



UK Health
Security
Agency

Guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza

Version 11, November 2021

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What has changed since the last version

The major changes from version 10.0 (September 2019) include:

- co-circulation of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) during coronavirus (COVID-19) pandemic and the diagnosis and management of influenza
- clarification of oseltamivir dose in severely immunocompromised patients
- removal of guidance on the aqueous zanamivir compassionate use programme following licensure and marketing of Dectova[®] zanamivir for intravenous (IV) infusion
- regulatory approval of baloxavir marboxil

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. Circulation of influenza

Prescribing of antivirals in England under General Medical Services contracts is limited to periods when: 'the Department of Health and Social Care (DHSC) has notified general medical practitioners that the influenza virus is circulating in the community.' This notification is issued by the Chief Medical Officer (CMO) for England or a deputy CMO.

This aligns to the NICE Technology Appraisals on influenza antivirals which recommend prescribing when 'national surveillance schemes indicate that influenza virus A or B is circulating'. NICE (National Institute for Health and Care Excellence) further defines this as: 'periods when there is a substantial likelihood that people presenting with an influenza-like illness are infected with influenza virus', based on assessment by the relevant national public health body using 'information from a range of clinical, virological and epidemiological influenza surveillance schemes'.

Epidemiologically, influenza circulates prior to periods when there is a substantial likelihood that ILI is influenza. This document therefore uses the terminology 'DHSC had notified GPs

that flu is circulating' to indicate the periods when antivirals may be prescribed through standard primary care routes.

4. Risk factors for complicated influenza

These include:

- 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 ([2](#)).

5. 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. Examples of severe immunosuppression include:

- 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 3 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

6. Point of care test (POCT)

A POCT is a medical diagnostic test, performed at or near the site of patient care, undertaken by healthcare professionals who may not be trained laboratory staff. It is a test to support clinical decision making, to help the physician to decide upon the best management options, and for which the results can be available in real time, usually in less than 90 minutes.

Introduction

Neuraminidase inhibitors (herein referred to as NAI or antivirals) are just one 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](#), [2](#)). This UK Health Security Agency (UKHSA) guidance recommends the targeted use of antiviral medicines for specific circumstances and groups of patients. Antivirals are currently recommended by a number of organisations including the National Institute for Health and Clinical Excellence (NICE) and the [European Centre for Disease Prevention and Control](#) (ECDC) for the treatment and prophylaxis of seasonal influenza ([3 to 5](#)).

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 (GPs) in England may only prescribe these medicines under the General Medical Services regulations when the Department of Health and Social Care (DHSC), usually through the CMO, has announced that influenza is circulating within the community (see [Appendix 2](#)).

The clinical diagnosis of influenza has been made more challenging by the similarity of presentation of coronavirus (COVID-19), with the co-circulation of SARS-CoV-2 also impacting on the use of epidemiological surveillance to guide diagnosis based on influenza prevalence. These factors favour increased use of virological testing to guide case management and outbreak response.

Laboratory testing of influenza also has particular importance 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 UKHSA guidance ([6](#))).

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 UKHSA only and not of the manufacturer.

Clinicians may be aware of a Cochrane Review on the efficacy of antivirals, published in 2014 ([7](#)). PHE had previously published a detailed response to this ([8](#)) and clinicians should note that the NICE guidelines for antiviral medications for influenza remain unchanged ([9](#)). This guidance should be used by clinicians in conjunction with the summary of product characteristics (SPC) for these medicines, particularly with reference to the contraindications, interactions and adverse events.

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 UKHSA public health laboratories. Local health protection teams should be contacted about localised influenza-related outbreaks, such as in care homes ([find your local health protection team](#)). Separate guidance on the management of influenza in these settings is available (see UKHSA's '[Guidance on the management of influenza like illness \(ILI\) care homes](#)' ([10](#))).

1. Seasonal influenza and COVID-19

Respiratory viruses such as influenza cause substantial health burden and health service utilisation each year. SARS-CoV-2, causing COVID-19, is a major addition to the respiratory virus threats faced by humans.

Although readily infectious, influenza is less transmissible than SARS-CoV-2, with a basic reproduction number of around 1.8 (and reproduction number of around 1.2 to 1.3 in a typical season), versus a basic reproduction number of at least 2.6 for SARS-CoV-2 ([11](#), [12](#), [13](#)). Non-pharmaceutical measures against COVID-19 also reduce transmission of influenza ([14](#)), however, influenza remain an important health risk when non-pharmaceutical interventions are not in place and in-person mixing occurs ([15](#)).

Fever and cough are typically considered relatively specific for clinical diagnosis of influenza during periods when influenza is highly prevalent but are less so if SARS-CoV-2 is also circulating. The potential for co-circulation due to the intrinsic higher infectiousness of SARS-CoV-2 and similarity in clinical presentation of COVID-19 make diagnosis challenging on clinical-epidemiological grounds alone.

Coinfection of a patient with influenza and SARS-CoV-2 is possible and may be associated with increased mortality ([16](#)).

Multiplex reverse transcriptase polymerase chain reaction (RT-PCR) and other validated diagnostic tests for SARS-CoV-2, influenza A, influenza B and potentially other respiratory viruses can be used to strengthen diagnosis and support prompt initiation of influenza antivirals where appropriate.

Recommendations on the use of COVID-19 and influenza diagnostic tests when considering neuraminidase inhibitors (NAI) initiation are outlined in [Table 1](#). Evidence synthesis of peer-reviewed literature for this guideline found no data to indicate any adverse impact of initiating neuraminidase inhibitors in patients with COVID-19. COVID-19 is not a contraindication to prescribing influenza antivirals where prompt initiation for suspected or confirmed influenza is required. There is no data to support prescribing of influenza antivirals for the treatment of COVID-19 and any such use should be as part of a clinical trial within an appropriate regulatory framework.

Table 1. Recommendations on the use of COVID-19 and influenza diagnostic tests when considering NAI initiation in at-risk patients

	Indication in eligible at-risk patient group	DHSC had notified GPs that flu is circulating (see Definitions section)	NAI initiation and testing for detection of COVID-19 (SARS-CoV-2) and/or influenza
1	Treatment: the person presents with complicated influenza-like illness, typically requiring hospitalisation	Year-round	If point of care tests (POCTs) for COVID-19 and influenza are unavailable, consider prompt NAI initiation prior to virological testing. Local or national surveillance may help inform this. Reassess indication for NAI once test results are available.
2a	Treatment: the person presents with an (uncomplicated) influenza-like illness and can start treatment within 48 hours (or within 36 hours for zanamivir treatment in children) of the onset of symptoms as per licensed indications.	No DHSC notification of influenza circulation	NAI use should usually be guided by influenza diagnostic tests. COVID-19 testing should be done if influenza is clinically suspected unless this has been specifically discounted. If the patient has onset during a virologically-confirmed influenza outbreak in a closed setting then this would be indication for empirical initiation of NAI.
2b	Treatment: the person presents with an (uncomplicated) influenza-like illness and can start treatment within 48 hours (or within 36 hours for zanamivir treatment in children) of the onset of symptoms.	DHSC had notified GPs that flu is circulating	COVID-19 testing should be done if influenza is clinically suspected unless this has been specifically discounted. Negative results for COVID-19 would usually be an indication for NAIs (in the absence of testing for other respiratory viruses) based on clinical-epidemiological probability. COVID-19 point of care testing with a lateral flow device may be used to inform antiviral use but is not a substitute for COVID-19 PCR testing in patients with relevant symptoms. If POCTs are unavailable, NAI should be started promptly without awaiting results of PCR testing if the clinician considers influenza to be highly probable (such as symptom onset following close contact with a confirmed influenza case). If available, testing for influenza should be undertaken alongside COVID-19 testing but is not required for NAI initiation.
3a	Post-exposure prophylaxis, where: i) The person has been exposed to an influenza-like illness and is able to begin prophylaxis within the timescale specified in the marketing authorisations of the individual drugs (within 36 hours of contact with an index case for zanamivir and within 48 hours of contact with an index case for oseltamivir); and ii) the person has not been effectively protected by vaccination	No DHSC notification of influenza circulation.	NAI use should usually be guided by influenza testing of the index case(s). COVID-19 testing of the index case(s) should be done if influenza is clinically suspected unless this has been specifically discounted.
3b	Post-exposure prophylaxis, where: i) The person has been exposed to an influenza-like illness and is able to begin prophylaxis within the timescale specified in the marketing authorisations of the individual drugs (within 36 hours of contact with an index case for zanamivir and within 48 hours of contact with an index case for oseltamivir); and ii) the person has not been effectively protected by vaccination.	DHSC had notified GPs that flu is circulating.	COVID-19 testing of the index case should be done if influenza is clinically suspected in the index case(s) unless this has been specifically discounted. Negative results for COVID-19 would usually be an indication for NAIs (in the absence of testing for other respiratory viruses). COVID-19 point of care testing with a lateral flow device may be used to inform antiviral use but is not a substitute for COVID-19 PCR testing in patients with relevant symptoms. If available, testing for influenza in the index case(s) should be undertaken alongside COVID-19 testing but is not required for NAI initiation.

Notes to Table 1

Suspected or confirmed COVID-19 is not a contraindication to NAI initiation where suspected or confirmed influenza is part of the differential diagnosis.

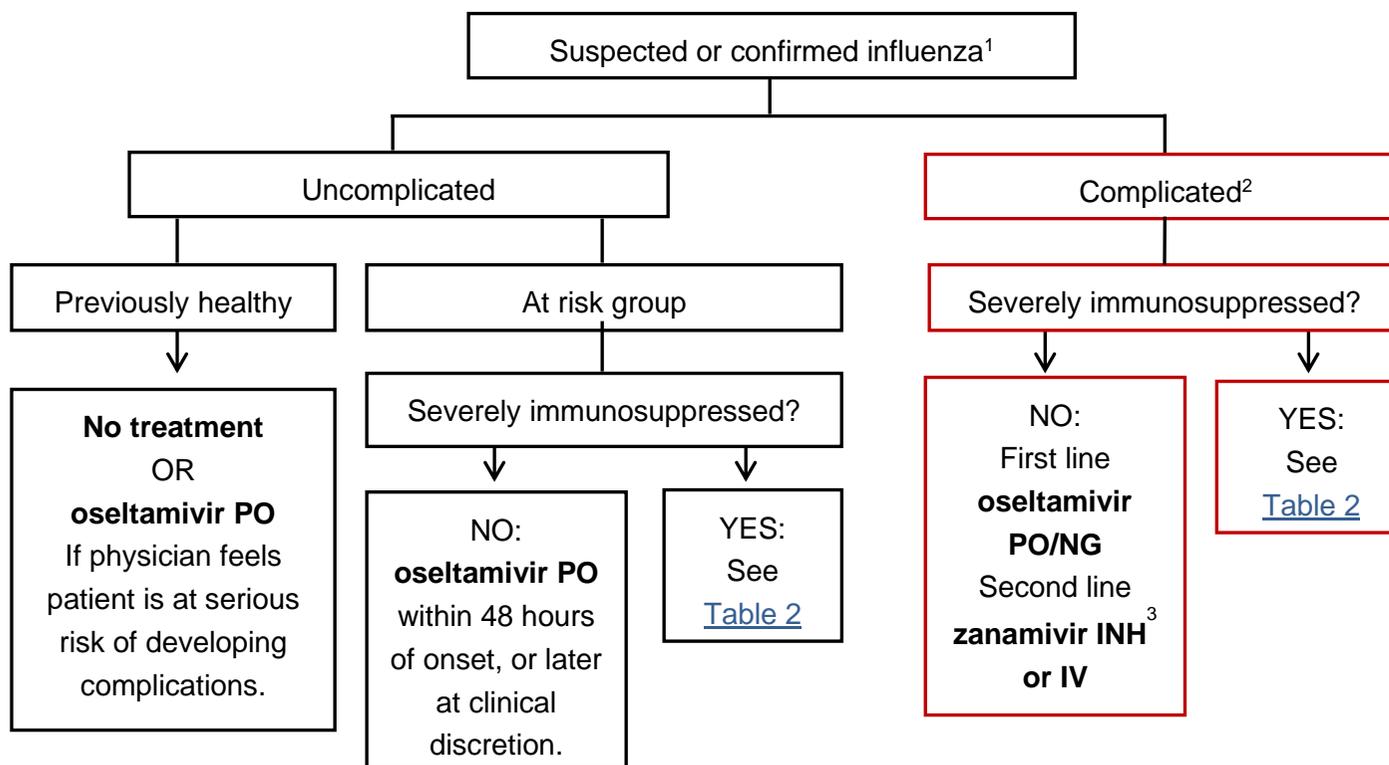
An episode of COVID-19 may result in prolonged detection of SARS-CoV-2 by RT-PCR such that a positive COVID-19 PCR result in such a patient does not exclude that recent onset symptoms are due to influenza or another respiratory virus.

For empirically-initiated NAI treatment clinicians may continue with NAI where there is strong clinical suspicion despite a negative influenza result, guided by factors such as an epidemiological link to a case, high community incidence of influenza and/or absence of an alternative diagnosis.

In community or primary care settings NAI should be provided through a suitable commissioned service for prophylaxis in- or out-of-season and for treatment outside of the CMO-declared flu season.

2. Treatment of suspected or confirmed influenza

Figure 1. Algorithm for selection of antiviral therapy for treatment of influenza



Please refer to the [definitions](#) and [Table 2](#) when using this algorithm.

¹ For treatment of suspected or confirmed oseltamivir-resistant influenza, see [section 2.3.3](#).

² For treatment of complicated influenza, see [section 2.2](#), including details of when to use second line treatment.

³ Where possible, patients who have good respiratory function despite their illness, can use the Diskhaler®. Inhaled zanamivir via Diskhaler® may not be an effective delivery route in some patients, including those unable to administer the Diskhaler® and patients with severe underlying respiratory disease. It is not licensed for use in children less than 5 years. The powder preparation for the Diskhaler® should NEVER be made into nebuliser solution or administered to a mechanically ventilated patient. Clinical scenarios where IV zanamivir may be appropriate are described in [section 2.2](#).

Accessible text version of Figure 1

There are 2 paths for selection of antiviral therapy for treatment of suspected or confirmed influenza¹.

Path 1: Uncomplicated illness

There are 2 risk categories for uncomplicated illness.

1.1 If case is previously healthy

No treatment.

OR

Oseltamivir 'per os', by mouth (PO) if physician feels patient is at serious risk of developing complications.

1.2 If case is in an at risk group

There are 2 risk categories for at risk cases.

1.2.1 If case is in an at risk group and is severely immunocompromised

See [Table 2](#).

1.2.2 If case is in an at risk group and not severely immunocompromised

Oseltamivir PO within 48 hours of onset

OR

Later at clinical discretion.

Path 2: Complicated² illness

There are 2 risk categories for complicated illness

2.1 If case is severely immunocompromised

See [Table 2](#).

2.2 If case is not severely immunocompromised

First line treatment: oseltamivir PO or NG.

Second line treatment: zanamivir INH³ or IV.

Antiviral resistance and the immunosuppressed patient

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)pdm09 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 [UKHSA weekly influenza reports](#). Table 2 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 2. Selection of antivirals for severely immunosuppressed patients

	Dominant circulating strain has a lower risk of oseltamivir resistance, for example A(H3N2), influenza B*	Dominant circulating strain has a higher risk of oseltamivir resistance, for example A(H1N1)pdm09*
Uncomplicated influenza	oseltamivir PO and clinical follow up. Commence therapy within 48 hours of onset (or later at clinical discretion).	Zanamivir inhaler (INH) (Diskhaler®) Commence therapy within 48 hours of onset (36 for children) 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	First line: oseltamivir PO/NG Second line: zanamivir INH ⁺⁺ Consider switching to zanamivir if: <ul style="list-style-type: none"> • poor clinical response • evidence of gastrointestinal dysfunction • subtype testing confirms a strain with potential oseltamivir resistance, for example A(H1N1)pdm09 (see right) 	zanamivir INH ⁺⁺ Commence therapy within 48 hours of onset (36 for children) or later at clinical discretion.

Notes to Table 2

* also applicable if this is the strain known to be infecting patient. However, treatment should not be delayed while waiting for test results.

++ Consider Zanamivir IV if patients:

- cannot use inhaled Zanamivir
- have severe complicated illness such as multi-organ failure

Note: commence as soon as possible and usually within 6 days. See section [2.3.5](#) for more information.

2.1 Treatment of adults and children in community or 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 [Dosage in adults for treatment of uncomplicated influenza](#). For paediatric dosing see [section 2.3.1](#).

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). 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 ([17](#)). Starting treatment more than 48 hours after onset 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; the risk of resistance is higher in people who are severely immunosuppressed who are given antivirals, and the selection of first line antivirals in severely immunosuppressed individuals should take account of the dominant circulating strain of influenza ([Table 2](#)). Oseltamivir PO is the first line treatment, unless the dominant circulating strain has a higher risk for developing oseltamivir resistance, for example, influenza A(H1N1)pdm09, in which case use zanamivir (INH) ([Table 2](#)). 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. When oseltamivir is indicated based on the above advice ([Table 2](#)), the manufacturer recommends a longer treatment course of 10 days for immunosuppressed patients. No dose adjustment is necessary.

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 off-label). 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 IV zanamivir; this would be outside the marketing authorisation (see [section 2.3.5](#)).

Dosage in adults for treatment of uncomplicated influenza

Oseltamivir 75mg PO twice daily for 5 days.

Zanamivir 10mg inhaler (INH) twice daily for 5 days.

Note: dose adjustments for obesity, renal dysfunction and use in children are provided later in this document. See specific advice for oseltamivir treatment duration in section for severely immunosuppressed patients, above.

2.2 Treatment of adults and children with complicated influenza

All patients with complicated influenza should receive treatment, often in hospital. Testing as soon as possible 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.

Ensure that appropriate infection control precautions are applied to the patients. See UKHSA guidance on [Infection control precautions to minimize transmission of acute respiratory tract infections in healthcare settings for further details](#) (1).

A history of influenza immunisation does not exclude influenza as a possible diagnosis. The duration of therapy depends on clinical response (treatment beyond 5 days' duration is an off-label use). Test for antiviral resistance in patients who do not respond after 5 days of treatment.

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 (18).

Second line treatment

If there is a poor clinical response to first line treatment switch to inhaled zanamivir. If there is evidence of gastrointestinal dysfunction, which could cause decreased absorption of enterically-administered medications, use inhaled zanamivir. Examples of gastrointestinal dysfunction 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. If zanamivir is indicated but patients cannot use a zanamivir (Relenza) Diskhaler® or have severe complicated illness such as multi-organ failure, IV zanamivir should be considered.

Exceptions

Severely immunosuppressed patients: oseltamivir (PO or NG) is the first line treatment, unless the dominant circulating strain has a higher risk for developing oseltamivir resistance for example influenza A(H1N1)pdm09 ([Table 2](#)). Treatment should start as soon as possible. Arrange influenza A subtype testing and monitor clinical condition closely. If there is a poor clinical response to oseltamivir use, consider switching to zanamivir inhaler and test for oseltamivir resistance. (See [Appendix 3](#) for more information on poor clinical response.)

If the dominant circulating strain is influenza A(H1N1)pdm09, (or patient testing indicates infection with a strain with a higher risk for developing oseltamivir resistance) use zanamivir inhaler as first line treatment ([Table 2](#)). Patients who cannot use inhaled zanamivir or those who have severe complicated illness such as multi-organ failure may be considered for IV zanamivir.

Suspected or confirmed oseltamivir resistance: for example, an individual developing complicated influenza infection following contact with a 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[®]). IV zanamivir may be considered for those patients unable to use inhaled zanamivir (Diskhaler[®]).

2.3 Supplementary material: Prescribing antivirals for treatment

2.3.1 Antiviral dosage and schedules

Table 3. Treatment dosage

Treatment	Premature (less than 36 weeks post conceptional age)	Infants under 12 months (36 weeks post conceptional age or greater)	Children 1 to 12 years: Dose according to weight below				Adults (13 years and over) ³
			10 to 15kg	more than 15 to 23kg	more than 23 to 40kg	over 40kg	
Oseltamivir PO (treatment course: 5 days) ¹	1mg/kg/dose twice a day (BD) Off-label ²	3mg/kg/dose BD	30mg BD	45mg BD	60mg BD	75mg BD	75mg BD
Zanamivir INH (treatment course: 5 days)	Not licensed for children less than 5 years old. Children over 5 years: 10mg BD					10 mg BD	

¹ Note recommendation from manufacturer regarding treatment length for immunosuppressed patients ([section 2.1](#)). Source: Summary of Product Characteristics updated April 2020.

² This is an off-label use of oseltamivir, and is based on evidence from the literature, and expert opinion [19](#), [20](#), [21](#).

³ If a person in this age group weighs 40kg or less, it is suggested that the more than 23 to 40kg dose for those aged 1 to 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.

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 ([22](#), [23](#)). See [Table 3 footnote 3](#) for dosing related to adults weighing 40kg or less.

Inhaled zanamivir: No dose adjustment is needed in obese patients.

IV zanamivir: For adult patients (and adolescents with actual body weight 50kg or greater) the dose is not weight adjusted.

In adolescents with actual body weight less than 50kg and in children, the dose is weight adjusted. For specific dosing information, please refer to the summary of product characteristics ([24](#)).

2.3.2 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. For older adults in care home and similar settings where renal function may be unknown (not available in clinical records or through urea and electrolytes testing in time to inform prescribing), please see the UKHSA care home guidance ([10](#)).

The choice of dose in renal failure is complicated by the different measures available to describe degree of renal impairment, as well as a lack of specific data in some circumstances. creatinine clearance (CrCl) is used in this document as it is a more accurate measure upon which to make dosing recommendations and is congruent with the manufacturers prescribing information for both oseltamivir and zanamivir. The limitations for using estimated glomerular filtration rate (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 (that is, 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, so do not use eGFR in this setting.

Table 4. Recommended oseltamivir treatment dosing in relation to renal function (adults and those aged 13 years or over)

Creatinine clearance (CrCL) (mL/min)	Oseltamivir PO treatment for 5 Days
Greater than 60mL/min*	75mg twice a day (BD)
31 to 60 mL/min*	30mg BD
11 to 30mL/min*	30mg OD
Less than or equal to 10mL/min**	30mg ONCE
Haemo-dialysis (HD)**	30mg ONCE and then 30mg after every HD session
Continuous Ambulatory Peritoneal Dialysis* (refer to Summary of Product Characteristics for advice in relation to automated peritoneal dialysis [APD] mode)	30mg ONCE
Haemo(dia)filtration** 1 to 1.8L/hr exchange rate	30mg OD
Haemo(dia)filtration** 1.9,3.6L/hr exchange rate	30mg BD
Haemo(dia)filtration** Greater than 3.6L/hr exchange rate	75mg BD

Source: Summary of Product Characteristics updated April 2020 (*). The recommendations for haemo-dialysis, 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 5. Adult zanamivir IV dosing for adults and children (6 years and over with a body weight of ≥50kg) in relation to renal function

CrCl (mL/min)	Dose
Greater than or equal to 80mL/min OR haemo(dia)filtration greater than 4.7L/hour exchange rate	Initial dose: 600mg and 12 hours later, maintenance dose: 600mg BD
50 to 79 OR haemo(dia)filtration 3.0 to 4.7L/hour exchange rate	Initial dose: 600mg and 12 hours later, maintenance dose: 400mg BD
30 to 49 OR haemo(dia)filtration 1.8 to 2.9L/hour exchange rate	Initial dose: 600mg and 12 hours later, maintenance dose: 250mg BD
15 to 29 OR Haemo(dia)filtration 1 to 1.7L/hour exchange rate	Initial dose: 600mg and 24 hours later, maintenance dose: 150mg BD
less than 15	Initial dose: 600mg and 48 hours later, maintenance dose: 60mg BD

Source: Adapted from the SPC ([24](#)).

Details of administering IV zanamivir are provided in the summary of product characteristics which specifies that:

‘the dose can be infused as supplied or diluted in sodium chloride 9 mg/mL (0.9%) solution for injection down to any concentration greater than or equal to 0.2 mg/mL ([24](#))’.

Details of use of IV zanamivir for patients under 18 years can be found in the SPC ([24](#)).

Further dosing information on dosing in haemodialysis, if needed, can be found in the SPC.

For children with renal dysfunction aged less than 13 years, adjust the oseltamivir dose as per the [Oseltamivir chapter in the British National Formulary \(BNF\) for children](#).

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.

2.3.3 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®. Those with complicated influenza may receive IV zanamivir as appropriate to their clinical condition (see [section 2.2](#)). In the event of changes in the epidemiology or clinical aspects of antiviral-resistant influenza during the season, UKHSA will alert clinicians and provide updated advice.

2.3.4 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 ([18](#), [25](#)). Increasing the dosage is not recommended in patients who are severely ill with influenza A due to a lack of evidence that it is any more effective ([26](#), [27](#)). 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. Patients in whom zanamivir is indicated but use of inhaled zanamivir is inappropriate, or those who have severe complicated illness such as multi-organ failure, should be considered for IV zanamivir. 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 UKHSA guidance '[Seasonal influenza: guidance for adult critical care units](#)' ([28](#), [29](#)).

2.3.5 Other licensed and unlicensed treatments

2.3.5.1 Licensed treatments

Peramivir

Peramivir (IV) is a neuraminidase inhibitor which has received marketing authorisation in 2018 within the European Union. However, [plans for launch in the UK are uncertain](#), with the EU marketing authorisation withdrawn by the EMA at the request of the MA holder on 9 December 2020). 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 reviewed in a future update of this guidance.

Peramivir is administered as a single dose of 600mg by intravenous infusion for the treatment of uncomplicated influenza in adults and children (from 2 years of age) within 2 days of onset of acute influenza symptoms. The dose should be adjusted according to the manufacturer's instructions for children weighing less than 50 kg. A dose adjustment is also required in renal impairment as peramivir is renally excreted. Evidence of efficacy is limited to mainly influenza A infection but there is no evidence to support the routine use of peramivir in treating serious influenza requiring hospitalisation. There is also no robust 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 ([30](#)). Peramivir should not be used in patients with known oseltamivir resistance unless susceptibility to peramivir has been demonstrated by laboratory tests.

If IV peramivir becomes available in the UK, it may be of use if a parenteral neuraminidase inhibitor is needed for treatment of uncomplicated influenza. The most commonly observed adverse reactions in adults in clinical trials, were decreased neutrophil counts (3.2%) and nausea (2.4%). In paediatric clinical trials, the safety profile of peramivir was similar to that reported in adults. Common adverse reactions in children not reported in adults were injection site rash, pyrexia, tympanic membrane hyperaemia, psychomotor hyperactivity, and pruritus. There is no information available in terms of safety of use in pregnancy or in breastfeeding. Peramivir is not licensed for prophylaxis.

Zanamivir

Zanamivir solution for infusion: Dectova® was launched in the UK in November 2019. Nebulised use of this product is not included in the marketing authorization.

Recommendations for when to consider use of intravenous delivery are included in sections [2.1](#) and [2.2](#) above. The SPC recommends IV zanamivir is commenced as soon as possible and usually within 6 days of the onset of symptoms of influenza. IV zanamivir is renally excreted and requires dose modification for patients with renal dysfunction including those on renal replacement therapy, see [Table 5](#) and the SPC. Further details of use of IV zanamivir for patients under 18 years can be found in the SPC ([24](#)).

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. Nebulisation of zanamivir aqueous solution is no longer recommended by UKHSA for any patient group, and the marketing authorisation of zanamivir aqueous solution in Europe is for IV administration only; if a patient requires zanamivir, but inhaled zanamivir via a Diskhaler is inappropriate (for example, the patient has critical illness and/or severe respiratory disease), IV zanamivir should be used.

Baloxavir Marboxil

Baloxavir marboxil (PO) is a 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 from the US FDA in October 2018. It was approved by the European Medicines Agency in January 2021 and by the MHRA in June 2021. The development of decreased susceptibility to baloxavir following treatment has been observed in

clinical trials and post-marketing surveillance in Japan ([31 to 33](#)). It is not currently marketed in Great Britain and pre-marketing use is recommended to be used in the context of an approved research protocol. Recommendations will be reviewed in a future update of this guidance.

2.3.5.2 Unlicensed treatments

All of the following influenza treatments in the rest of [section 2.3.5](#) are unlicensed for this purpose in the UK. 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.

Ribavirin

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

Favipiravir (PO) inhibits RNA-dependent RNA polymerase of viruses. This has been investigated for influenza and other viruses and has been approved for use in Japan, only in patients infected with novel or re-emerging influenza viruses (that is, 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

Laninamivir (INH) is a neuraminidase inhibitor which has been licensed in Japan for the treatment and prophylaxis of influenza. It is not licensed for use in the UK and should only be used in the context of an approved research protocol.

3. 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](#)) 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, namely if:

- 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 UKHSA guidance on the management of outbreaks of influenza like illness (ILI) in care homes ([10](#)).

For further information on which contacts of an influenza case should receive prophylaxis, refer to guidance from NICE ([3](#)). 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. Use outside the NICE recommendations is a matter for individual clinical judgement within local governance and operational arrangements.

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. These individuals should receive close clinical monitoring following exposure with arrangements to receive prompt treatment following onset of ILI symptoms.

Table 6. Selection of antivirals for post-exposure prophylaxis

	If identified strain in index case or dominant circulating strain is lower risk for oseltamivir resistance for example, influenza A (H3N2), influenza B	If identified strain in index case or dominant circulating strain is higher risk for oseltamivir resistance for example, influenza A (H1N1)pdm09	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 hours of last exposure or after 48 hours on specialist advice only.	Oseltamivir PO once daily for 10 days, if therapy can be started within 48 hours of last exposure; or after 48 hours on specialist advice only.	Zanamivir INH once daily for 10 days, if therapy can be started within 36 hours of last exposure; or after 36 hours 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 hours of last exposure; or after 48 hours on specialist advice only.	Zanamivir INH once daily for 10 days, if therapy can be started within 36 hours of last exposure; or after 36 hours on specialist advice only. If unable to administer zanamivir INH, oseltamivir PO once daily for 10 days, if therapy can be started within 48 hours 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 hours of last exposure; or after 36 hours on specialist advice only. If unable to administer zanamivir INH, monitor closely and begin treatment promptly if ILI symptoms develop.
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 hours of last exposure; or after 48 hours on specialist advice only.	Oseltamivir PO once daily for 10 days, if therapy can be started within 48 hours of last exposure, or after 48 hours on specialist advice only.	Monitor closely and begin treatment promptly if ILI symptoms develop.

Note to Table 6: Commencing prophylaxis with oseltamivir later than 48 hours after last exposure, or with zanamivir, later than 36 hours after last 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)

3.1 Supplementary information: prophylaxis

3.1.1 Antiviral dosage and schedules

Table 7. Prophylaxis dosage

Prophylaxis	Premature (less than 36 weeks post conceptional age)	Infants under 12 months (36 weeks post conceptional age or greater)	Children 1 to 12 years: Dose according to weight below				Adults (13 years and over) ²
			less than or equal to 15kg	more than 15 to 23kg	more than 23 to 40kg	more than 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 under 5 years old. Adults and children equal or greater than 5 years old: 10mg od						10mg od

¹ Although it may be possible to provide half the treatment frequency, each day for 10 days, there is currently no publicly available dosing information for oseltamivir prophylaxis in pre-term infants, and so is outside the product licence (source: expert advice).

² If a person in this age group weighs 40kg or less, it is suggested that the greater than 23 to 40kg dose for those aged 1 to 12 years, is used.

Oseltamivir oral suspension should be prioritised as previously described in [section 2.3.1](#), 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 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.

3.1.2 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 2.3.2](#)), except that the dosage of oseltamivir in Table 8 should be used.

Table 8. 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
More than 60mL/min*	75mg OD
31 to 60 mL/min*	30mg OD
11 to 30mL/min*	30mg every 48 hours
Less than or equal to 10mL/min**	30mg ONCE, repeated after 7 days
Haemodialysis (HD)**	30mg ONCE and then 30mg after every second HD session
Continuous Ambulatory Peritoneal Dialysis* (refer to Summary of Product Characteristics for advice in relation to automated peritoneal dialysis [APD] mode)	30mg ONCE, repeated after 7 days
Haemo(dia)filtration** 1-1.8L/hr exchange rate	30mg every 48 hours
Haemo(dia)filtration** 1.9 to 3.6L/hr exchange rate	30mg OD
Haemo(dia)filtration** Greater than 3.6L/hr exchange rate	75mg OD

Source: Summary of Product Characteristics April 20 (*). The recommendations for haemo-dialysis, haemo(dia)filtration and established renal failure are based on expert opinion (**).

Note to Table 8: 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 BNF for Children](#).

Appendix 1. Use of antivirals in pregnancy, breastfeeding and hepatic dysfunction

Use in pregnant women

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

Oseltamivir remains the first line option for the vast majority of pregnant women with influenza, including during seasons that are dominated by influenza A(H1N1)pdm09. For pregnant women who meet additional criteria for requiring zanamivir first line, further assessment (that is, 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 is 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 oral oseltamivir or inhaled zanamivir ([34](#), [35](#), [36](#)). However, published data is limited.

The use of oseltamivir may be considered during pregnancy if necessary and after considering the available safety and benefit information, including the pathogenicity of the circulating influenza virus strain. For manufacturer’s information on use in pregnant women please refer to [SPC](#) sections 4.6 ‘Pregnancy’ and 5.1 ‘Treatment of influenza in pregnant women’ ([37](#)).

For manufacturer’s information on use of inhaled Relenza[®] (zanamivir) in pregnancy please refer to SPC section 4.6 ‘Pregnancy’, and for IV zanamivir use section 4.6 of the Dectova[®] SPC ([24](#), [38](#)).

Use during breastfeeding

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

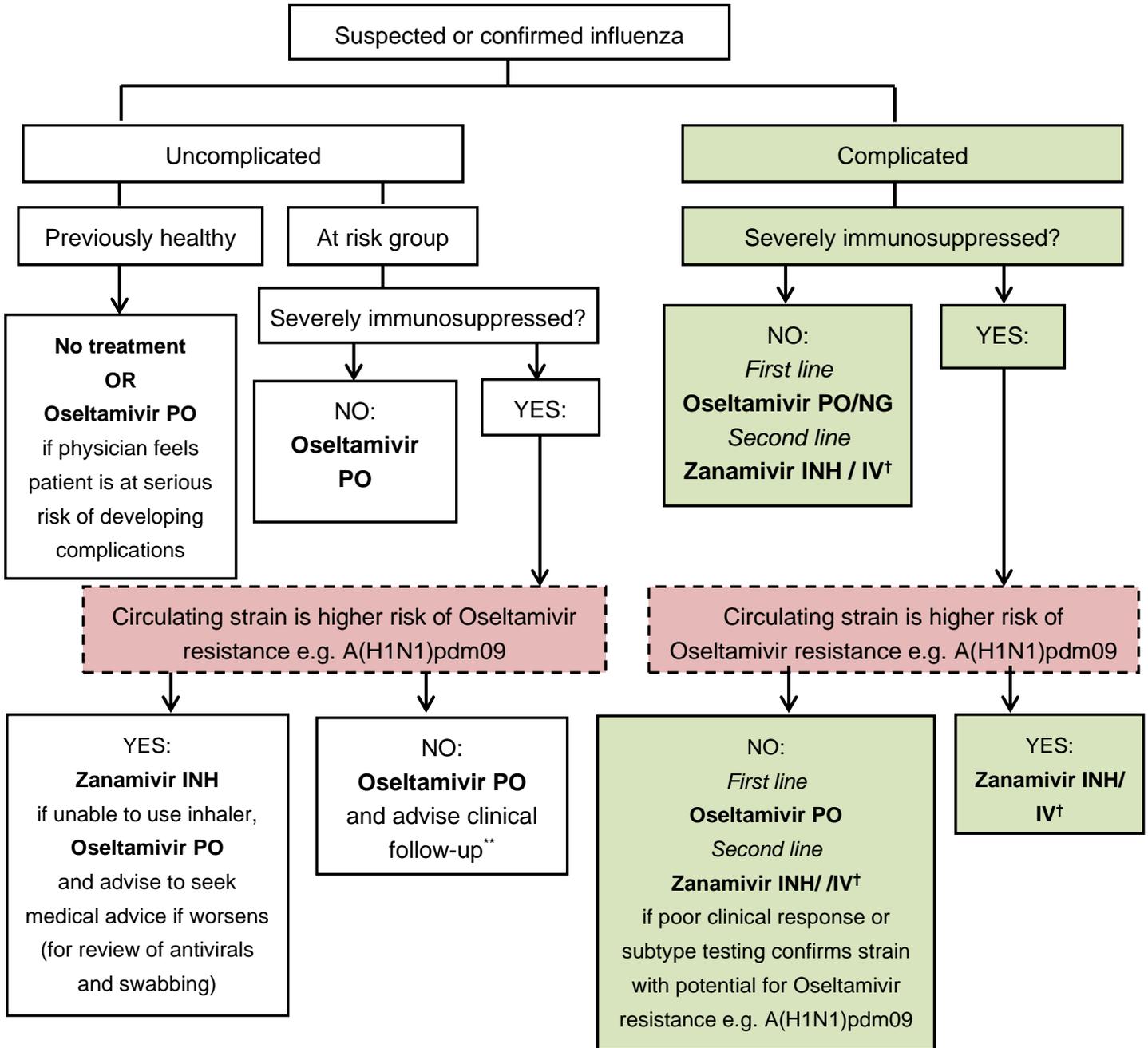
Use in hepatic dysfunction

Table 8. Recommended dosage for hepatic dysfunction

	Liver dysfunction
Oseltamivir PO	Standard dosing
Zanamivir INH (Diskhaler [®])	Standard dosing
Zanamivir IV	Refer to the SPC

Appendix 2. Summary algorithm for prescribing antiviral treatment for influenza

Prescribing antivirals for treatment of influenza



Accessible text version of Appendix 2 figure 'Prescribing antivirals for treatment of influenza'

There are 2 paths for selection of antiviral therapy for treatment of suspected or confirmed influenza:

Path 1: Uncomplicated illness

There are 2 risk categories for uncomplicated illness.

1.1 If case is previously healthy

No treatment.

OR

Oseltamivir PO if physician feels patient is at serious risk of developing complications.

1.2 If case is in an at risk group

There are 2 risk categories for cases in an at risk group

1.2.1 If case is in an at risk group and is not severely immunosuppressed

Oseltamivir PO.

1.2.2 If case is in an at risk group and severely immunosuppressed

Treatment type depends on whether circulating strain is higher risk of oseltamivir resistance for example, A(H1N1)pdm09.

1.2.2.1 If circulating strain is higher risk of oseltamivir resistance for example A(H1N1)pdm09

Zanamivir INH

If unable to use inhaler, oseltamivir PO and advise to seek medical advice if worsens (for review of antivirals and swabbing).

1.2.2.2 If circulating strain is not higher risk of Oseltamivir resistance

Oseltamivir PO and advise clinical follow-up.

Path 2: Complicated illness

There are 2 risk categories for complicated illness

2.1 If case is not severely immunocompromised

First line treatment: oseltamivir PO/NG.

Second line treatment: zanamivir INH/IV†

2.2 If case is severely immunocompromised

Treatment type depends on whether circulating strain is higher risk of oseltamivir resistance for example, A(H1N1)pdm09.

2.2.1 If circulating strain is higher risk of oseltamivir resistance for example, A(H1N1)pdm09

Zanamivir INH/IV†

2.2.1 If circulating strain is not higher risk of oseltamivir resistance

First line: oseltamivir PO/NG.

Second line: zanamivir INH/IV† if poor clinical response or subtype testing confirms strain with potential for oseltamivir resistance for example for example, A(H1N1)pdm09.

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 CMO at DHSC 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. Additional clinical scenarios and considerations

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 (39). Extending the duration of treatment to at least 10 days may be appropriate in patients with severe influenza (for example, critically ill patients) and in severely immunosuppressed patients. The manufacturer of oseltamivir recommends a longer treatment course of 75mg PO twice daily for 10 days for immunosuppressed patients. Prolonged treatment can be associated with 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 (except for oseltamivir use in immunosuppressed persons, as above).

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)pdm09 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 for example 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.

Groups of patients in whom influenza viruses with reduced antiviral susceptibility are 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 (40).

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 was 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 (41).

Use of oseltamivir if zanamivir resistance is suspected

Recent antiviral resistance surveillance data for seasonal influenza viruses demonstrates 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 (for example, 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 UKHSA.

The role of repeat or follow-up 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 the World Health Organization (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 (for example 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.

Use of influenza antiviral prophylaxis in healthcare workers who are unvaccinated and with no underlying illness

Currently, prophylaxis is only given to at-risk groups and is not recommended as an alternative to flu 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 UKHSA Immunisation and Vaccine-Preventable Diseases Division. 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 COVID-19 or 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.

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 one influenza virus, and the infection later in the season with a different type or subtype so there would not be a protective effect from the first exposure.

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 is, 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 under 12 months in the UK who were hospitalised with Influenza A(H1N1pdm09) during the 2009 to 2010 pandemic ([42](#)).

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 3 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. More detailed advice on use in breastfeeding should be sought from the SPC and the UK DILAS advice.

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 given advice on non-pharmaceutical measures to reduce transmission, include advice 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.

UKHSA 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 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 ([43](#), [44](#)).

Performing diagnostic sampling for influenza 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.

Use of double the standard treatment dose of oseltamivir when treating patients with severe illness caused by seasonal influenza infection

An increase in dosage is not recommended in patients with severe illness caused by influenza A virus infection, due to a lack of evidence that it is any more effective ([26](#), [27](#), [29](#)).

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 ([45](#)), there is insufficient evidence that double-dosing in patients with Influenza B has a clinical benefit ([46](#)).

Administering attenuated influenza vaccine (LAIV) at the same time as influenza antiviral agents

Chapter 19 (Influenza) of 'Immunisation against Infectious Diseases' states:

'There is a potential for influenza antiviral agents to lower the effectiveness of LAIV.

Therefore, influenza antiviral agents and LAIV should not be administered concomitantly.

LAIV should be delayed until 48 hours following the cessation of treatment with influenza antiviral agents. Administration of influenza antiviral agents within 2 weeks of administration of LAIV may adversely affect the effectiveness of the vaccine ([2](#)).

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Contributors and conflict of interest declaration

Version 10.0 of the guidance was reviewed and agreed in 2019, by a working group comprising: Richard Pebody (chair), Gavin Dabrera, Angie Lackenby, Jake Dunning, Matthew Donati, Bryan O'Farrell, Mark Borthwick, Robert Shulman, Jim McMemamin, and Arlene Reynolds.

Version 11 was reviewed and updated in 2021 by Conall Watson in consultation with colleagues from the NHS, DHSC and UKHSA, and agreed by the UKHSA Immunisation and Countermeasures Influenza Scientific Advisory Forum. Fernando Capelastegui provided scientific secretariat support.

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. MD chairs the UK Clinical Virology Network (UK CVN) which is a registered charity with partial financial support from a number of commercial diagnostics companies.

PHE (which has since transferred functions to UKHSA) received an unrestricted grant from GSK to undertake a study on the outcome of patients who received parenteral zanamivir. The funder received data and interim reports from PHE but did not influence analysis and reporting of the study. None of the AV working group members were involved in the study.

AL has been involved in the production of reports for a joint virological study on Influenza viruses with Imperial College London; this study was funded by Roche.

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Published: November 2021
Publishing reference: GOV-10342



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