensed in Ireland and should only be used in the context of an approved research protocol.
Appendix C: Frequently asked questions

Q. When should I consider extending antiviral therapy beyond 5 days?
The recommended duration of antiviral treatment is 5 days. However, longer treatment regimens based on clinical judgement may be necessary in severely ill hospitalised patients or patients with immunosuppression. The optimal duration of treatment for hospitalised patients with influenza is not clear. Persistent detection of viral ribonucleic acid (RNA) and ‘rebound’ of previously undetectable viral RNA have been described in patients with severe influenza who completed 5 or 7 day courses of oseltamivir. Extending the duration of treatment to at least 10 days may be appropriate in patients with severe influenza (e.g. critically ill patients) and in severely immunosuppressed patients. The manufacturer of oseltamivir recommends a longer treatment course of 75mg PO twice daily for 10 days for immunosuppressed patients. Prolonged treatment can be associated with development of antiviral resistance, particularly in immunosuppressed patients, and antiviral resistance monitoring is recommended. Use of oseltamivir as treatment for longer than 5 days is an off-label use.

Q. What is meant by “poor clinical response to first line treatment”?
A poor clinical response in a patient receiving first line antiviral medication may constitute any of the following:

- No clinical improvement
- Progressive lower respiratory tract signs or symptoms
- New or progressive multi-organ dysfunction

Potential explanations for a poor clinical response include, but are not limited to, antiviral resistance. Antiviral resistance has been rare in recent influenza seasons, but is most frequently observed in cases of infection with influenza A(H1N1)pdm09 as opposed to other seasonal influenza viruses. Additional risk factors for antiviral resistance include severe immunosuppression.

Absence of clinical improvement, or clinical deterioration, may also be caused by the natural progression of acute lung injury and the inflammatory response that accompanies influenza infection, or by secondary infection, e.g. bacterial co-infection. Therefore, decisions regarding the presence or absence of a “poor clinical response”, and the underlying aetiology, must be made by the treating physician on a case-by-case basis, guided by these considerations.

Q. Which groups of patient are at risk of antiviral resistance?
Among patients in receipt of influenza antiviral treatment, immunocompromised individuals and young children are at increased risk of harbouring viruses that demonstrate antiviral resistance. This may be explained by prolonged duration of infection and/or higher viral burden compared to other patient groups. Rapid emergence of oseltamivir resistance (as early as 48 hours after initiation of treatment) has been described, particularly in severely immunocompromised individuals.

Between July 2009 and April 2010, 285 cases of oseltamivir-resistant pandemic influenza A(H1N1)pdm09 infection were reported globally, including 45 cases in the UK. Of these UK cases, data regarding underlying medical conditions were available for 28. Of these 28 cases, 21 (75%) were immunosuppressed, the most common underlying condition being leukaemia (11 of 21).

Q. If zanamivir resistance is suspected, should I switch to oseltamivir?
No. Recent antiviral resistance surveillance data demonstrate that oseltamivir resistance remains more common than zanamivir resistance. Several mutations that confer resistance to zanamivir are also associated with resistance or reduced susceptibility to oseltamivir. If zanamivir resistance is suspected (e.g. as a causative factor in poor clinical response to antiviral treatment), then zanamivir treatment should be continued and urgent testing for resistance should be undertaken. Advice should be sought from local infection specialists, e.g. consultant medical virologist.
Q. What is the role of repeat sampling and laboratory testing in patients undergoing treatment with antiviral medication?

It can be challenging to assess clinical improvement in specific patient groups that may demonstrate atypical or minimal clinical signs and symptoms, e.g. immunosuppressed patients, or may be unable to describe their symptoms, e.g. unconscious/ventilated patients. In such patients with confirmed influenza infection who are receiving antiviral therapy, repeat/“follow-up” sampling for detection of viral RNA by polymerase chain reaction (PCR) may be considered under the following circumstances:

- Clinical deterioration or unresolved illness despite at least 5 days of antiviral medication, potentially necessitating a prolonged duration of antiviral treatment
- Development of influenza illness while in receipt of prophylactic-dose antivirals; either test at time of symptom onset or test according to clinical deterioration

Repeat sampling is not routinely recommended in patient groups or clinical contexts beyond those described above.

When repeat testing has been performed due to suspected treatment failure, antiviral resistance testing on any positive sample should be considered, and is recommended if the patient is immunosuppressed. Comparing estimated viral load in the initial and repeat samples may be helpful in assessing the antiviral effect.

If oseltamivir resistance is suspected and further treatment is required, consider switching to zanamivir without awaiting results of resistance testing. Treatment interruption should be avoided as it may promote development of antiviral resistance.

If repeat/follow-up testing yields positive results, the need for ongoing IPC measures for inpatients must be considered by healthcare workers (HCW).

In some cases repeat testing may be undertaken when considering transfer of a patient with laboratory confirmed influenza from an isolation room to an open ward/unit. In this scenario, repeat testing requests should be discussed with the testing laboratory, as an immunofluorescence assay (IFA) may provide more useful information than PCR testing. This is because PCR testing detects residual viral RNA and is likely to remain positive in patients with influenza who are no longer infectious, but IFA only detects viable virus and is likely to be negative in patients who are no longer infectious, providing support for decisions to transfer such patients to an open ward/unit.

Q. Should unvaccinated hospital-based healthcare workers (HCW) with no underlying illness be offered antiviral chemoprophylaxis?

In the hospital setting, chemoprophylaxis is only recommended for at-risk groups and should not be considered as an alternative to vaccination. The use of prophylactic antivirals in individuals who are not in risk groups as an influenza outbreak control measure in the hospital setting is not recommended. HCWs who are not in risk groups may continue to work, using appropriate personal protective equipment (PPE), and should be advised to immediately report any signs or symptoms of illness. They should be promptly excluded from work if they develop any signs or symptoms of influenza/ILI. It is imperative that the importance of annual seasonal influenza vaccination, and non-attendance at work if unwell, is emphasised to HCWs.

Q. What is the role of previous laboratory-confirmed influenza when a person presents with a new episode of ILI in the same influenza season?

The two episodes of infection should be considered separately and treatment prescribed, if indicated, on both occasions. It is entirely possible that the first infection is with an influenza A virus and the subsequent infection is with an influenza B virus, or vice versa, or subsequent infection may be with a different A/subtype or B/lineage virus, so there would be no protective effect from the first exposure.

Q. Should antiviral medication be offered in neonates exposed to mothers with seasonal influenza?

As pregnancy confers increased risk of complicated influenza, antiviral treatment of a pregnant woman with seasonal influenza should be strongly considered, commensurate with recommendations outlined
earlier in this guidance document. A particular clinical challenge arises with regard to the neonate if a pregnant woman develops laboratory confirmed seasonal influenza shortly before the onset of labour. The potential mode of transmission to the neonate in such a scenario is via direct contact with the infected respiratory secretions of the mother rather than via breastmilk.

There are limited data regarding seasonal influenza infection in neonates. The Influenza Clinical Information network (Flu-CIN) study reported severe outcomes in 9.3% of children aged less than 12 months in the UK who were hospitalised with influenza A(H1N1)pdm09 during the 2009-2010 pandemic.\textsuperscript{(40)}

The Summary of Product Characteristics (SPC) for Tamiflu\textsuperscript{®} (oseltamivir) \textit{oral suspension} states that the medicine can be used for post-exposure prevention of influenza in infants aged over 1 year; therefore oseltamivir prophylaxis for infants aged less than 1 year is an off-label use. Treatment of seasonal influenza in children, including full term neonates, is however, specified in the SPC for capsules and Tamiflu\textsuperscript{®} (oseltamivir) 6mg/ml Powder for Oral suspension. Relenza\textsuperscript{®} (zanamivir) inhalation powder is not licensed for treatment or prophylaxis in children less than 5 years of age.

There are three potential options which may be considered by mothers and clinicians in relation to neonates:

1. 
   Oseltamivir oral suspension for post-exposure prophylaxis in the neonate, as an off-label use.
   As prophylaxis reduces but does not eliminate the risk of infection, infants should be closely monitored for signs and symptoms of Influenza. The mother should be advised of measures to reduce risk of transmission including respiratory hygiene and cough etiquette, use of a facemask during close contact and handwashing with soap and water, particularly before breast feeding or touching any other item that the neonate may come in contact with. If expressing breast milk using a pump, this should be cleaned as per the manufacturer's instructions.

2. 
   Physical separation of the symptomatic mother and asymptomatic neonate until 5 days after symptom onset.
   Disadvantages for the neonate would include not being able to benefit from breastfeeding-related transfer of immune factors and nutrients. These considerations should be included in the discussion with the mother. Women should be encouraged to express breastmilk so that the neonate can receive the benefits of breastmilk, and to maintain the mother's milk supply in order that breastfeeding can continue once mother and baby are reunited.

3. 
   No prophylaxis for the neonate and no separation of neonate and mother.
   This will require careful monitoring for symptoms of influenza, a discussion in advance with the mother about prompt antiviral treatment of the neonate, and advance arrangements for rapidly accessing oseltamivir oral suspension if required (as this is more readily available via hospital pharmacies than community pharmacies). There should also be consideration of laboratory testing of a symptomatic neonate, as per existing local arrangements. In this situation, the mother should be advised of measures to reduce risk of transmission, including respiratory hygiene and cough etiquette, use of personal protective equipment such as a facemasks, and handwashing with soap and water, particularly before breast feeding or touching any other item that the neonate may come in contact with. If expressing breast milk using a pump, this should be cleaned as per the manufacturer's instructions.

Decisions regarding the most appropriate course of action should be made on a case-by-case basis and are likely to involve detailed discussion between the mother and physician regarding the relative advantages and disadvantages of each potential option. This advice does not constitute a specific endorsement of the routine use of oseltamivir oral suspension for prophylaxis in neonates, but recognises that this may occur as an off-label use in specific circumstances. Such clinical scenarios highlight the importance of seasonal influenza vaccination of pregnant women; previous research has shown that this was 71\% effective in preventing influenza infection in infants aged less than 6 months in England.\textsuperscript{(41,42)}
Q. Should diagnostic sampling for influenza be performed when commencing antiviral post-exposure prophylaxis?

When a decision has been made to administer antiviral prophylaxis to contacts of a confirmed case, diagnostic sampling of the contacts for influenza virus detection is recommended before or at the time of commencing antiviral prophylaxis in immunosuppressed and critically ill patients.

This is based on expert advice as symptoms and signs of influenza may be absent, minimal or atypical in these patient groups, or may be difficult to assess due to their clinical status. It is important to note that prophylactic doses of antivirals can promote antiviral resistance in patients already infected with influenza virus, especially when there is underlying immunosuppression.

While prophylaxis should not be postponed while the results of influenza testing are awaited, influenza virus testing should be expedited. If testing demonstrates that a patient in receipt of a prophylactic dose of an antiviral is actually infected with influenza virus, then prophylaxis should be stopped and treatment-dose antivirals should be commenced immediately. Any prophylactic doses received should not be counted when determining the duration of treatment-dose antivirals.

Following the positive influenza test result, physicians and HCWs should be reminded that IPC measures should be implemented and that it is not possible to predict duration of viral shedding for individual patients. It should be noted in advance of implementing this advice, that in the absence of influenza symptoms, cessation of IPC measures will need to be considered locally by an infection specialist, on a case by case basis.

Q. Should the standard treatment dose of Oseltamivir be doubled (“double-dosing”) when treating patients with severe illness caused by seasonal influenza infection?

An increase in dosage is no longer recommended in patients with severe illness caused by influenza A virus infection, due to a lack of evidence that it is any more effective than standard dosing. (43)

Although it has been previously reported that higher inhibitory concentrations of oseltamivir carboxylate are required to produce an effect on Influenza B in in-vitro tests (43,44), there is insufficient evidence to support double-dosing in patients with Influenza B in vivo. (45)
References

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