



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

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. We do this through world-leading science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland

For queries relating to this document, please contact: respiratory.lead@phe.gov.uk



© Crown copyright 2018

You may re-use this information (excluding logos) free of charge in any format or medium, under the terms of the Open Government Licence v3.0. To view this licence, visit [OGL](https://www.ogilive.com/). Where we have identified any third party copyright information you will need to obtain permission from the copyright holders concerned.

Published October 2018
PHE publications
gateway number: 2018571

PHE supports the UN
Sustainable Development Goals



Contributors

This version of the guidance was reviewed and agreed in 2018, by a working group comprising:

Richard Pebody; Head of Influenza and Other Respiratory Viruses, National Infection Service, Public Health England (PHE) – Chair of Working Group

Gavin Dabrera; Consultant in Public Health – Acute Respiratory Infections, National Infection Service, PHE

Angie Lackenby; Post-doctoral Healthcare Scientist, Respiratory Viruses Unit, Virus Reference Department, National Infection Service, PHE

Jake Dunning; Consultant in Infectious Diseases, National Infection Service, PHE and Honorary Consultant, Royal Free London NHS Foundation Trust

Matthew Donati; Consultant Medical Virologist/Head of Virology, PHE Bristol Public Health Laboratory

Bryan O'Farrell; Critical Care Senior Pharmacist – Intensive Care & Theatres Royal Free London NHS Foundation Trust Royal Free Hospital

Mark Borthwick; Consultant Pharmacist, Critical Care, John Radcliffe Hospital

Robert Shulman; Lead Pharmacist - Critical Care, Pharmacy Department, University College London Hospitals NHS Foundation Trust

Faye Chappell; Highly Specialist Pharmacist Paediatric Infectious Disease – Paediatric Pharmacy Department, Evelina London Children's Hospital, St Thomas' Hospital, London

Secretariat: Fran Parry-Ford; Respiratory Diseases Scientist; Influenza preparedness and response, National Infection Service, PHE, Colindale

Contents

Contributors	3
Foreword	5
What has changed since the last version	6
Definitions	7
Acronyms used in this document	8
Part 1: Treatment of suspected or confirmed influenza	9
Algorithm: selection of antiviral therapy for treatment of influenza	9
1.1 Treatment of adults and children in the community or A&E with uncomplicated influenza	11
1.2 Treatment of adults and children with complicated influenza	12
1.3 Supplementary material: Prescribing antivirals for treatment	14
1.3.1 Antiviral dosage and schedules	14
1.3.2 Dosing in patients with renal dysfunction	15
1.3.3 Treatment of oseltamivir resistant influenza	17
1.3.4 Management of influenza in critical care	17
1.3.5 Other licensed and unlicensed treatments	18
Part 2: Post exposure prophylaxis	21
2.1 Supplementary information: prophylaxis	23
2.1.1 Antiviral dosage and schedules	23
2.1.2 Dosing in patients with renal dysfunction	24
Appendix 1: Use of antivirals in pregnancy, breastfeeding and hepatic dysfunction	26
Appendix 2: Summary algorithm for prescribing antiviral treatment	28
Appendix 3: Frequently asked questions	30
Appendix 4: Supply of Zanamivir aqueous solutions on a named patient basis from GlaxoSmithKline	35
Appendix 5: Sources of information	39
Appendix 6: Conflict of interest declaration	43

Version Control: This version 9.0 updates version 8.0 (September 2017). See page 6 for additional information on changes since the last version. **Please refer to the PHE website to ensure you are using the most recent version of this document.**

Suggested Citation: *PHE guidance on use of antiviral agents for the treatment and prophylaxis of influenza (2018 to 2019)*. Version 9.0 Public Health England. October 2018

Foreword

Neuraminidase inhibitors (herein referred to as antivirals) are just 1 aspect of a comprehensive approach to prevent severe influenza-related illness and death, which also includes annual seasonal influenza vaccination and the use of infection prevention and control practices (1).

Antivirals are currently recommended by a number of organisations including the National Institute for Health and Care Excellence (NICE) and ECDC (2), for the treatment and prophylaxis of seasonal influenza. This Public Health England (PHE) guidance recommends the targeted use of antiviral medicines for specific circumstances and groups of patients.

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 under the General Medical Services regulations 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 (see the PHE guidance on 'Surveillance and laboratory testing of influenza neuraminidase inhibitor resistance') (3).

The guidance in this document is based on available information from a range of data sources as well as expert opinion. Some of the recommendations included in this guidance involve the off-label use of licensed medications, or use of 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 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 (see PHE 'Guidelines on the management of influenza like illness (ILI) in care homes' (4)).

Clinicians may be aware of a Cochrane Review on the efficacy of antivirals, published in 2014 (5). PHE has previously published a detailed response to this and clinicians should note that the NICE guidelines for antiviral medications for influenza remain unchanged (6).

What has changed since the last version?

The major changes from version 8.0 (2017 to 2018) include:

- further information on the recommended dosing for renal dysfunction in adults and children for treatment (Section 1.3.2) and prophylaxis (Section 2.1.2)
- updated information on Peramivir and Baloxavir Marboxil (Section 1.3.5)
- additional information on antivirals and breastfeeding (Appendix 1)
- updates to the FAQ on management of neonates exposed to mothers with confirmed seasonal influenza (FAQs – page 39)

Definitions

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

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:

- neurological, hepatic, renal, pulmonary and chronic cardiac disease
- diabetes mellitus
- severe immunosuppression
- age over 65 years
- pregnancy (including up to 2 weeks post partum)
- children under 6 months of age
- morbid obesity (BMI ≥ 40)

For full details refer to *Immunisation against infectious disease*, known as the Green Book (7).

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:

- severe primary immunodeficiency
- current or recent (within 6 months) chemotherapy or radiotherapy for malignancy.
- solid organ transplant recipients on immunosuppressive therapy
- bone marrow transplant recipients currently receiving immunosuppressive treatment, or within 12 months of receiving immunosuppression
- patients with current graft-versus-host disease
- patients currently receiving high dose systemic corticosteroids (equivalent to ≥ 40 mg prednisolone per day for >1 week in an adult, or ≥ 2 mg/kg/day for ≥ 1 week in a child), and for at least three months after treatment has stopped
- HIV infected patients with severe immunosuppression (CD4 $< 200/\mu\text{l}$ or $< 15\%$ of total lymphocytes in an adult or child over 5; CD4 $< 500/\mu\text{l}$ or $< 15\%$ of total lymphocytes in a child aged 1 to 5; expert clinical opinion in a child aged under 1)
- patients currently or recently (within 6 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

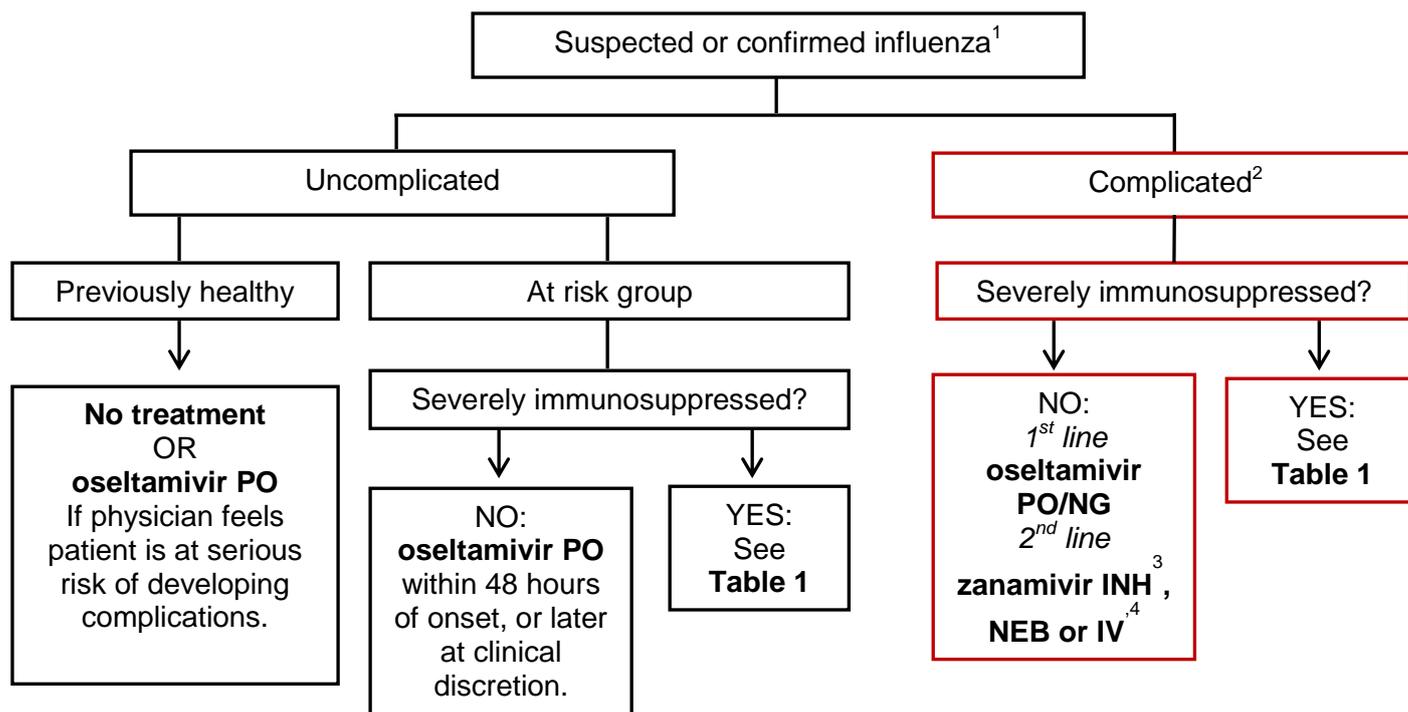
NG – nasogastric (administration via a nasogastric tube)

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 7, and **Table 1** on page 10 when using this algorithm.

¹For treatment of suspected or confirmed **oseltamivir resistant** influenza, see **section 1.3.3**.

²For 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.

³Inhaled 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 5 years. The powder preparation for the Diskhaler[®] should NEVER be made into nebuliser solution or administered to a mechanically ventilated patient.

⁴Zanamivir 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[®] may receive inhaled zanamivir. Clinical scenarios where nebulised 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: 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	oseltamivir PO and clinical follow up. Commence therapy within 48 hours of onset (or later at clinical discretion)	zanamivir INH (Diskhaler®) Commence therapy within 36 hours of onset (or later at clinical discretion) OR if unable to take inhaled preparation use oseltamivir PO and clinical follow up. Commence therapy within 48 hours of onset (or later at clinical discretion)
Complicated influenza	<i>1st line:</i> oseltamivir PO/NG <i>2nd line:</i> zanamivir INH, NEB or IV Consider switching to zanamivir if: <ul style="list-style-type: none">- Poor clinical response- Subtype testing confirms a strain with potential oseltamivir resistance, eg A(H1N1)	zanamivir INH, NEB or IV 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 5 days after onset (8). 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[®] (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 1.3.5](#) 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.

Ensure that appropriate infection control precautions are applied to the patients (see PHE guidance on [Infection control precautions to minimize transmission of acute respiratory tract infections in healthcare settings](#) for further details (9)).

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 5 days of treatment.

The following recommendations include the use of IV antivirals and nebulised aqueous zanamivir, which are **unlicensed medications** (see [Section 1.3.5](#) 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 (10).

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[®] 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.

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[®]). 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 36 weeks post conceptual age)	0–12 months (36 weeks post conceptual age or greater)	>1–12 years: Dose according to weight below				Adults (13 years and over) ²
			≤15kg	>15- 23kg	>23- 40kg	>40kg	
Oseltamivir PO (treatment course: 5 days)	1mg/ kg /dose BD <u>Unlicensed</u> ¹	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

¹This is an unlicensed use of oseltamivir, and is based on evidence from the literature, and expert opinion (11,12,13).

²If 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 prioritised for those unable to use capsules (as described below), such as for children under the age of 1 year. It is available as Tamiflu[®] 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[®] 6 mg in 1 mL powder for oral suspension should state the dose in millilitres. Children over 1 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 1 year of age and/or adults, there may not be adequate quantities of the powder for suspension to meet demand for the less than 1 year age group. It is important that the powder for suspension is reserved for the under 1 year age group.

Aqueous zanamivir solution for nebulised or IV administration is an unlicensed medicine. Dosing information for the IV route is provided in Table 4 on Page 16 and for the nebulised route on page 19. Further 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 hepatic dysfunction, see [Appendix 1](#).

Note on dosing for extremes of weight:

- **oseltamivir:** no dose adjustment is needed in obese patients (14,15)
- **inhaled or nebulised zanamivir:** no dose adjustment is needed in obese patients (16)
- **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 Table 4 on Page 15 or the physician's guidance document supplied by GSK (16))

1.3.2 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.

Table 3: Recommended oseltamivir treatment dosing in relation to renal function (adults and those aged 13 years or over)

CrCL (ml/min)	Oseltamivir PO Treatment for 5 Days
>60mL/min*	75mg BD
31-60 mL/min*	30mg BD
11-30mL/min*	30mg OD
≤10mL/min**	30mg ONCE
Haemo-dialysis (HD)*	30mg ONCE and then 30mg after every HD session
Peritoneal dialysis*	30mg ONCE
Haemo(dia)filtration** 1-1.8L/hr exchange rate	30mg OD
Haemo(dia)filtration** 1.9 – 3.6L/hr exchange rate	30mg BD
Haemo(dia)filtration** > 3.6L/hr exchange rate	75mg BD

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 the some of the advice for dosing in renal impairment presented in Table 3 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.

Table 4: Adult zanamivir IV dosing in relation to renal function

CrCl (ml/min)	Dose
≥80ml/min OR haemo(dia)filtration >4.7L/hour exchange rate	Initial dose: 600mg and 12 hours later, maintenance dose: 600mg BD
50-79 OR haemo(dia)filtration 3.0-4.7L/hour exchange rate	Initial dose: 600mg and 12 hours later, maintenance dose: 400mg BD
30-49 OR haemo(dia)filtration 1.8-2.9L/hour exchange rate	Initial dose: 600mg and 12 hours later, maintenance dose: 250mg BD
15-29 OR Haemo(dia)filtration 1-1.7L/hour exchange rate	Initial dose: 600mg and 24 hours later, maintenance dose: 150mg BD
<15	Initial dose: 600mg and 48 hours later, maintenance dose: 60mg BD

Source: Adapted from the GSK Physicians Guidance Document (16). Please note, this may be updated by the manufacturer after publication of the PHE guidance document – please use the Physicians Guidance document that is supplied with the medication, if this is an edition with a later publication date

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 years can be found in the manufacturer's guidance (16). Further dosing information on dosing in haemodialysis, if needed, can be found in the manufacturer's physician guidance document supplied with the medication. 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>

Some patients receiving renal replacement therapy in critical care will also have some residual renal function, and renal replacement therapy itself may be interrupted for a variety of reasons. Critical care units should discuss further dose adjustments with their pharmacist.

1.3.3 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[®] (or nebulised aqueous zanamivir if the Diskhaler[®] 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.

1.3.4 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 (17,18). 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 (19, 20). 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** and the PHE guidance: **Seasonal influenza: guidance for adult critical care units** (21, 22).

1.3.5 Other licensed and unlicensed treatments

Peramivir (IV) is a neuraminidase inhibitor which has received marketing authorisation in 2018 within the European Union. However, at the time of writing, it is unclear when this medicine will be marketed within the UK. Therefore, background information is provided about this medicine and it has not been included in the main recommendations for use in this document at this stage. This will be kept under review.

Peramivir is administered as a single intravenous infusion for the treatment of influenza in adults and children (from 2 years of age) 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 (23). 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. If IV peramivir becomes available 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.

All of the following influenza treatments in section 1.3.5 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 by 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, see table 4 on Page 16 for details.. Consult [Appendices 2 and 4](#) 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.

Further details of use of IV and nebulised zanamivir for patients under 18 years can be found in the manufacturer's guidance (16) supplied with the medication.

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, 4 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 nebuliser chamber, immediately prior to administration. The solution should be nebulised to dryness.

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 use in Japan, only in patients infected with novel or re-emerging influenza viruses (ie in the event of a pandemic), and only when that virus is resistant to other influenza antivirals. 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. Concerns about teratogenicity have been raised based on information from animal models.

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.

Baloxavir marboxil (PO) is a novel, single-dose, oral agent that has antiviral activity against influenza A and B viruses. It is a cap-dependent endonuclease inhibitor and therefore has a different mode of action from the neuraminidase inhibitors. Baloxavir

received regulatory approval in Japan in February 2018 and is undergoing priority review by the US FDA; it is not currently licensed in Europe. Phase III trials have been completed in uncomplicated influenza and in individuals who are at risk of complications of influenza. The results of further phase III trials in paediatric and hospitalised patients with severe influenza are awaited. The development of decreased susceptibility to baloxavir following treatment has been observed in clinical trials (24).

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.

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 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 on the management of outbreaks of influenza like illness \(ILI\) in care homes \(4\)](#).

For further information on which contacts of a case of influenza should receive prophylaxis, refer to guidance from NICE [\(25\)](#). Special considerations may apply to localised incident situations; specialist advice in relation to incidents such as influenza outbreaks, may be sought from local health protection teams.

Prophylaxis is normally not considered in at-risk groups who have been vaccinated against seasonal influenza at least 14 days before exposure, with the above exceptions. Clinicians should note however, that such use is outside the NICE guidance recommendations and would therefore be a matter for individual clinical judgement.

Inhaled zanamivir is not licensed for children under 5 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[®] effectively. Severely immunosuppressed children under 5 years and all other severely immunosuppressed patients who cannot use the Diskhaler[®] 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[®], including severely immunosuppressed children aged less than 5 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 1.3.5](#)).

Table 5: Selection of antivirals for post-exposure prophylaxis

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

Note: Commencing prophylaxis with oseltamivir later than 48 hours after exposure, or with zanamivir, later than 36 hours after exposure is an off-label use. Specialist advice referred to in this table may be obtained from a local infection specialist such as a virologist.

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 with a relevant pharmacy 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 6: Prophylaxis dosage

PROPHYLAXIS	Premature (less than 36 weeks post conceptual age)	0 to 12 months (36 weeks post conceptual age or greater)	>1–12 years: Dose according to weight below				Adults (13 years and over) ²
			≤15kg	>15-23kg	>23-40kg	>40kg	
Oseltamivir PO (prophylaxis course: 10 days)	See below ¹	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

¹Although 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, and so is outside the product licence. ² 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 prioritised as previously described in Section 1.3.1, such as for children under the age of 1 year. 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 1 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 1 year of age and/or adults, there may not be adequate quantities of the powder for suspension to meet demand for the under 1 year age group. It is important that the powder for suspension is reserved for the less than 1 year age group. Inhaled zanamivir is not licensed for children aged under the age of 5.

2.1.2 Dosing in patients with renal dysfunction

General considerations about prescribing for renal impairment discussed in the treatment section may also be applicable when prescribing for prophylaxis (see [section 1.3.2](#)), except that the dosage of oseltamivir in Table 7 should be used.

Table 7: Recommended oseltamivir prophylaxis dosing in relation to renal function (adults and those aged 13 years or over)

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

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 the 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 flux and low flux intermittent haemodialysis (HD) is recommended due to a lack of published clinical data on oseltamivir carboxylate levels in high-flux 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 1: Use of antivirals in pregnancy, breastfeeding and hepatic dysfunction

Table 8: Recommended dosage for hepatic dysfunction

	Liver dysfunction
Oseltamivir PO	Standard dosing
Zanamivir INH (Diskhaler [®])	Standard dosing
Zanamivir solution IV/NEB	Refer to the physician's guidance document supplied by the manufacturer with the medication

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 (26, 27).

The Summary of Product Characteristics (SPC) for Tamiflu[®] (oseltamivir) states the following: "While no controlled clinical studies have been conducted on the use of oseltamivir in pregnant women data on use in pregnancy has been collected from 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[®] after considering the available safety information, the pathogenicity of the circulating influenza virus strain, and the underlying condition of the pregnant woman.”(28).

The Summary of Product Characteristics (SPC) for Relenza[®] (zanamivir) states the following: "The safe use of zanamivir during pregnancy has not been established. In rats and rabbits zanamivir has been shown to cross the placenta. High doses of zanamivir were not associated with malformations in rats or rabbits and only minor alterations were reported. The potential risk for humans is unknown. Zanamivir should not be used in pregnancy unless the expected benefit to the mother is thought to outweigh any possible risk to the foetus" (29).

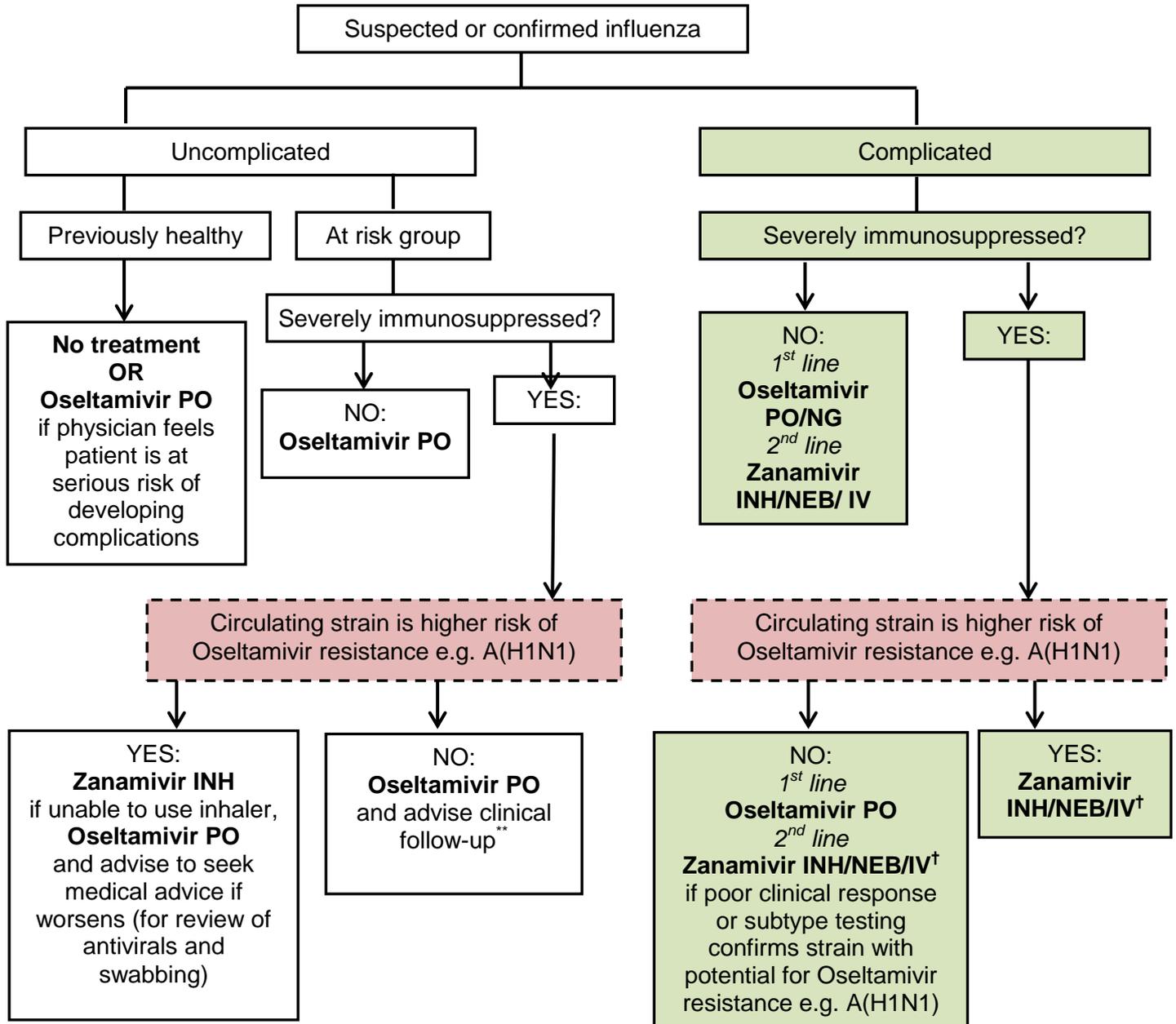
Use during breastfeeding

The UK Drugs in Lactation Advisory Service (UK DILAS) has published advice on the use of Oseltamivir and Zanamivir while breastfeeding:

www.sps.nhs.uk/articles/oseltamivir-or-zanamivir-can-mothers-breastfeed-after-treatment-for-influenza-2/

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 under the General Medical Services (GMS) regulations 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 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: 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 (30). 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 1 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 (31).

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 2 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 5 had chronic lymphocytic leukaemia (32).

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 PHE. Healthcare workers who are not in an at-risk group may continue to work, using appropriate personal protective equipment 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 2 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. It should be noted that the potential mode of influenza transmission in this situation is via direct contact from infected respiratory secretions rather than via breastmilk itself.

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 (33).

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 capsules and Tamiflu® (oseltamivir) 6mg/ml Powder for Oral suspension. 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 which may be considered by mothers and clinicians in a joint discussion 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. The disadvantages for the neonate would include not being able to benefit from breastfeeding-related transfer of immune factors to help protect the baby and nutrients for development; 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 so that breastfeeding can continue once they 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 arrangements made in advance for rapidly 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. In this situation, the mother should be advised to wash their hands with soap and water, particularly before breast feeding or touching any other item that the neonate will have contact with. If expressing breast milk using a pump, this should be cleaned as per the manufacturer's instructions.

PHE recognises that the decision on which action to take is likely to involve a detailed discussion between the mother and their clinicians about the relative advantages and disadvantages of each potential option in relation to their own individual situation. 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; previous research has shown that this was 71% effective in preventing influenza infection in infants aged less than 6 months in England (34, 35).

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 patients and critically ill patients.

This is based on expert advice as symptoms and signs of influenza may be absent or minimal despite influenza virus infection in these patient groups, or may be difficult to assess due to their clinical status. Antivirals administered at prophylactic doses can promote antiviral

resistance when given to patients already infected with influenza virus, especially when there is underlying immunosuppression.

Prophylaxis should not be postponed while the results of influenza testing are awaited and influenza virus testing should be expedited. If testing reveals that a patient commenced on 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, clinicians should be reminded that infection control measures should be implemented and it is currently not possible to predict how long shedding of virus may last for individual patients. It should be noted in advance of implementing this advice, that in the absence of influenza symptoms, cessation of these infection control measures will need to be considered locally by an infection specialist, on a case by case basis.

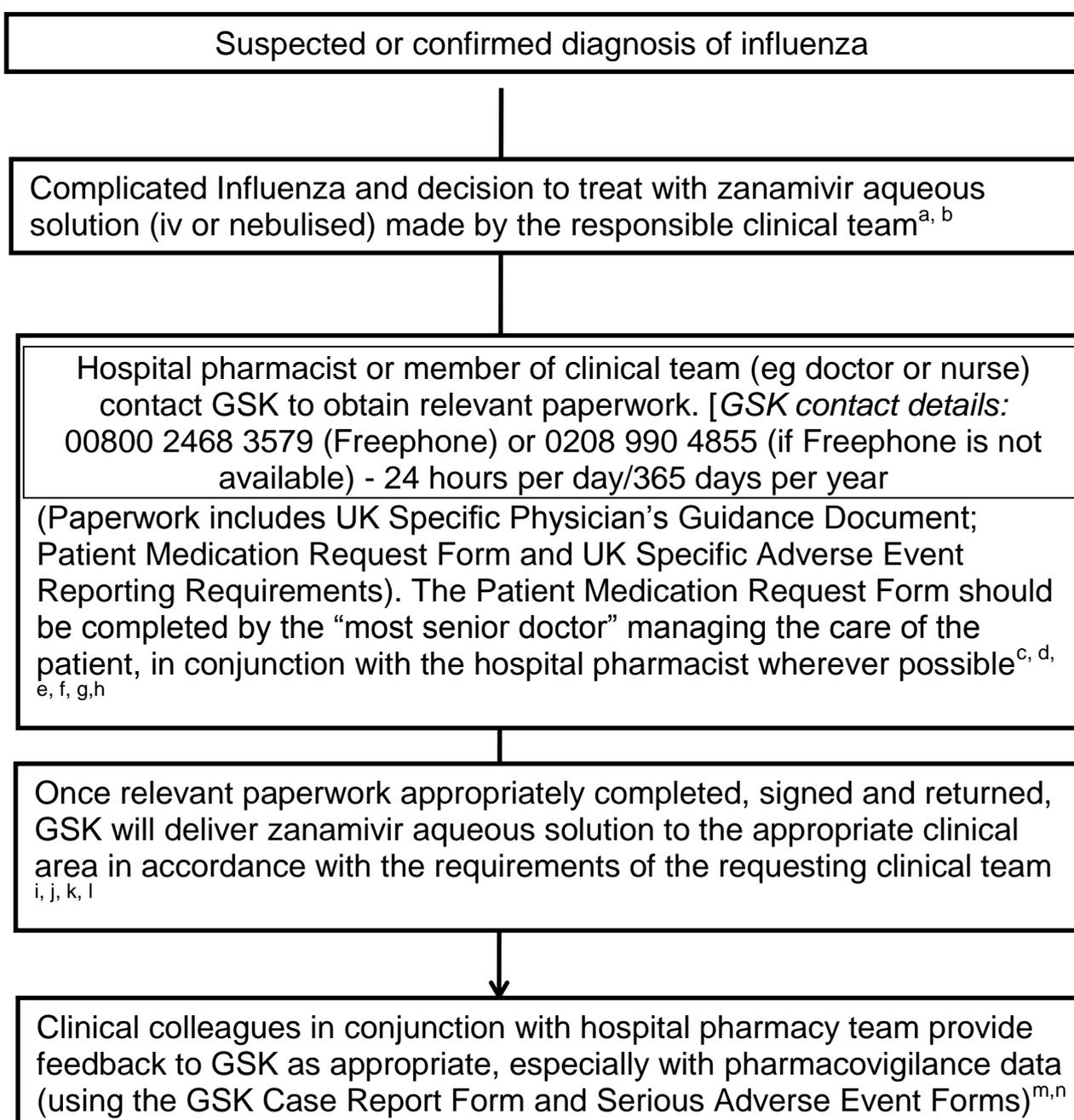
Q: Should the standard treatment dose of Oseltamvir be doubled (“double-dosing”) when treating patients with severe illness caused by seasonal influenza infection?

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 (22, 36)

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 (36,37), there is insufficient evidence that double-dosing in patients with Influenza B has a clinical benefit (38).

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 dispatch for zanamivir aqueous solution in 2018/19 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 22 December 2018: 8am – 3pm

Sunday 23 December 2018: 8am – 3pm

Monday 24 December 2018: 8am – 3pm

Tuesday 25 December 2018 : 8am – 3pm (Christmas Day)

Wednesday 26 December 2018: 8am – 3pm (Boxing Day)

Thursday 27 December 2018: 8am – 3pm

Friday 28 December 2018: 8am – 3pm

Saturday 29 December 2018: 8am – 3pm

Sunday 30 January 2018: 8am – 3pm

Monday 31 January 2018: 8am – 3pm

Tuesday 1 January 2019: 8am – 3pm (New Year’s Day)

Normal shipment service will resume on Wednesday 2 January 2019.

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. (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 dispatch 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 dispatch, 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 dispatch supplies, but depending on the time of receipt of the completed documentation, same day dispatch **cannot** be guaranteed.

l. Dispatch, delivery and receipt

- i. Once the relevant paperwork has been completed and confirmed, GSK will dispatch 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.

Appendix 5: Sources of information

- (1) Public Health England. **Respiratory Tract Infections: infection control** www.gov.uk/government/collections/seasonal-influenza-guidance-data-and-analysis#management-and-treatment
- (2) European Centre for Disease Prevention and Control (2017). **Expert opinion on neuraminidase inhibitors for the prevention and treatment of influenza - review of recent systematic reviews and meta-analyses** <https://ecdc.europa.eu/en/publications-data/expert-opinion-neuraminidase-inhibitors-prevention-and-treatment-influenza-review>
- (3) Public Health England (2016). **Surveillance and Laboratory Testing of Influenza Neuraminidase Inhibitor Resistance** www.gov.uk/government/publications/influenza-antiviral-susceptibility-surveillance-and-diagnosis-of-resistance
- (4) Public Health England (2016). **PHE guidelines on the management of outbreaks of influenza like illness (ILI) in care homes** www.gov.uk/government/publications/acute-respiratory-disease-managing-outbreaks-in-care-homes
- (5) Cochrane Acute Respiratory Infections Group (2014). **Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children:** <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/abstract>
- (6) Public Health England (2014), **The use of antivirals for the treatment and prophylaxis of influenza PHE summary of current guidance for healthcare professionals:** www.gov.uk/government/publications/influenza-treatment-and-prophylaxis-using-anti-viral-agents
- (7) Department of Health (2013) **Immunisation against Infectious Disease** (The Green Book), Updated 2015: www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book
- (8) Muthuri et al (2014) **Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data.** *Lancet Respirator Medicine*; 2014 May;2(5):395-404. www.ncbi.nlm.nih.gov/pubmed/24815805
- (9) Public Health England (2016). **Infection control precautions to minimize transmission of acute respiratory tract infections in healthcare settings** www.gov.uk/government/publications/acute-respiratory-disease-managing-outbreaks-in-care-homes
- (10) Ariano RE et al (2010). **Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza.** *CMAJ* 2010; 182: 357–63. www.ncbi.nlm.nih.gov/pubmed/20159892

- (11) Acosta EP, Jester P, Gal P et al (2010) **Oseltamivir Dosing for Influenza Infection in Premature Neonates**. J Infect Dis; 2010, 202(4):563–566
www.ncbi.nlm.nih.gov/pubmed/20594104
- (12) McPherson C, Warner B, Hunstad DA et al. (2012) **Oseltamivir Dosing in Premature Infants**. J Infect Dis. 2012, 206(6): 847–850. www.ncbi.nlm.nih.gov/pubmed/22807525
- (13) Centers for Disease Control and Prevention (2015) **Guidance on the use of influenza antiviral agents – antiviral dosage** www.cdc.gov/flu/professionals/antivirals/antiviral-dosage.htm
- (14) Thorne-Humphrey LM et al. (2011). **Oseltamivir pharmacokinetics in morbid obesity (OPTIMO trial)**. J Antimicrob Chemother 2011; 66: 2083–2091.
www.ncbi.nlm.nih.gov/pubmed/21700623
- (15) Jittamala P et al. (2014). **Pharmacokinetics of Orally Administered Oseltamivir in Healthy Obese and Non obese Thai Subjects**. Antimicrob Agents Chemother. 2014 Volume 58 Number 3: 1615–1621. www.ncbi.nlm.nih.gov/pubmed/24366750
- (16) 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.
- (17) 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.
www.ncbi.nlm.nih.gov/pmc/articles/PMC2831695/
- (18) Giraud C et al, (2011) **High levels and safety of oseltamivir carboxylate plasma concentrations after nasogastric administration in critically ill children in a pediatric intensive care unit**. Antimicrob. Agents Chemother. 2011 Jan; 55(1):433-435.
www.ncbi.nlm.nih.gov/pubmed/20937783
- (19) Lee et al (2013), **A prospective intervention study on higher does oseltamivir treatment in adults hospitalized with influenza A and B infections**, *Clinical Infectious Diseases*. 2013 Dec; 57(11):1511-9.
- (20) 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.
- (21) Public Health England (2011), **Critical Care Management of children with influenza H1N1**:
www.gov.uk/government/collections/seasonal-influenza-guidance-data-and-analysis#management-and-treatment
- (22) Public Health England (2017) **Seasonal influenza: guidance for adult critical care units** www.gov.uk/government/publications/seasonal-influenza-managing-cases-in-critical-care-units

- (23) Lackenby et al (2018) **Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors and status of novel antivirals, 2016-17.** *Antiviral Resistance*. 2018 Sep;157:38 – 46
- (24) Hayden et al (2018) **Baloxavir Marboxil for uncomplicated influenza in adults and adolescents.** *N Engl J Med*. 2018 Sep; 379: 913-923
- (25) National Institute for Clinical Excellence (2009). **Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza:** www.nice.org.uk/guidance/ta168?unlid=13544702920163505336
- (26) Dunstan HJ, Mill AC, Stephens S, Yates LM, Thomas SH (2014), **Pregnancy outcome following maternal use of zanamivir or oseltamivir during the 2009 influenza A/H1N1 pandemic: a national prospective surveillance study** *BJOG*. 2014 Jun;121(7):901-6. www.ncbi.nlm.nih.gov/pubmed/24602087
- (27) Wollenhaupt M, Chandrasekaran A, Tomianovic D (2014), **The safety of oseltamivir in pregnancy: an updated review of post-marketing data.** *Pharmacoepidemiol Drug Saf*. 2014 Oct;23(10):1035-42. www.ncbi.nlm.nih.gov/pubmed/24995623
- (28) Roche Products Limited (2015) **Summary of Product Characteristics for Tamiflu** www.medicines.org.uk/emc/medicine/10446/SPC/Tamiflu+75mg+hard+capsule/
- (29) GlaxoSmithKline (2015) **SPC for Relenza 5mg/dose inhalation powder** www.medicines.org.uk/emc/medicine/2608
- (30) Lee, N, Chan PKS, Wong CK, et al (2011) **Viral clearance and inflammatory response patterns in adults hospitalised for pandemic 2009 influenza A(H5N1) virus pneumonia.** *Antiviral Therapy* 2011; 16: 237-247 www.intmedpress.com/serveFile.cfm?sUID=818bbc6c-5093-4a1b-b047-e7274387a7e2
- (31) Inoue M, Barkham T, Leo Y-S, et al (2010) **Emergence of Oseltamivir-Resistant Pandemic (H1N1) 2009 Virus within 48 Hours.** *Emerging Infectious Diseases* Vol. 16, No. 10, October 2010: 1633-1636 wwwnc.cdc.gov/eid/article/16/10/pdfs/10-0688.pdf
- (32) Calatayud L, Lackenby A, Reynolds A, et al. (2011) **Oseltamivir - resistant pandemic (H1N1) 2009 virus infection in England and Scotland, 2009-2010.** *Emerging Infectious Diseases*, vol 17(10); 1807-1815 wwwnc.cdc.gov/eid/article/17/10/11-0117_article
- (33) Myles PR, Semple MG, Lim WS, Openshaw PJM, Gadd EM, Read RC, et al (2012). **Predictors of clinical outcome in a national hospitalised cohort across both waves of the influenza A/H1N1 pandemic 2009-2010 in the UK.** *Thorax*. 2012 Aug 1;67(8):709–17 <http://thorax.bmj.com/content/67/8/709.full.pdf+html>

- (34) Creanaga AA, Johnson TF, Graitcer FC, et.al. (2010). **Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women.** Obstetrics and Gynaecology. April 2010- volume 115 – issue 4, pp 717-726.
<http://journals.lww.com/greenjournal/pages/articleviewer.aspx?year=2010&issue=04000&article=00008&type=abstract>
- (35) Dabrera G, Zhao H, Andrews N, et.al. (2014). Rapid Communications. **Effectiveness of seasonal influenza vaccination during pregnancy in preventing influenza infection in infants, England 2013/14.** Euro. Surveill.2014;19(45), article 1.
www.eurosurveillance.org/images/dynamic/EE/V19N45/art20959.pdf
- (36) South East Asia Infectious Disease Clinical 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 randomised controlled trial.** BMJ.2013;346,f3039.
www.bmj.com/content/346/bmj.f3039
- (37) Farrukee R, Mosse J, Hurt AC (2013). **Review of the clinical effectiveness of the neuraminidase inhibitors against influenza B viruses** Expert Rev Anti Infect Ther. 2013 Nov;11(11):1135-45 www.ncbi.nlm.nih.gov/pubmed/24093683
- (38) Dixit R, Khandaker G, Hay P et.al. (2015). **A randomized study of standard versus double dose oseltamivir for treating influenza in the community.** Antivir Ther. 2015;20(7):689-98.
www.ncbi.nlm.nih.gov/pubmed/24912485

Appendix 6: Conflict of interest declaration

No member declared a relevant personal interest, bar MD who was paid for lecturing by Sanofi-Pasteur in 2016 and RS who received an honorarium paid by Roche for speaking at a launch of a new flu product in 2016. MD also declared a non-personal specific interest receiving partial financial support for an educational meeting from Genmark in 2016 and Speedx Ltd 2017.

PHE received an unrestricted grant from GSK to undertake a study on the outcome of patients who received parenteral zanamavir. The funder received data and interim reports from PHE but did not influence analysis and reporting of the study. None of the antiviral working group members were involved in the study.