



Public Health  
England

Protecting and improving the nation's health

# **PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza**

Version 7.0, October 2016

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**Version Control:** This version 7.0 updates version 6.0 (September 2015) with the addition of sections on use in pregnant women, algorithms for prescribing in primary and secondary care and frequently asked questions.

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## Foreword

Antiviral medicines known as neuraminidase inhibitors are only one part of a wider package of measures to prevent severe influenza-related illness and death; other measures include seasonal influenza vaccination at the start of the influenza season and infection prevention and control practices (1).

These medicines (herein referred to as antivirals), are currently recommended by a number of organisations including the National Institute for Health and Clinical Excellence (NICE) and the World Health Organization (WHO) for the treatment and prophylaxis of seasonal influenza. In keeping with other organisations' recommendations, this Public Health England (PHE) guidance recommends the targeted use of antiviral medicines for the treatment of or prophylaxis against seasonal influenza for specific clinical settings.

In England, antiviral medicines may be prescribed at any time in the secondary care setting for patients with suspected seasonal influenza infection. However, general practitioners in England may only prescribe these medicines in primary care when the Chief Medical Officer has announced that influenza is circulating within the community (see [Appendix 2](#)). Laboratory testing to confirm or refute influenza may be undertaken. This is particularly important if an individual develops symptoms despite antiviral prophylaxis, or has a persistent infection despite antiviral treatment, in order to identify the potential development of antiviral resistance. ([PHE guidance](#)).

The guidance in this document is based on available information from a range of data sources as well as expert opinion. It should be noted that some of the recommendations included in this guidance involve the off-label use of licensed medications, or unlicensed medications, for which there may be limited safety and efficacy data. In these instances, such recommendations are the views of PHE only and not of the manufacturer.

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 infection specialists. Further advice for infection specialists is available from virologists based in regional PHE public health laboratories. Local health protection teams should be contacted about localised influenza-related outbreaks, such as in care homes ([link to find your local health protection team](#)). Separate guidance on the management of influenza in these settings is available.

Clinicians may be aware of a Cochrane Review on the efficacy of antivirals, published in 2014 (2). PHE has previously published a detailed response to this and clinicians should note that the NICE guidelines for antiviral medications for influenza remain unchanged (3).

## Definitions

**1. Uncomplicated influenza:** Influenza presenting with fever, coryza, generalised symptoms (headache, malaise, myalgia, arthralgia) and sometimes gastrointestinal symptoms, but without any features of complicated influenza.

**2. 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.

**3. Risk factors for complicated influenza:**

- a. Neurological, hepatic, renal, pulmonary and chronic cardiac disease.
- b. Diabetes mellitus.
- c. Severe immunosuppression.
- d. Age over 65 years.
- e. Pregnancy (including up to two weeks post partum).
- f. Children under 6 months of age.
- g. Morbid obesity (BMI  $\geq 40$ ).

For full details refer to *Immunisation against infectious disease*, known as the Green Book (4).

**4. Severe immunosuppression:** Examples of severe immunosuppression relevant to this guidance are given 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 within 12 months of receiving immunosuppression.
- e. Patients with current graft-versus-host disease.
- f. Patients currently receiving high dose systemic corticosteroids (equivalent to  $\geq 40$  mg prednisolone per day for  $>1$  week in an adult, or  $\geq 2$ mg/kg/day for  $\geq 1$  week in a child), and for at least three months after treatment has stopped.
- g. HIV infected patients with severe immunosuppression (CD4  $< 200/\mu\text{l}$  or  $< 15\%$  of total lymphocytes in an adult or child over five; CD4  $< 500/\mu\text{l}$  or  $< 15\%$  of total lymphocytes in a child aged one to five; expert clinical opinion in a child aged under one).
- h. Patients currently or recently (within six months) on other types of highly immunosuppressive therapy or where the patient's specialist regards them as severely immunosuppressed.

## Acronyms used in this document

bd – twice a day

BNF – British National Formulary

CrCl – creatinine clearance

eGFR – estimated glomerular filtration rate

INH – inhaled

IV – intravenous

NEB – nebulised

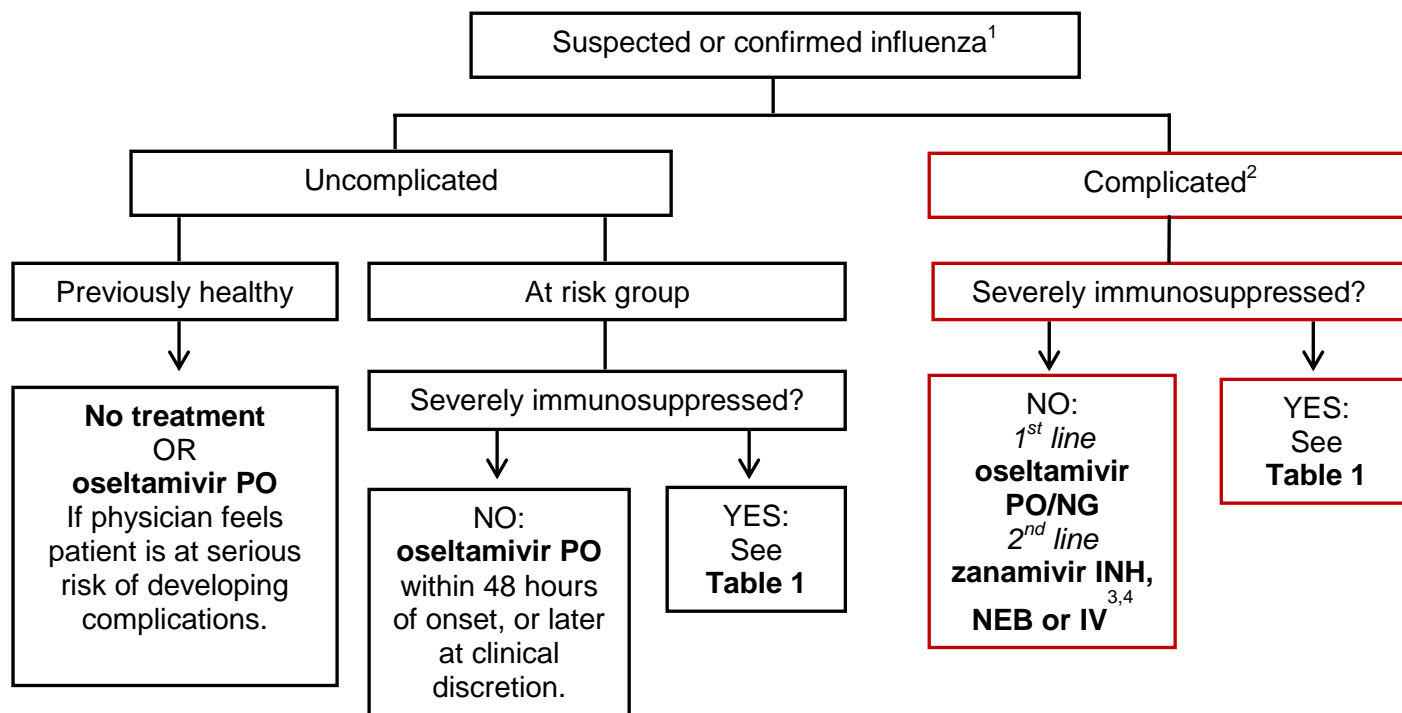
NG – nasogastric (administration via a nasogastric tube)

OD – once a day

PO – “Per Os”; by mouth

# Part 1: Treatment of suspected or confirmed influenza

## Algorithm: Selection of antiviral therapy for treatment of influenza



Please refer to the **definitions** provided on page 6, and **Table 1** on page 9 when using this algorithm.

<sup>1</sup>For treatment of suspected or confirmed **oseltamivir resistant** influenza, see **section 1.3.2**.

<sup>2</sup>For treatment of complicated influenza, see **section 1.2**. Use second line treatment if there is poor response to oseltamivir, or if there is poor gastrointestinal absorption.

<sup>3</sup>Inhaled zanamivir via Diskhaler<sup>®</sup> may not be an effective delivery route in some patients, including those unable to administer the Diskhaler<sup>®</sup> and patients with severe underlying respiratory disease. It is not licensed for use in children less than five years. The powder preparation for the Diskhaler<sup>®</sup> should NEVER be made into nebuliser solution or administered to a mechanically ventilated patient.

<sup>4</sup>Zanamivir solution for IV or nebulised administration is an unlicensed medication and is available on a compassionate use basis for named patients in the UK, see **section 1.3**. Where possible, patients who have good respiratory function despite their illness and can use the Diskhaler<sup>®</sup> may receive inhaled zanamivir. Clinical scenarios where nebulized or IV zanamivir may be more appropriate (eg critical illness) are described in **section 1.2**.



Some influenza subtypes are associated with a greater risk of developing oseltamivir resistance. The risk of resistance is greatest in people who are severely immunosuppressed. The selection of first line antivirals in severely immunosuppressed individuals should take account of the subtype of influenza causing infection, or if not yet known, the dominant strain of influenza that is circulating during the current influenza season.

In general, influenza A (H1N1) is considered to be a higher risk for the development of oseltamivir resistance, whilst 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 Microbiologist or Consultant Virologist.

The dominant circulating strain of influenza is obtainable from the PHE weekly influenza reports: <https://www.gov.uk/government/statistics/weekly-national-flu-reports>. Table 1 (below) provides guidance on the selection of antivirals for severely immunosuppressed patients, taking into account the dominant circulating strain of influenza, and the risk of developing oseltamivir resistance.

**Table 1: Selection of antivirals for severely immunosuppressed patients**

	Dominant circulating strain has a <u>lower risk</u> of oseltamivir resistance, eg A(H3N2), influenza B *	Dominant circulating strain has a <u>higher risk</u> of oseltamivir resistance, eg A(H1N1) *
Uncomplicated influenza	<b>oseltamivir PO</b> and clinical follow up.  Commence therapy within 48 hours of onset (or later at clinical discretion)	<b>zanamivir INH (Diskhaler®)</b>  Commence therapy within 36 hours of onset (or later at clinical discretion)  <b>OR</b> if unable to take inhaled preparation <sup>4</sup> use  <b>oseltamivir PO</b> and clinical follow up.  Commence therapy within 48 hours of onset (or later at clinical discretion)
Complicated influenza	<i>1<sup>st</sup> line:</i> <b>oseltamivir PO/NG</b> <i>2<sup>nd</sup> line:</i> <b>zanamivir INH, NEB or IV</b> Consider switching to zanamivir if: <ul style="list-style-type: none"><li>- <b>Poor clinical response</b></li><li>- Subtype testing confirms a strain with potential oseltamivir resistance, eg A(H1N1)</li></ul>	<b>zanamivir INH, NEB or IV</b>  Commence therapy within 48 hours of onset (36 for children) or later at clinical discretion  (if there are delays in obtaining aqueous zanamivir, use oseltamivir as a bridging treatment until zanamivir is available)

\* = (also applicable if this is the strain known to be infecting patient; treatment however, should not be delayed while waiting for test results).

## 1.1 Treatment of adults and children in community/A&E with uncomplicated influenza

All patients should be advised of the symptoms of complicated influenza and told to seek medical help should their condition worsen. The following recommendations for adults refer to dosages in **Box 1**. For paediatric dosing, see section 1.3.1.

- **previously healthy people (excluding pregnant women):** No antiviral treatment, or if physician feels patient is at serious risk of developing serious complications from influenza, then oseltamivir PO
- **at risk population, including pregnant women (but excluding the severely immunosuppressed):** Oseltamivir (PO). 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 even if started up to five days after onset (5). Treatment after 48 hours is an off-label use of oseltamivir and clinical judgement should be exercised
- **severely immunosuppressed patients:** Some influenza subtypes are associated with a greater risk of developing oseltamivir resistance, and the selection of first line antivirals in severely immunosuppressed individuals should take account of the dominant circulating strain of influenza (Table 1). The risk of resistance is highest in people who are severely immunosuppressed and have complicated influenza, who are given antivirals. Oseltamivir PO is the first line treatment, unless the dominant circulating strain is influenza A(H1N1) which has a higher risk for developing oseltamivir resistance, in which case use zanamivir (INH) (Table 1). Treatment should start as soon as possible. If clinical condition does not improve, continue with Zanamivir, take a specimen for resistance testing and consider other possible causes for a failure to improve
- **suspected or confirmed oseltamivir resistant influenza in a patient who requires treatment:** Zanamivir (INH). Treatment should be started as soon as possible
- **management of patients for whom zanamivir is indicated, who are unable to self-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 self-administer the Diskhaler<sup>®</sup> (this includes children under 5, for whom zanamivir is unlicensed). 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. Patients who have suspected or confirmed oseltamivir resistant infection and cannot take inhaled zanamivir should be considered for nebulised aqueous zanamivir. This is an unlicensed medication and the dose is provided on the manufacturer's guidance supplied with the drug (see Section 1.3.4 and Appendix 4).

**Box 1. Dosage in adults for treatment of uncomplicated influenza**

**Oseltamivir 75mg PO twice daily for 5 days**

**Zanamivir 10mg INH twice daily for 5 days**

**Note: dose adjustments for obesity, renal dysfunction and use in children are provided later in this document.**

## 1.2 Treatment of adults and children with complicated influenza

**All patients with complicated influenza should receive treatment, often 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.**

A history of influenza immunisation does not exclude influenza as a possible diagnosis. The duration of therapy depends on clinical response. Test for antiviral resistance in patients who do not respond after five days of treatment.

The following recommendations include the use of IV antivirals and nebulised aqueous zanamivir, which are **unlicensed medications** (see [Section 1.3.4](#) and [Appendix 4](#)).

- **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 (6)
- **second line treatment:** If there is a poor clinical response to first line treatment switch to zanamivir. If there is evidence of gastrointestinal dysfunction, which could cause decreased absorption of enterically-administered medications, use zanamivir. Examples include known gastroparesis, clinical evidence of malabsorption, uncontrollable vomiting, and gastrointestinal bleeding. Some patients who are considered to have good respiratory function despite their illness may be able to use inhaled zanamivir. Those who cannot use a zanamivir Diskhaler<sup>®</sup> should be considered for nebulised aqueous zanamivir. The following patients may be considered for IV zanamivir: patients who have already failed to respond to nebulised zanamivir; patients who have developed respiratory conditions affecting nebuliser delivery (eg airways disease, pulmonary oedema); patients who have multi-organ involvement or who require intensive care

## Exceptions:

**Severely immunosuppressed patients:** Oseltamivir (PO or NG) is the first line treatment, unless the dominant circulating strain is influenza A(H1N1) (Table 1). Treatment should start as soon as possible. Arrange influenza A subtype testing and monitor clinical condition closely. If there is a poor clinical response, consider switching to zanamivir and test for oseltamivir resistance. Ensure that appropriate infection control precautions are applied to the patients; see PHE guidance for further details:

<https://www.gov.uk/government/publications/respiratory-tract-infections-infection-control>

If the dominant circulating strain is influenza A(H1N1), use zanamivir (INH or NEB) as first line treatment (Table 1). Patients who cannot use inhaled zanamivir should be considered for nebulised aqueous zanamivir (unlicensed). IV zanamivir (unlicensed) may be considered for patients who have already failed to respond to nebulised zanamivir; patients who have developed respiratory conditions affecting nebuliser delivery; patients who have multi-organ involvement or who require intensive care.

**Suspected or confirmed oseltamivir resistance:** for example, contact of known oseltamivir resistant case. Do not use oseltamivir. Some patients considered to have good respiratory function despite their illness may be able to use inhaled zanamivir (Diskhaler<sup>®</sup>). Those who cannot should be considered for nebulised aqueous zanamivir (unlicensed). IV zanamivir (unlicensed) may be considered for patients who have already failed to respond to nebulised zanamivir; patients who have developed respiratory conditions affecting nebuliser delivery; patients who have multi-organ involvement or who require intensive care.

## 1.3 Supplementary material: Prescribing antivirals for treatment

### 1.3.1 Antiviral dosage and schedules

**Table 2: Treatment dosage**

TREATMENT	Premature (less than 38 weeks post conceptual age)	Premature (38–40 weeks post conceptual age)	0–12 months	>1–12 years: Dose according to weight below				Adults (13 years and over) <sup>2</sup>
				≤15kg	>15- 23kg	>23- 40kg	>40kg	
Osetamivir PO (treatment course: 5 days)	1mg/ kg /dose bd <u>Unlicensed</u> <sup>1</sup>	1.5mg/ kg /dose bd <u>Unlicensed</u> <sup>1</sup>	3mg/kg/dose bd	30mg bd	45mg bd	60mg bd	75mg bd	75mg bd
Zanamivir INH (treatment course: 5 days)	Not licensed for children <5 years old. Children >5 years: 10mg bd							10 mg bd

<sup>1</sup>This is an unlicensed use of oseltamivir, and is based on evidence from the literature, and expert opinion (7,8,9).

<sup>2</sup>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.

Osetamivir oral suspension should be used only for children under the age of one. It is available as Tamiflu<sup>®</sup> oral suspension (Roche, 6mg/mL oral suspension reconstituted from powder). The pack includes an oral dispenser, which is marked in millilitres (mLs), since prescriptions for Tamiflu<sup>®</sup> 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 over one year of age and adults with swallowing difficulties, and those receiving nasogastric oseltamivir, should use capsules which are opened and mixed into an appropriate sugary liquid as oseltamivir has a very bitter taste. If the powder for suspension is used for children over one year of age and/or adults, there may not be adequate quantities of the powder for suspension to meet demand for the less than one year age group. It is important that the powder for suspension is reserved for the under one year age group.

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.

**For the use of oseltamivir and zanamivir in pregnancy, breastfeeding, or renal or hepatic dysfunction, see Appendix 1.**

**Note on dosage in obese patients:**

- **oseltamivir:** No dose adjustment is needed in obese patients (9-11)
- **inhaled or nebulised zanamivir:** No dose adjustment is needed in obese patients (12)
- **IV zanamivir:** For adult patients (and adolescents with actual body weight 50kg or greater) the dose is not weight adjusted. However, in patients with an actual body weight greater than 100 kg or with BMI >30 kg/m<sup>2</sup> and who also have renal impairment, the Lean Body Weight (LBW) rather than actual body weight should be used in the Cockcroft and Gault calculation and other adjustments may be required. Please refer to the physician’s guidance document supplied by GSK (12)

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 (12).

The calculation for Lean Body Weight is shown below and requires the patient’s body mass index (BMI) (kg/m<sup>2</sup>).

**Table 3: Lean body weight calculation**

Lean Body Weight (kg)	Male	$\frac{9270 \times \text{Actual Body Weight}}{(216 \times \text{BMI}) + 6680}$
	Female	$\frac{9270 \times \text{Actual Body Weight}}{(244 \times \text{BMI}) + 8780}$

**1.3.2 Treatment of oseltamivir resistant influenza**

In deciding who to treat the same criteria apply as for influenza without known oseltamivir resistance. Previously healthy people with uncomplicated disease, or those who have recovered with or without oseltamivir, do not require treatment. Those who do require treatment should have zanamivir. Those with uncomplicated influenza should receive inhaled zanamivir via Diskhaler<sup>®</sup> (or nebulised aqueous zanamivir if the Diskhaler<sup>®</sup> powder route is unsuitable): those with complicated influenza may receive inhaled, nebulised or intravenous zanamivir as appropriate to their clinical condition (see section 1.2). In the event of changes in the epidemiology or clinical aspects of antiviral-resistant influenza during the season, PHE will alert clinicians and provide updated advice.

**1.3.3 Management of influenza in critical care**

The principles of antiviral treatment are the same as for complicated influenza. 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 (15,16). Increasing the dosage is

no longer recommended in patients who are severely ill with influenza A due to a lack of evidence that it is any more effective (13,14). Specialist advice should be sought for dosage of patients critically ill with influenza B. Zanamivir should be used when there is suspected poor gastrointestinal absorption or failure to respond to oseltamivir. In intensive care, zanamivir should be given intravenously for situations such as multi-organ failure.

Further guidance on management of influenza on intensive care is provided in the Practice Note **Critical Care Management of Children with Influenza H1N1** (17).

### 1.3.4 Unlicensed treatments

**All of the following influenza treatments are unlicensed medicines. They can be issued for individual patient use. The prescription of unlicensed medicines is the clinical responsibility of the prescribing physician. It is part of the prescribing responsibility of the physician to return the case data requested to the manufacturer, as this is an important source of safety monitoring data. Always seek specialist advice before initiating an unlicensed treatment for influenza.**

**Zanamivir aqueous solution:** Zanamivir is available as a powder for inhalation (licensed) or in aqueous solution (unlicensed). Aqueous zanamivir may be administered through a nebuliser or intravenously. It is the only unlicensed treatment recommended by PHE in certain circumstances for first and second line therapy based on the significant experience of its use during the 2010/11 influenza season. It is available on a compassionate use basis for named patients from GlaxoSmithKline (GSK). Details of how to obtain aqueous zanamivir are provided in [Appendix 4](#). Recommendations for when to use nebulised or intravenous delivery are included in sections [1.1](#) and [1.2](#) above.

IV zanamivir is renally excreted and requires dose modification for patients with renal dysfunction including those on renal replacement therapy. Consult [Appendix 1](#) and the manufacturer's physician guidance document supplied with the medication. The required dose of IV zanamivir should be diluted in a convenient volume of 0.9% sodium chloride solution and administered over approximately 30 minutes.

Details of use of IV and nebulised zanamivir for patients under 18 can be found in the manufacturer's guidance (12).

#### Nebulised administration

Zanamivir powder for inhalation should NOT be nebulised by dissolving the capsules in water. This practice has been linked to deaths in ICU believed to be due to blockage of ventilator tubes. If nebulisation is required, then the unlicensed IV aqueous solution should be used for this purpose.

The dosage for administration by nebuliser is 25mg four times daily. No dosage adjustment is required based on age, weight or renal function.

Use of aseptic techniques is required throughout preparation of the dose. Withdraw 2.5mL zanamivir (10mg/mL) from the vial using a sterile syringe and transfer to the nebulizer chamber, immediately prior to administration. The solution should be nebulized to dryness.

**Peramivir (IV)** is a neuraminidase inhibitor which has been licensed in the USA. It is available as an unlicensed drug in the UK, in a preparation for intravenous use. In the USA, it is licensed for the treatment of acute uncomplicated influenza in adults aged 18 years and over. Peramivir is administered as a single dose within 2 days of onset of acute influenza symptoms. Evidence of efficacy of the 600mg dose is limited to mainly Influenza A infection but 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.

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.

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. Although IV peramivir is unlicensed in the UK, it may be of use if a parenteral neuraminidase inhibitor is required but IV zanamivir cannot be obtained and there are no concerns about oseltamivir or peramivir resistance.

**Ribavirin (IV)** is unlicensed for the treatment of influenza and should be used in combination with other antivirals only in the context of an approved research protocol. It should never be used for treatment or prophylaxis of influenza in pregnant women.

**Favipiravir (PO)** is a novel antiviral drug compound which inhibits RNA-dependent RNA polymerase of viruses. This has been investigated for future use relating to influenza and other viruses and has been approved for stockpiling against influenza pandemics in Japan. It is not licensed for use in the UK and is not recommended currently for therapeutic use, and should only be used in the context of an approved research protocol.

**Laninamivir (INH)** is a neuraminidase inhibitor which has been licensed in Japan for the treatment and prophylaxis of influenza. Recent data show laninamivir may be useful for Post Exposure Prophylaxis (PEP) and at least in Japan has retained clinical activity against influenza A. It is not licensed for use in the UK and should only be used in the context of an approved research protocol.



## Part 2: Post exposure prophylaxis

NICE has provided guidance stating that oseltamivir and zanamivir may be used for prophylaxis of persons in at risk groups (see definitions on [page 7](#) of this guidance) following exposure to a person in the same household or residential setting with influenza-like illness when influenza is circulating in the community. This may also be given at other times, when there has been exposure to virologically confirmed influenza infection.

As per NICE guidance, prophylaxis should be issued if the contact is not adequately protected by vaccination, that is:

- the vaccination is not well matched to the circulating strain, or
- there has been less than 14 days between vaccination and date of first contact with influenza.

In addition, the guidance also states that – if the individual has been exposed as part of a localised outbreak (such as in a care home), antiviral prophylaxis may be given regardless of vaccination status. For further guidance on care home outbreaks, see PHE guidance:

<https://www.gov.uk/government/publications/acute-respiratory-disease-managing-outbreaks-in-care-homes>

For further information on which contacts of a case of influenza should receive prophylaxis, refer to guidance from NICE (18). Specialist advice in relation to incidents such as influenza outbreaks, may be sought from local health protection teams.

Inhaled zanamivir is not licensed for children under five years old, and is unlikely to be an effective delivery route in these patients. Some other patients, such as those with severe underlying respiratory disease or impaired cognition, may also be unable to use the Diskhaler<sup>®</sup> effectively. Severely immunosuppressed children under five years and all other severely immunosuppressed patients who cannot use the Diskhaler<sup>®</sup> and require prophylaxis after exposure to currently circulating antiviral sensitive strains of influenza should receive oral oseltamivir, with advice to seek immediate medical attention if symptoms develop subsequently.

Severely immunocompromised patients who are unable to use the Diskhaler<sup>®</sup>, including severely immunosuppressed children aged less than five years, and who are exposed to suspected or confirmed oseltamivir resistant influenza should be discussed with a specialist. The use of unlicensed nebulised aqueous zanamivir may be considered based on an individual risk assessment (see [section 1.3.4](#)).

**Table 4: Selection of antivirals for post-exposure prophylaxis**

	<b>If identified strain in index case or dominant circulating strain is lower risk for oseltamivir resistance e.g. influenza A (H3N2), influenza B</b>	<b>If identified strain in index case or dominant circulating strain is known to higher risk for oseltamivir resistance e.g. influenza A (H1N1)</b>	<b>Exposed to suspected or confirmed oseltamivir resistant influenza</b>
<b>Previously healthy (excluding pregnant women)</b>	No prophylaxis	No prophylaxis	No prophylaxis
<b>At risk of complicated influenza (including pregnant women but excluding severely immunosuppressed patients and excluding children under 5 years)</b>	<b>Oseltamivir PO once daily for 10 days</b> , if therapy can be started within 48 hrs of exposure; or after 48 hrs on specialist advice only	<b>Oseltamivir PO once daily for 10 days</b> , if therapy can be started within 48 hrs of exposure; or after 48 hrs on specialist advice only	<b>Zanamivir INH once daily for 10 days</b> , if therapy can be started within 36 hrs of exposure; or after 36 hrs on specialist advice only
<b>Severely immunosuppressed patients (excluding children under 5 years)</b>	<b>Oseltamivir PO once daily for 10 days</b> , if therapy can be started within 48 hrs of exposure; or after 48 hours on specialist advice only	<b>Zanamivir INH once daily for 10 days</b> , if therapy can be started within 36 hrs of exposure; or after 36 hrs on specialist advice only. If unable to administer zanamivir INH, <b>oseltamivir PO once daily for 10 days</b> , if therapy can be started within 48 hrs of exposure; or after 48 hours on specialist advice only	<b>Zanamivir INH once daily for 10 days</b> , only if therapy can be started within 36 hrs of exposure; or after 36 hrs on specialist advice only. If unable to administer zanamivir INH, discuss with specialist and consider nebulised aqueous zanamivir (unlicensed) after individual risk assessment
<b>Children under 5 years in at risk groups including severely immunocompromised children</b>	<b>Oseltamivir PO once daily for 10 days</b> , if therapy can be started within 48 hrs of exposure; or after 48 hrs on specialist advice only	<b>Oseltamivir PO once daily for 10 days</b> , if therapy can be started within 48 hrs of exposure; or after 48 hrs on specialist advice only	<b>Discuss with specialist.</b> Consider nebulised aqueous zanamivir (unlicensed) after individual risk assessment

Specialist advice is available from local **health protection teams** and **public health virologists** for prophylaxis in healthcare settings where repeated or ongoing exposure is suspected.

An alternative to prophylaxis in some clinical settings may be to monitor persons exposed to an influenza case and start antiviral treatment promptly when symptoms of influenza start. It is recommended that such an arrangement is undertaken only when:

- the patient (or their carer) has been provided with information on symptoms prompting antiviral use, potential adverse events, and has decided to take antiviral medicines for treatment rather than prophylaxis
- AND
- the clinician has made arrangements in advance for the patient to promptly receive and start antiviral treatment within 48 hours of symptom onset (or 36 hours for zanamivir treatment in children)

## 2.1 Supplementary information: Prophylaxis

### 2.1.1 Antiviral dosage and schedules

**Table 5: Prophylaxis dosage**

PROPHYLAXIS	Premature (less than 38 weeks post conceptual age)	Premature (38–40 weeks post conceptual age)	0 to 12 months	>1–12 years: Dose according to weight below				Adults (13 years and over) <sup>2</sup>
				≤15kg	>15-23kg	>23-40kg	>40kg	
Oseltamivir PO (prophylaxis course: 10 days)	See below <sup>1</sup>	See below <sup>1</sup>	3mg/kg od	30mg od	45mg od	60mg od	75mg od	75mg od
Zanamivir INH (prophylaxis course: 10 days)	Not licensed for children <5 years old. Adults and children ≥5 years: 10mg od						10mg od	

<sup>1</sup>Although it may be possible to provide half the treatment frequency, each day for 10 days, this would be at the clinician's own risk as there is currently no publicly available dosing information for oseltamivir prophylaxis in pre-term infants.

<sup>2</sup> 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.

Oseltamivir oral suspension should be used only for children under the age of one. It is available as Tamiflu® oral suspension (Roche, 6mg/mL powder for oral suspension). This preparation replaces the 12 mg in 1 mL suspension. The new 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 over one and adults with swallowing difficulties, and those receiving nasogastric oseltamivir, should use capsules which are opened and mixed

into an appropriate sugary liquid as oseltamivir has a very bitter taste. If the powder for suspension is used for children over one year of age and/or adults, there may not be adequate quantities of the powder for suspension to meet demand for the under one year age group. It is important that the powder for suspension is reserved for the less than one year age group. Inhaled zanamivir is not licensed for children aged under the age of 5.

## Appendix 1: Use of antivirals in pregnancy, breastfeeding, hepatic or renal dysfunction

**Table 6: Recommended dosage for hepatic dysfunction, pregnancy and breastfeeding**

	Liver dysfunction	Renal dysfunction
Oseltamivir PO	Standard dosing	See <a href="#">Table 7</a> .
Zanamivir INH (Diskhaler <sup>®</sup> )	Standard dosing	Standard dosing
Zanamivir solution IV/NEB	Refer to the physician's guidance document supplied by the manufacturer with the medication	This information is provided by the manufacturer when IV zanamivir is supplied

### 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).

For pregnant women who meet additional criteria for requiring zanamivir first line, further assessment (ie 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 (19, 20).

The Summary of Product Characteristics (SPC) for Tamiflu<sup>®</sup> (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 post-marketing 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<sup>®</sup> after considering the available safety information, the pathogenicity of the circulating influenza virus strain, and the underlying condition of the pregnant woman.”(21).

The Summary of Product Characteristics (SPC) for Relenza<sup>®</sup> (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". (22)

### Use during breastfeeding

**For Oseltamivir PO and Zanamivir INH (Diskhaler<sup>®</sup>),** the amount secreted in breast milk is probably too small to be harmful; use only if benefit outweighs risk. For **Zanamivir IV/NEB, refer to the manufacturer’s guidance.**

### Dosing in patients with renal dysfunction

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 give the first dose 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. 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 ([Link](#)). 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 (ie 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 the following tables). 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.

For treatment of adult patients with renal dysfunction using IV Zanamivir, doses can be found in the manufacturer's guidance (available when requesting this medicine from the manufacturer).

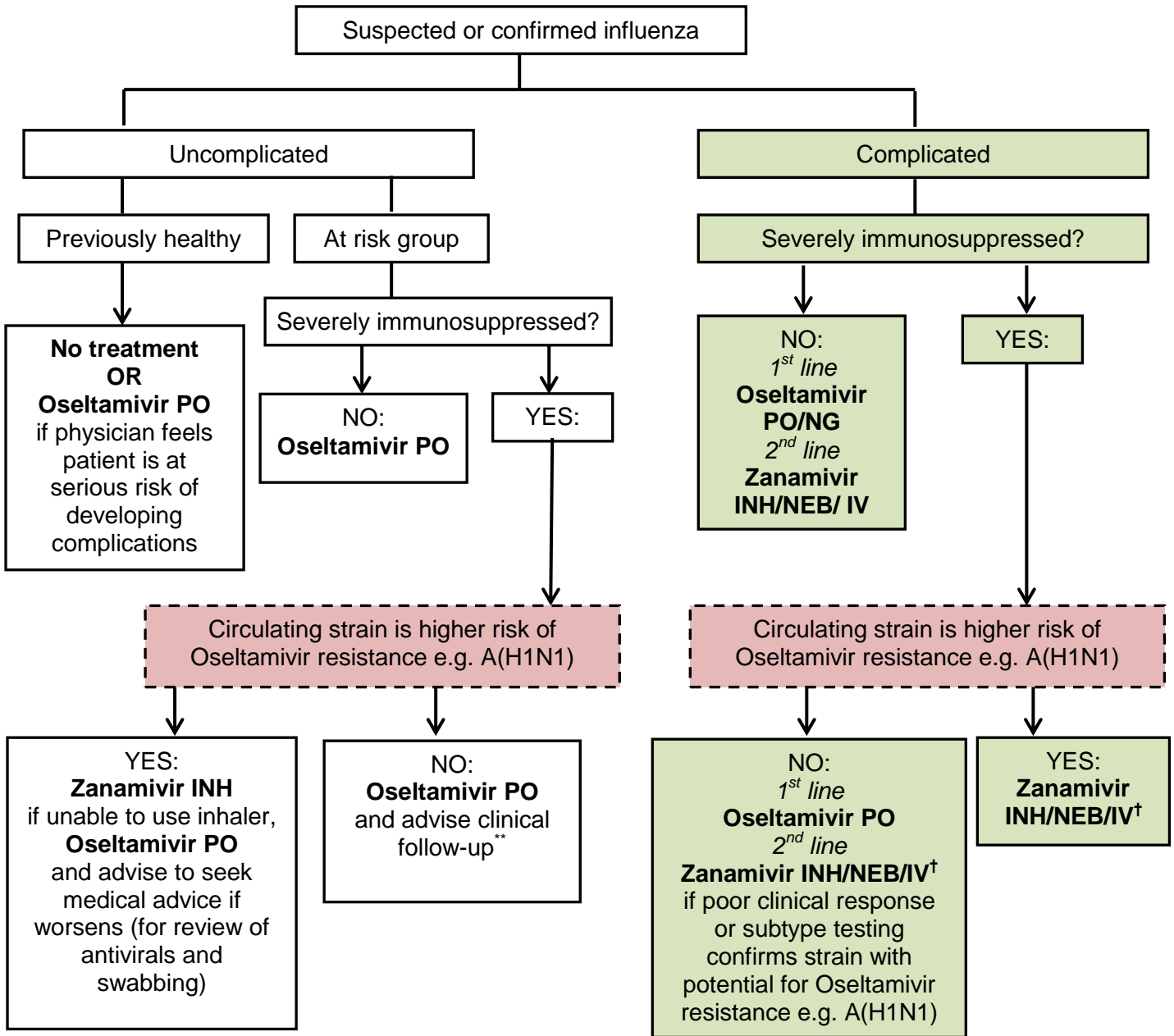
**Table 7: Recommended dosage of oseltamivir in patients with renal dysfunction (adults aged 13 years or over)**

	<b>Oseltamivir PO Treatment - 5 Days</b>	<b>Oseltamivir PO Prophylaxis – 10 Days</b>
Moderate impairment (CrCL 30-60 mL/min)*	30mg BD	30mg OD
Severe impairment (CrCL 10-30mL/min)*	30mg OD	30mg every 48 hours
Established renal failure (CrCL <10mL/min)**	30mg once	30mg once, repeated after 7 days
Haemodialysis*	30mg once, and then 30 mg after each haemodialysis session	30mg once, and then 30 mg after every second haemodialysis session
Peritoneal dialysis*	30mg once	30mg once, repeated after 7 days
Haemo(dia)filtration** 1-1.8L/hr exchange rate	30mg OD	30mg every 48 hours
Haemo(dia)filtration** Greater than 1.8L/hr exchange rate	30mg BD	30mg OD

**Source:** Summary of Product Characteristics June 2015 (\*). The recommendations for haemo(dia)filtration and established renal failure are based on expert opinion (\*\*)

# Appendix 2: Summary algorithm for prescribing antiviral treatment for influenza

## Prescribing antivirals for treatment of influenza in primary and secondary care



**Note: Commencing oseltamivir and zanamivir treatment more than 48 hours after symptom onset (36 hours for zanamivir use in children) is an off-label use.**

† The following hospitalised patients may be considered for IV zanamivir: patients who have already failed to respond to nebulised zanamivir; patients who have developed respiratory conditions affecting nebuliser delivery (eg airways disease, pulmonary oedema); patients who have multi-organ involvement or who require intensive care.

\*\* clinical follow-up – advise patient to seek medical attention if illness worsens. Patient may need to be re-swabbed for influenza testing if this occurs, noting on the form that they are already on antiviral treatment.

The circulating influenza strain can be checked via the [National Flu Report](#).



### **Prescribing in primary care**

GPs may only prescribe antiviral medicines for the prophylaxis and treatment of influenza at NHS expense when the Chief Medical Officer (CMO) has confirmed that influenza is circulating in the community. The CMO announcement is issued to the NHS through the DH Central Alerting System (CAS).

GPs have the discretion to prescribe antiviral medicines for people who are not in the specified at-risk groups but who are considered to be at risk of complications if not treated with an antiviral medicine.

### **Prescribing in secondary care**

Clinicians in secondary care can use their clinical judgement to prescribe antiviral medicines whether or not the CMO has announced influenza is circulating in the community, and also for patients not in the specified 'at risk' groups.

## Appendix 3: Sources of information

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<https://www.gov.uk/government/publications/influenza-treatment-and-prophylaxis-using-anti-viral-agents>
- (4) Department of Health (2013) **Immunisation against Infectious Disease** (The Green Book), Updated 2015: <https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book>
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- (12) GSK (2016). **Zanamivir aqueous solution for compassionate use in serious influenza illness: physician's guidance document**. Version 10.0 UK Final January 2016. [Unpublished] Available from GSK on request.
- (13) Lee et al (2013), **A prospective intervention study on higher doses of oseltamivir treatment in adults hospitalized with influenza A and B infections**, *Clinical Infectious Diseases*. 2013 Dec; 57(11):1511-9.
- (14) South East Asia Infectious Disease Research Network (2013), **Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomized controlled trial**. *British Medical Journal*. 2013 May 30;346.
- (15) Ariano RE et al, (2010) **Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza**. *CMAJ*. 2010 Mar 9, 182(4):457-363. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2831695/>
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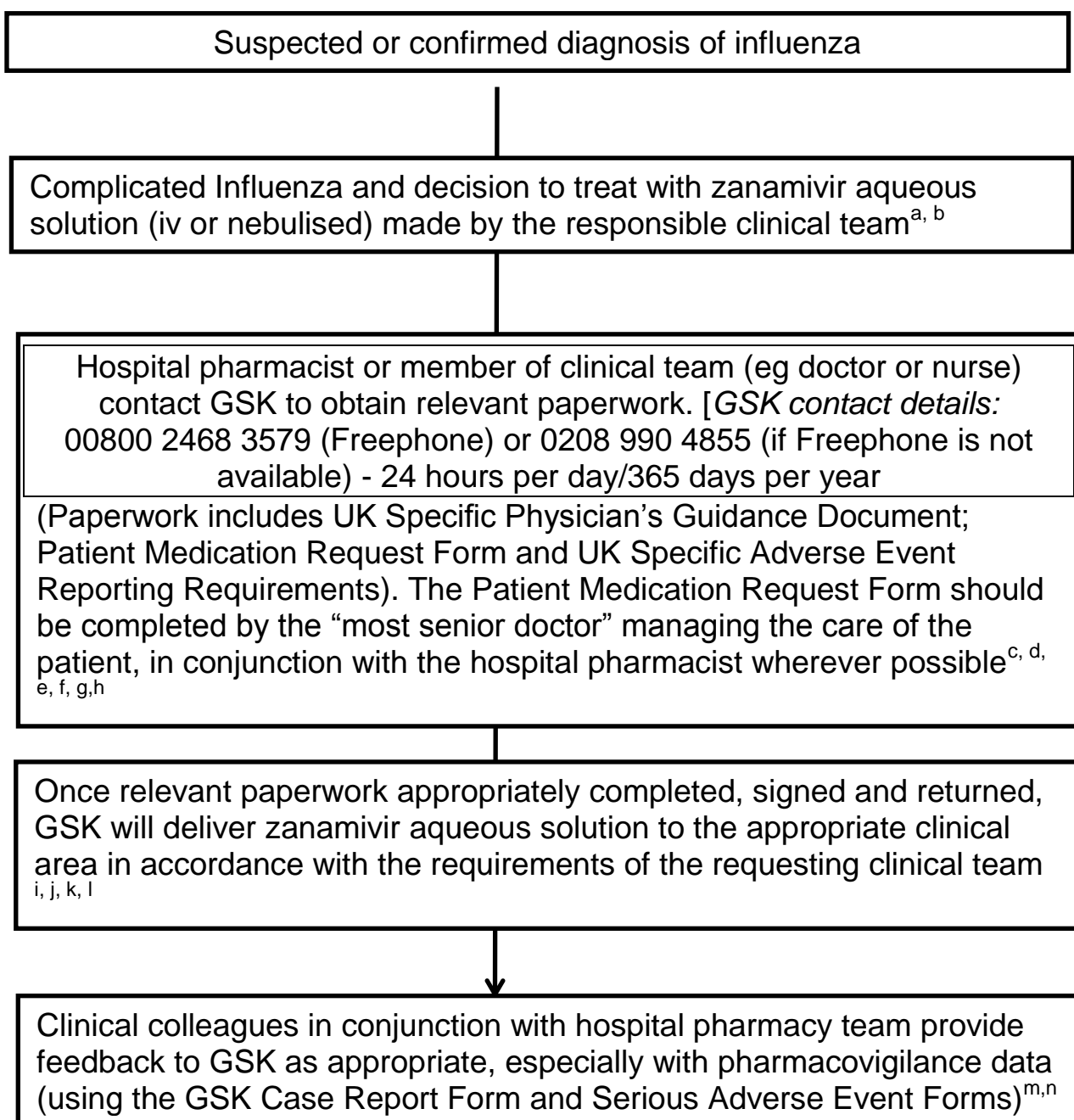
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## Appendix 4: Supply of zanamivir aqueous solution on a named patient basis from GlaxoSmithKline (GSK)

(Note: The use of nebulised or intravenous aqueous zanamivir is unlicensed. Clinicians should make a very careful judgement about the use of unlicensed zanamivir – see Guidance Notes 1, 2.)



## Guidance notes

### General

a. Zanamivir aqueous solution is a globally unlicensed medicine, only available on a named patient supply basis. Clinicians should therefore make a very careful judgement about the use of unlicensed zanamivir. **The clinician prescribing zanamivir as an unlicensed medicine, either for use as a nebulised treatment or intravenously, accepts clinical and professional responsibility for their prescribing decision.**

b. NHS Trusts should also follow their own Unlicensed Medicines Policies and MHRA Guidance Note 14 “*The Supply of Relevant Medicinal Products for Individual Patients*” in conjunction with this guidance. For example (but not limited to), trusts should ensure the recording of batch number and expiry dates of zanamivir aqueous solution received and supplied.

c. Wherever possible, ordering of zanamivir aqueous solution should follow ‘normal’ medicines processes in trusts, ie the hospital pharmacy should, if possible, order zanamivir aqueous solution.

d. GSK hours of despatch for zanamivir aqueous solution are **[See additionally, points j. and k. below]:**

i. Monday to Friday: 8am – 7pm

ii. Saturday & Sunday: 8am – 3pm

iii. Over the Christmas and New Year period, hours of dispatch are as follows:

Saturday 24 December 2016: 8am – 5pm

Sunday 25 December 2016: 8am – 3pm – Christmas Day

Monday 26 December 2016: 8am – 3pm – Boxing Day (Bank Holiday)

Tuesday 27 December 2016 : 8am – 3pm – (Bank Holiday substitute for Christmas Day)

Wednesday 28 December 2016: 8am – 3pm

Thursday 29 December 2016: 8am – 3pm

Friday 30 December 2016: 8am – 3pm

Saturday 31 December 2016: 8am – 3pm

Sunday 1 January 2017: 8am – 3pm New Year’s Day

Monday 2 January 2017: 8am – 3pm (Bank Holiday substitute for New Year’s Day)

Tuesday 3 January 2017: 8am – 3pm

A normal shipment service will resume on Wednesday 4 January 2017.

### Requesting a Named Patient Supply

e. When a decision to prescribe zanamivir aqueous solution is confirmed, contact should be made with **GSK on 00800 2468 3579 (Freephone) or 0208 990 4855 (if Freephone is not available) – 24 hours per day/365 days per year**, or by email: [GSKClinicalSupportHD@gsk.com](mailto:GSKClinicalSupportHD@gsk.com). (Fax number 0207 192 6397). The hospital pharmacy team can make this initial contact with GSK, or GSK will also accept an initial request from a member of the clinical team looking after the patient (ie senior nurse or doctor) **[See additionally, points j. and k. below.]** **[Note:** Any out-of-hours requests for zanamivir aqueous solution should be notified to the hospital pharmacy team through the usual pharmacy on call/residency arrangements as soon as possible and by close of play the next working day at the latest].

f. Whilst GSK can be contacted 24 hours a day to discuss medical emergencies, GSK will not despatch outside of the hours 8am–7pm Monday to Friday or 8am–3pm Saturday/Sunday. Therefore, consideration should be given by the clinical team whether GSK should be contacted after 7pm Monday to Friday/ 3pm Saturday/Sunday and before 7am in the morning.

g. GSK will email the relevant paperwork (ie UK Specific Physicians Guidance Document; Patient Medication Request Form; UK Specific Adverse Event Reporting Requirements) to the requestor and to the ‘most senior doctor’.

h. This paperwork **MUST** be completed and signed by the ‘most senior doctor’ managing the care of the patient. **[Note:** The ‘most senior doctor’ may be the consultant physician (or surgeon), consultant anaesthetist / intensivist managing the care of the patient or could be a senior trainee (ST grade doctor) or specialty doctor].

i. The completed paperwork must be faxed back to GSK with a follow up telephone call, to confirm request.

j. To guarantee same day despatch, hospitals are asked to allow up to 2 hours for processing of their request prior to close of dispatch, ie to send in their requests to GSK by:

- i. 5pm Monday – Friday or by
- ii. 1pm Saturday and Sunday

k. For requests received by GSK between 5pm-7pm, GSK will make every effort to process the request and despatch supplies, but depending on the time of receipt of the completed documentation, same day despatch **cannot** be guaranteed.

### l. Despatch, delivery and receipt

- i. Once the relevant paperwork has been completed and confirmed, GSK will despatch via courier, zanamivir aqueous solution to the requesting hospital. a.

Zanamivir aqueous solution should be delivered direct to the relevant clinical area. This is to ensure a simple and robust logistics solution recognising the variable opening hours of hospital pharmacy departments.

ii. Care must be taken to ensure the delivery details are clear and unambiguous. Zanamivir aqueous solution should **NOT**, for example be delivered to a hospital reception desk.

iii. The clinical area receiving zanamivir aqueous solution should sign for the receipt of the product, retain all paperwork, record the batch number and expiry date and inform the hospital pharmacy team of the delivery by close of play the next working day at the latest.

m. Once dispatched, GSK will email the 'most senior doctor' named on the patient medication request form and the pharmacy contact name, if provided, with details of the estimated arrival time of the supplies, together with a case report form and serious adverse event forms for collection of outcomes and pharmacovigilance data.

n. **Pharmacovigilance information**

Clinical colleagues in conjunction with the hospital pharmacy team **MUST** provide feedback to GSK to aid pharmacovigilance data collection. The case report form and serious adverse event forms provided in the email confirming the estimated time of arrival of the supplies, should be used for this purpose, as appropriate.



## Frequently asked questions

### **Q. When should I consider continuing antiviral therapy beyond 5 days?**

The optimal duration of treatment is not clear for hospitalised patients with influenza. Persistent detection of viral ribonucleic acid (RNA) and 'rebound' of previously undetectable viral RNA have been described in patients with severe influenza who received 5 or 7 day courses of oseltamivir (23). Extending the duration of treatment to at least 10 days may be appropriate in patients with severe influenza (eg critically ill patients) and in severely immunosuppressed patients. Prolonged treatment can be associated with the development of antiviral resistance, particularly in immunosuppressed patients, and antiviral resistance monitoring is recommended. Prescribers are reminded that 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 may manifest as failure to improve, progressive lower respiratory tract signs or symptoms, or new or progressive multi-organ dysfunction in a patient receiving first line antiviral treatment. Antiviral resistance (pre-existing or new on-treatment resistance) is just one potential explanation for a poor clinical response. Antiviral resistance is more likely to occur in patients infected with influenza A(H1N1) virus, rather than infections caused by other seasonal influenza viruses. It is also more likely to occur in patients with known risk factors for antiviral resistance, for example, severely immunosuppressed patients. However, failure to improve or clinical deterioration may also be explained by the natural progression of acute lung injury and the inflammatory response seen in influenza illness, or by secondary infections e.g. bacterial co-infection. Therefore, the assessment of whether a patient has a poor clinical response can only be made by the treating clinician, guided by these considerations.

### **Q. In which groups of patients are influenza viruses with reduced antiviral susceptibility more likely to emerge?**

Patients who are undergoing treatment with influenza antiviral drugs, particularly immunocompromised patients and young children, are more likely to harbour viruses with reduced antiviral drug susceptibility. This might be explained by prolonged durations of infection and/or greater viral burden, compared to other groups. Rapid emergence of oseltamivir resistance (as early as 48h after starting treatment) has been described, particularly in severely immunocompromised patients (24).

Between July 2009 and April 2010, 285 oseltamivir-resistant cases of pandemic influenza A (H1N1)pdm09 infection were reported worldwide, including 45 in the UK. Data were available from 34 of the patients from England and Scotland. Of 28 for whom there was information on underlying conditions, 21 (75%) were classified as being immunosuppressed. All but two of the immunosuppressed patients had a hematologic cancer, and 8 of them had undergone hematopoietic cell transplantation. The most common condition was leukaemia (11 of 21), of which five had chronic lymphocytic leukaemia (25).

**Q. If zanamivir resistance is suspected, should I switch to oseltamivir?**

No. Recent antiviral resistance surveillance data for seasonal influenza viruses demonstrate that resistance to oseltamivir remains more common than resistance to zanamivir. Several mutations that confer resistance to zanamivir are also associated with resistance or reduced susceptibility to oseltamivir. If zanamivir resistance is believed to be a possibility (eg as a potential reason for failure to improve), then continue zanamivir treatment and arrange urgent resistance testing. Seek advice from local infection specialists. Additional advice is available from regional public health virologists and from the Respiratory Virus Unit at PHE.

**Q. What is the role of repeat sampling and laboratory testing in patients receiving antivirals?**

It is recognised that it can be challenging to assess clinical improvement in specific patient groups such as the immunosuppressed or unconscious/ventilated, because they may have atypical or minimal clinical signs and symptoms or be unable to describe symptoms. In such patients with confirmed influenza who are receiving antivirals, repeat or 'follow-up' sampling for detection of viral RNA by polymerase chain reaction (PCR) can be considered if the patient:

- deteriorates or has a non-resolving illness despite at least 5 days of antivirals and may require an extended duration of antiviral treatment
- develops influenza illness whilst receiving prophylactic-dose antivirals; either test at the outset or test according to non-resolving deterioration

When repeat testing has been performed because of suspected treatment failure, antiviral resistance testing should be considered on any positive sample, and is recommended in the context of immunosuppression. Comparing estimated viral load between the initial and repeat sample can be helpful in determining the antiviral effect. Repeat sampling is not routinely recommended for patient groups other than those described above.

The policy on the surveillance and laboratory diagnosis of antiviral resistant influenza, to support reporting of UK information to WHO is available [here](#).

If oseltamivir resistance is suspected and further treatment is required, then consider switching to zanamivir before the results of resistance testing are known. Treatment interruption should be avoided (eg when awaiting results of follow-up testing), since it can be associated with the development of antiviral resistance.

Clinicians should be mindful of the potential need for continued infection control measures for inpatients if repeat sampling for PCR testing provides positive results.

**Q. Should healthcare workers with no underlying illness who are unvaccinated be offered antiviral prophylaxis?**

Currently, prophylaxis is only given to at-risk groups and is not recommended as an alternative to immunisation. The use of prophylactic antivirals in individuals not in risk-

groups as a way of controlling an outbreak in hospital settings is not recommended by the PHE Respiratory Diseases Department. Healthcare workers who are not in an at-risk group may continue to work and should rapidly report any illness. They should then be excluded from work promptly if they develop symptoms consistent with influenza. The importance of seasonal influenza immunisation of healthcare workers needs to be emphasised as does the advice for staff not to come to work if they are ill.

**Q. What is the role of previously diagnosed influenza (laboratory detected) when a person presents with a new influenza-like illness in the same season?**

The two infections should be considered separately and treatment given, if indicated, on both occasions. It is entirely possible that the first infection is with an influenza A virus and the infection later in the season with an influenza B virus so there would not be a protective effect from the first exposure.

**Q. What are the recommendations with regard to use of oseltamivir in neonates exposed to mothers with seasonal influenza?**

Clinicians may be faced with particular situations where a pregnant woman develops laboratory confirmed seasonal influenza infection shortly before onset of labour. Questions may then arise about recommendations for the use of antivirals in this situation.

As previously stated in this guidance, pregnant women experience an increased risk of developing complicated influenza and associated severe outcomes, such as ICU admission and death. Therefore, antiviral treatment of a pregnant woman with seasonal influenza should be strongly considered in line with the recommendations featured earlier in this guidance document.

There are, however, limited data on seasonal influenza infection in neonates. The Influenza Clinical Information Network (Flu-CIN) study reported severe outcomes in 9.3% of children aged <12 months in the UK who were hospitalised with Influenza A(H1N1pdm09) during the 2009-10 pandemic (26).

The Summary of Product Characteristics 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 would be an off-label use. Treatment of seasonal influenza in children including full term neonates are however, specified in the summary of product characteristics for Tamiflu® (oseltamivir) capsules. Relenza® (zanamivir) inhalation powder is not licensed for treatment or prophylaxis in children under 5 years of age.

In addition to the recommendation for antiviral treatment of pregnant mothers, there are three potential options clinicians may consider in these situations in relation to neonates:

1. Oseltamivir oral suspension for post-exposure prophylaxis in the neonate, as an off-label indication.

2. Physical separation of the symptomatic mother and asymptomatic neonate until 5 days after the onset of symptoms.
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 arrangements made in advance for accessing oseltamivir oral suspension (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 practice.

This advice does not constitute a specific PHE 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 scenarios highlight the importance of seasonal influenza vaccination of pregnant women to avoid these situations; previous research has shown that this was 71% effective in preventing influenza infection in infants aged less than 6 months in England (27, 28).