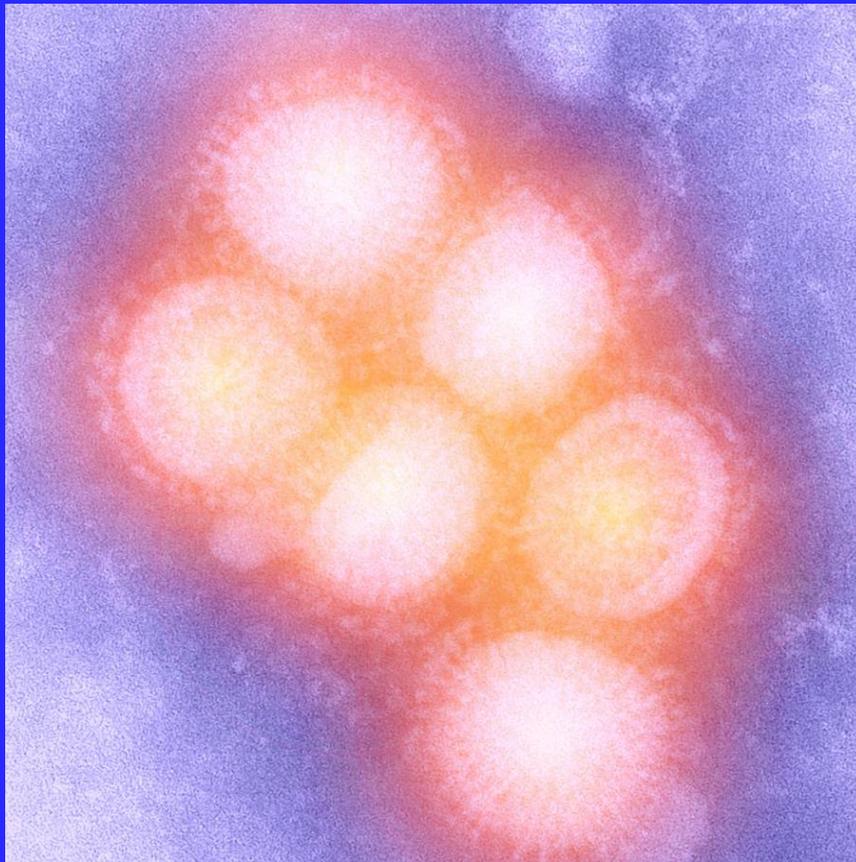


Antiviral management of
Influenza A
(H1N1, H3N2)
in critical care

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Version 5.0



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Summary

Oseltamivir Summary

- Oral/nasogastric oseltamivir is currently first line therapy for treating influenza in critically ill patients.
- The main adverse effects are headaches and vomiting which usually resolve after 1-2 days.
- Although a recent study suggests that standard dosing of 75mg twice daily is sufficient,¹ critical care physicians in the UK are accustomed to the use of high dose oseltamivir for a longer duration (150mg twice daily up to 10 days) in critically ill patients.²
- There is limited evidence on appropriate dosing for patients receiving haemofiltration; but 75mg once daily should be adequate though twice daily is often used in critical illness;.
- Unlicensed IV oseltamivir is available though there is very limited experience of its use. It should be considered when an alternative to IV zanamivir is required.
- In pregnancy, current safety data indicates that oseltamivir 75mg twice daily may be considered equally efficacious to inhaled zanamivir.
- In the clinical setting, resistance to oseltamivir has been associated with the use of the drug in both prophylaxis and treatment of the immunocompromised. However, for critically-ill immunocompromised patients, oral oseltamivir should still be the first-line treatment unless:
 - patients have laboratory-confirmed resistant virus
 - patients are part of an outbreak involving known resistant virus
 - patients deteriorate or fail to improve clinically with oseltamivir-sensitive virusTherapy changes involving questions of drug resistance should be discussed with expert virology advice.
- There is little potential benefit of co-prescribing probenecid with oseltamivir in critically ill patients. Probenecid is associated with side effects and has not been proven to improve influenza outcomes when used in combination with oseltamivir. There are also theoretical concerns that probenecid may reduce oseltamivir carboxylate (OC) penetration into respiratory secretions despite increased plasma concentrations.

Zanamivir Summary

- There is inadequate data to establish the safety or effectiveness of inhaled zanamivir in seriously ill influenza patients, especially those with pneumonia or bronchospasm.
- Zanamivir powder from the Diskhaler device should not be made into a solution and given by nebulisation in mechanically ventilated patients, as ventilator dysfunction may occur.
- Intravenous (IV) zanamivir should be considered the treatment of choice in critically ill influenza patients who:
 - are not absorbing from the gastrointestinal tract
 - are known to have oseltamivir-resistant virus
 - have oseltamivir-sensitive virus but show poor clinical response after 5 days of oseltamivir therapy

Peramivir Summary

Intravenous Peramivir is not currently available in the UK. But should this change, it potentially could have a role as an unlicensed alternative to IV zanamivir in patients not absorbing from the gastrointestinal tract.

Because of cross-resistance, peramivir is likely to be ineffective in patients with documented or highly suspected oseltamivir resistance

Ribavirin Summary

The use of ribavirin by any route is controversial because of the lack of a robust evidence base. There are safety concerns regarding the potential to cause haemolytic anaemia and other metabolic abnormalities with oral or intravenous administration. Bronchospasm may occur when given by aerosol. There are reproductive risks for the patient. Health care workers may also be exposed to these risks, particularly when ribavirin is aerosolised. Enteral or intravenous ribavirin should only be considered in critically ill patients who:

- fail to clear zanamivir sensitive virus despite therapy with intravenous zanamivir (ribavirin should be added to intravenous zanamivir therapy)
- are suspected or known to have oseltamivir and zanamivir resistant virus (ribavirin should be added to oral oseltamivir / intravenous zanamivir therapy)

Such combination therapy should first be discussed with the Health Protection Agency.

Corticosteroid Summary

Corticosteroids should not be routinely used to treat acute lung injury or adult respiratory distress syndrome in critically ill patients with suspected or proven H1N1pdm infection.

'Low dose' corticosteroid therapy for refractory shock states should be used cautiously and in accordance with the Surviving Sepsis Campaign guidelines.³

Introduction

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The current treatment options in the UK for influenza A are oseltamivir (Tamiflu®) and zanamivir (Relenza®). Both drugs are selective inhibitors of neuraminidase (NA), a major influenza virus surface enzyme which is critical for release of newly-replicated influenza virus from the cell. The influenza virus envelope exhibits another important antigenic protein, haemagglutinin (HA) which is responsible for the initial attachment of the virus to a cell at the start of the infection cycle. Currently, there are 16 known HA subtypes (H1–H16) and 9 different NA subtypes (N1-N9).⁴ At present, the two major circulating influenza viruses - pandemic H1N1 (H1N1pdm) and H3N2 - are resistant to amantadine and related drugs; these should not be used in management.

The information below is intended to support prescribing and decision making for antiviral neuraminidase inhibitors in critically ill patients with influenza A on the Intensive Care Unit (ICU), and may change as more clinical experience and published data become available.

It is possible that the predominant circulating sub-type of influenza – either H1N1pdm or H3N2 – may change from year to year. These guidelines are applicable to infections with either sub-type.

Note that both neuraminidase inhibitor drugs are also effective against infection with influenza B; a related influenza virus which also causes outbreaks during the winter months.

Oseltamivir (Tamiflu®) Treatment

Background

Oseltamivir is a neuraminidase (NA) inhibitor which is licensed for the prophylaxis and treatment of influenza. It is a potent and selective inhibitor of influenza A NA subtypes.⁴ Based on registrational studies in uncomplicated influenza in ambulatory patients, the licensed dose for adults, adolescents and children (>40kg) is 75mg twice a day.⁵ In response to the initial H1N1pdm pandemic, the Health Protection Agency (HPA) issued a clinical practice note on managing adult critically ill cases⁶ and in March 2010⁷, the World Health Organisation (WHO) also issued guidelines on the pharmacological management of pandemic H1N1pdm in 2010. Both report that clinicians doubled the licensed dose of oseltamivir to treat critically ill patients on the intensive care unit, and used a longer duration of treatment depending on clinical response. This approach to treatment appears to have been made on the basis that critically ill patients have (i) higher acute viral loads, (ii) reduced drug concentration in damaged lower respiratory tract tissues, (iii) reduced enteric absorption of the drug (iv) greater volumes of drug distribution and (v) there is also potential for viral load to rebound after 5 days therapy,. Despite new data¹ suggesting that standard dosing of 75mg twice daily is pharmacologically sufficient, in the absence of adverse effects associated with higher dosing critical care clinicians will be likely to prefer a tried-and-trusted regimen of 150mg bd for up to 10 days.

An unlicensed intravenous oseltamivir is available for use as an alternative to IV zanamivir, but there is very limited experience of its use in the UK.

Clinical Evidence

Below is a summary of the published literature on the use of higher doses in healthy adults.

A randomized controlled trial was performed in 726 previously healthy adults presenting with febrile influenza-like illness.⁸ The patients were divided into three treatment arms and randomised to receive either oseltamivir 75mg twice daily, 150mg twice daily or placebo twice daily for 5 days. Of the 726 patients randomised, 475 had confirmed influenza infection. The median duration of illness was significantly shorter in the treatment groups (75mg (median duration of 29h), 150mg (median duration of 35h)) compared to placebo (median duration of 116.5h). The main adverse effects reported in the trial were nausea and vomiting. These effects were more frequent in the oseltamivir groups than placebo and generally occurred at the start of treatment, resolving within 1-2 days.

A similar trial was performed in 629 adults with febrile respiratory illness.⁹ This was a double-blind placebo-controlled study where patients were randomised to receive either oseltamivir 75mg twice daily (n=211), 150mg twice daily (n=209) or placebo twice daily (n=209). Of the 629 patients randomised, 374 were infected with influenza. In this group treatment with oseltamivir reduced the duration of illness significantly compared to placebo (75mg (median duration of 71.5hrs), 150mg (median duration of 69.9hrs) placebo (median duration of 103.3hrs). Nausea and vomiting occurred more frequently in the oseltamivir group. In both studies the frequencies of adverse events did not differ significantly between the lower and higher dose oseltamivir groups.

A recent study has questioned the concept of using double-dose oseltamivir in critically ill patients¹ This study involved 41 patients, 5 of whom required renal replacement therapy. Investigators reported the dosage of 75 mg twice daily achieved plasma levels that were comparable to those in ambulatory patients and were far in excess of concentrations required to maximally inhibit neuraminidase activity of the virus. Furthermore volume of distribution of the oseltamivir carboxylate (OC) metabolite did not increase with increasing body weight. This finding is also supported by the recent OPTIMO trial. The OPTIMO trial studied the pharmacokinetic profile of

75mg oseltamivir administered orally to healthy, morbidly obese (BMI >40) (n=10) and healthy, non-obese patients (BMI<30) (n=10)⁶⁴. The study shows that with single and multiple dosing, the systemic exposure to the active metabolite, OC, is largely unchanged with increasing body weight and that a dose adjustment is not needed in morbidly obese patients. A possible exception are those of extreme body weight (>250Kg) who could be potentially under-exposed to the active metabolite, OC, following a 75mg BD regimen.

Intravenous (IV) Oseltamivir

There is currently no clinical data on efficacy of IV oseltamivir and only very limited safety data. Four studies (unpublished) have been conducted in 81 healthy volunteers exposed to single doses of oseltamivir.¹⁰ These studies were conducted to investigate safety, tolerability and pharmacokinetics of the pro-drug oseltamivir and its active metabolite oseltamivir carboxylate (OC). A dose of 100mg of IV oseltamivir was found to produce OC exposures most closely matched to those following the licensed 75 mg oral dose. Intravenously administered oseltamivir was found to be generally well tolerated and no difference in the overall incidence of adverse events was seen between the oral and IV oseltamivir groups. IV administration results in a reduced level of first pass metabolism and a higher systemic exposure of Oseltamivir (parent compound) compared to oral administration. For this reason the safety profile of the IV formulation may differ from the known safety profile of the oral formulation¹⁰. IV oseltamivir is currently being investigated in clinical trials and is available only on compassionate use basis from Roche.

Case Reports in Haemofiltration Patients:

To date there is very limited information on oseltamivir use in patients on haemofiltration.

The pharmacokinetic parameters of nasogastrically-administered oseltamivir have been reported for three patients,¹¹ presenting with severe H5N1 or H3N2, undergoing haemofiltration. Each patient was given 150mg twice daily oseltamivir via nasogastric tube within 24 hours of ICU admission. The details for each patient are as follows:

Patient A: Male, 30yr, started oseltamivir 6 days after onset of illness, CVVH ultrafiltration rates 2.75L/h

Patient B: Female, 22 yrs, pregnant, started oseltamivir 7 days after onset of illness; CVVH ultrafiltration rates 2.2L/hr

Patient C: Female 76 yrs, started oseltamivir 8 hrs after onset of illness, CVVH ultrafiltration rates 2L/hr.

Patient A had a severe headache and persistent vomiting when off the ventilator therefore the oseltamivir had to be stopped after 8 days of treatment. Tracheal aspirates went from influenza A positive to negative within 5 days of treatment. The trough concentration of oseltamivir carboxylate (OC), the active metabolite, was 376 ng/ml.

Patient B had tracheal aspirates, pleural fluid, stool and plasma which were influenza A H5N1 positive 1 day after starting treatment. The trough concentration of OC was 575 ng/ml.

Patient C: Nasal swabs went from influenza A H3N2 positive to negative after 5 days of treatment. The trough concentration of OC was 2730 ng/ml.

For all three patients the dose of 150mg twice daily was found to produce trough concentrations ranging between 376 – 2730 ng/ml. These exceeded the H5N1 IC₅₀ MIC (0.69ng/ml). This shows that high trough levels of OC are achieved after 150mg twice daily doses.

In addition to the above case reports, a recent study reported the pharmacokinetic values obtained from a subset of 5 patients on continuous renal replacement therapy following dosing of 75mg 12 hourly.¹ The area under the curve was almost six times higher than in patients with normal renal function. The authors advocate a dose of 30mg daily or 75mg every 48 hours to provide adequate plasma levels. Despite the data presented in this study, the critical care community is currently treating with oseltamivir 150mg 12 hourly and hence in our view it would be logical to halve this dose for patients who are haemofiltered.

Dosing decisions have been very difficult in this group of patients and ideally one would recommend drug level monitoring in these patients to minimise toxicity and resistance developing. Refer to the renal impairment section further in the document for dosing guide in this patient group.

Combination with probenecid:

- There have been some discussions on the use of oseltamivir used in combination with probenecid. Unless oseltamivir supplies become limited, there is no real benefit of using probenecid in critically ill patients. Probenecid is known to inhibit renal tubular urate resorption and to decrease the excretion of several medications including oseltamivir. The co-administration of a single 150 mg dose of oseltamivir and probenecid (500 mg orally four times a day for 4 days) resulted in steady-state oseltamivir carboxylate concentrations that were 2.5-fold higher than those achieved with oseltamivir administration alone.¹² This combination has only been studied in healthy volunteers, and has not been studied extensively, and so at present it would not be considered for mainstream use. Also there is a theoretical concern of reducing OC penetration into respiratory secretions.¹³ It should be noted that probenecid interacts with several drugs used in critical care and it may increase concentrations of meropenem, rifampicin, aciclovir, some quinolones, lorazepam and paracetamol. Lower doses of thiopentone may be required and it may increase the speed of induction with midazolam.

There appears to be insufficient evidence of benefit in using this combination outside the context of clinical trials.

Administration and dosing schedule

Oral/Nasogastric Oseltamivir

Presentation: Oseltamivir (as phosphate) 30mg, 45mg, 75mg capsules⁵

Treatment doses in adults: 75mg twice a day may be adequate¹, though 150mg twice a day for up to 10 days has been advocated.^{6,7,14}

In pregnancy the WHO state that there is insufficient safety data for doses higher than 75 mg twice daily.¹⁴ Prolonged courses should be discussed with Virology.

Administration via nasogastric tube:

- Stop enteral feed.¹⁵
- Flush enteral feeding tube with the recommended volume of water.
- Empty the contents of the capsule into a medicine pot.
- Add 5mL of water and stir to mix thoroughly.
- Draw the dispersion into an appropriate enteral syringe taking care to draw up all particles.
- Flush this via the feeding tub
- Add another 5mL of water to the medicine pot, stir and draw into the syringe. This will ensure no residual dose remains in the pot.
- Flush this via the feeding tube.
- Finally, flush with the recommended volume of water.
- Re-start the feed, unless a prolonged break is required.

Treatment doses in children:

	0-1month	1-3 months	3-12 months	1-13 years: Dose according to weight below			
				<15kg	15-23kg	23-40kg	>40kg
<u>Oseltamivir</u> <u>PO/NG</u>	<u>2mg/kg</u> <u>BD</u>	<u>2.5mg/kg</u> <u>BD</u>	<u>3.g/kg</u> <u>BD</u>	<u>30mg</u> <u>BD</u>	<u>45mg</u> <u>BD</u>	<u>60mg</u> <u>BD</u>	<u>75mg</u> <u>BD</u>

Oseltamivir oral suspension should be used for children under the age of one. It is available as Tamiflu oral suspension (Roche, 12mg/ml). This is an off-label use of oseltamivir but is supported by the BNF for children. The supplied syringe is too large for infant dosing; use a small volume syringe to ensure an accurate dose. Children over one and adults with swallowing difficulties, and those receiving nasogastric oseltamivir, should use capsules which are opened and mixed into an appropriate liquid.

Intravenous Oseltamivir

Presentation

100mg powder vials ^{1,2}

Reconstitution

Add 1.1ml water for injection to each 100mg powder vial. One (1.0) mL of this reconstituted solution contains 100 mg of oseltamivir free base. ^{1,2}

Dilution

Dilute 1 ml of the reconstituted solution to a final volume of 50 ml with 0.9 % sodium chloride (giving a concentration of 2mg/ml). This solution may be diluted further with 0.9 % sodium chloride as required. Under no circumstances can oseltamivir be administered if the concentration exceeds 4 mg/mL.

IV oseltamivir is compatible only with sodium chloride 0.9%. It is incompatible with glucose 5%. The compatibility of oseltamivir with drugs and other intravenous solutions has not been established. ^{1,2}

Administration Oseltamivir IV must be administered by IV infusion using a rate controlled pump over a minimum of **2 hours**. ^{1,2}

Dosing Schedule:

Treatment

Adults & Adolescents (>13 years): 100mg BD

Children 1 to 12 years:

Weight ≤ 23 kg	3 mg/kg BD
Weight > 23 to 40 kg	2.5 mg/kg BD
Weight > 40 kg	Use adult BD dosing

Infants from birth to 1 year post natal age: No recommendations are possible given the absence of data on safety and pharmacokinetic studies in this population.

Studies are currently underway investigating posology for this group. ^{1,2}

Duration: The recommended duration of treatment with oseltamivir IV is 5 days, ^{16,17} Prolonged courses should be discussed with virology.

Intravenous oseltamivir can be obtained on a compassionate patient-specific basis from Roche (Tel: 01707 366 000). It is an unlicensed product at present. To obtain supplies a request form (available from Roche) must be completed by the requesting physician, this must then be assessed by a medic at Roche who will authorise supply where appropriate. The drug will usually be dispatched during working hours, however if the request is urgent the drug can be dispatched as soon as the request is approved.

NOTE: Where there is suspected poor gastrointestinal absorption or failure to respond to PO/NG administered oseltamivir, IV zanamivir should be used.

Clinical Pharmacokinetics

Oral/Nasogastric Oseltamivir

Oseltamivir is readily absorbed from the gastrointestinal tract and is converted by hepatic esterases to the active metabolite oseltamivir carboxylate (OC). The bioavailability of the OC from orally administered oseltamivir phosphate is 80%. OC is detectable in plasma within 30 minutes and reaches maximal concentrations after 3 to 4 hours. The half life of OC is 6 to 10 hours. OC is largely renally cleared by glomerular filtration and renal tubular secretion. The half life extends to 36 hours in patients with end stage renal failure. Oseltamivir phosphate is 42% bound to plasma proteins; OC is 3% bound to plasma proteins. The mean volume of distribution of OC is approximately 23 litres and it has a sieving coefficient of 1.¹⁸

Intravenous Oseltamivir

IV oseltamivir, like the oral preparation, is converted by hepatic esterases to the active metabolite oseltamivir carboxylate (OC). A higher dose is required for IV administration compared to oral administration as there is a reduced level of first-pass metabolism when the drug is administered IV. The recommended IV dose of 100mg twice daily produces a similar pharmacokinetic profile to that achieved with oral dosing of 75mg twice daily.¹⁰ The half life of OC is 7.9 hours after IV administration, compared to 6-10 hours for oral dosing however concentrations of the pro-drug are 3-4 times higher for C_{max} and AUC_{inf} when the drug is given IV.¹⁰ The high concentration of the pro-drug may be a significant safety concern especially in babies and small children, since increased toxicity have been observed in young animals and clinical data is not available. Values for volume of distribution, protein binding and sieving coefficient, are the same as those of the oral preparation.¹⁰

Renal Impairment

Oseltamivir Oral/Nasogastric

There is very limited data on the use of oseltamivir in critically ill patients. Below is a guide to assist dosing for treatment and prophylaxis of oseltamivir for H1N1pdm for critically ill adults with renal impairment.¹⁹

GFR (ml/min)	Recommended treatment dose (usually for 5 days but prolonged courses need to be discussed with Virology).	Recommended prophylactic dose (usually for 10 days but prolonged courses need to be discussed with Virology).
>30ml/min	75mg -150mg BD	75mg OD
>10 to 30ml/min	75mg OD - BD	75mg every second day
<10ml/min	75mg STAT repeated every 5 days if required	30mg STAT every 7 days (usually 2 doses)
Continuous Veno-Venous Haemofiltration (CVVH)		
Greater than 30ml/min [†] (High Flux, or Low Flux with urine output)	75mg-150mg BD	75mg OD
Less than 30ml/min [†] (Low Flux with no urine output)	75mg OD-BD	75mg every second day

[†]Total renal clearance of oseltamivir should be estimated by considering the clearance from the renal replacement therapy and any residual renal function

Intravenous Oseltamivir

The IV doses recommended below for patients with renal impairment and patients undergoing renal replacement therapy (CVVH) are based on limited data from two oral pharmacokinetic studies.^{1,11} The recommendations are based on a 5 day treatment period. If required, the drug may be given to cover a 10 day treatment period but ideally, patients should not be dosed for a period greater than 10 days. In these patients, the drug continues to accumulate with each dose administered.^{16,17}

Dosing in Renal Impairment and Renal Replacement Therapy^{16,17} Adolescents and adults > 13 years of age

GFR (ml/min)	Recommended treatment dose (usually for 5 days but prolonged courses need to be discussed with Virology)
>30ml/min	40mg BD
>10 to 30ml/min	40mg OD
<10ml/min	Not recommended
Continuous Veno-Venous Haemofiltration (CVVH)	
>30ml/min [†]	40mg BD
10-30ml/min [†]	40mg OD

[†]Total renal clearance of oseltamivir should be estimated by considering the clearance from the renal replacement therapy and any residual renal function

Hepatic Impairment

No dose adjustment necessary,⁵ even in moderate hepatic impairment.²⁰ *In vitro* studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment. To date there is no information in acute liver failure and severe hepatic impairment.

Side Effects

In adults, the most commonly reported adverse drug reactions (ADRs) were vomiting and nausea in the treatment studies, and nausea and headache in the prevention studies. The majority of these ADRs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. In children, the most commonly reported adverse drug reaction was vomiting.⁵

Further post marketing surveillance data on selected serious adverse drug reactions

(This is information from the medicines compendium and has been included in this information pack to ensure the awareness of adverse effects that have been reported)⁵

The adverse events considered at least possibly related to the treatment are listed below by absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

Very common	Headache, nausea
Common	Vomiting, pain (general)
Uncommon	Hypersensitivity reaction, eczema, dermatitis, rash, urticaria, elevated liver enzymes, cardiac arrhythmia, altered level of consciousness, convulsion
Rare	Thrombocytopenia, anaphylactic reactions, anaphylactoid reactions agitation, abnormal behavior, anxiety, confusion, delusions, delirium, hallucination, nightmares, self-injury, visual disturbances, gastrointestinal bleeding, hemorrhagic colitis, fulminant hepatitis, hepatic failure, hepatitis, angioneurotic oedema, erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis.

IV oseltamivir was found to be generally well tolerated in three studies and no difference in the overall incidence of adverse events was seen between the oral and IV oseltamivir dose groups. Two subjects experienced hypotension (accompanied by dizziness, sweating, blurred vision, nausea and feeling hot) when given the active metabolite OC by IV infusion over one hour and this lasted for 20 minutes. Hypotension was not observed in subjects who received the pro-drug, oseltamivir, IV. In another study, two adverse events (abdominal pain; 75mg oral dose) and headache (400mg; IV dose) were assessed as possibly related to the study medication. All of the infusion-related adverse events in the 400mg IV group were assessed as probably related to the study medication; no probably-related adverse events were reported in the 75mg oral, 100mg IV or 200mg IV groups.¹⁰

Whilst side effects for IV oseltamivir are similar to those of the oral preparation, infusion-related adverse effects may occur and consequently systemic monitoring of heart rate and blood pressure is mandatory. If there are any unexplained changes in any of these parameters, the infusion must be withheld.^{16,17} Additionally, if oseltamivir is administered through peripheral venous access, the site of administration must be monitored frequently for extravasation, thrombophlebitis and infusion site pain.^{16,17}

When to Monitor	Monitoring Parameters
Before the start of infusion:	Blood pressure and heart rate for all patients.
During the infusion and for 1 hour following the infusion:	Heart rate Blood pressure at 15, 30, 60, 90 and 120 minutes following the start of the infusion and 60 minutes following the end of the infusion Pulse oximetry (at clinician's discretion).

Drug Interactions

Oseltamivir phosphate and its active metabolite, OC, are not metabolised by and do not inhibit cytochrome P-450 isoenzymes; interactions with drugs that are substrates for or inhibitors of these enzymes are unlikely.⁵

Monitoring treatment efficacy

There are no formal recommendations for how to assess whether oseltamivir is working, and at the time of writing there are no routinely-available therapeutic drug monitoring services for determining drug levels. However a general approach based on monitoring influenza virus load by reverse-transcriptase polymerase chain reaction (RT-PCR) of respiratory tract samples is possible (the RT-PCR should be internally-controlled for sample processing efficiency and reaction inhibition). Firstly, endotracheal aspirates or bronchial lavage samples (either non-directed or broncho-alveolar) should be taken at least 5-day intervals, and preferably daily or every other day while intubated, whenever a new 5-day course of drug is commenced, or whenever a drug change is instigated. A fall in relative viral load of approximately 100-fold between two such samples – tested in the same assay run – would likely indicate an antiviral effect and be expected to accompany a clinical improvement in the patient's condition. Where a fall in relative viral load is not evident, and a patient is not suspected to have gastric problems which might limit absorption, then virology laboratory investigations should be conducted to rule out development of antiviral resistance.

As a general infection control rule, critically-ill patients should have two consecutive negative RT-PCR results 24 hours apart, before being brought out of respiratory isolation.

Note that in critically-ill patients, where the main site of viral replication is the lower respiratory tract, the use of naso-pharyngeal swabs is not recommended in this approach to monitoring because misleadingly low viral load results might be obtained by sampling the upper respiratory tract.

Drug Resistance

Resistance to the neuraminidase inhibitors is a complex subject, which may even involve the viral haemagglutinin as well as the neuraminidase genes. However, the simplest and most commonly encountered form of oseltamivir resistance is dependent on a structural characteristic of the drug: the molecule of oseltamivir carboxylate possesses a bulky side chain, and the neuraminidase enzyme of influenza A must undergo a conformational change in order to accommodate it. Unfortunately this provides an Achilles heel to the antiviral strategy, since a simple inhibition of this conformational change will prevent binding of the drug whilst leaving the active site receptive to the natural substrate. During influenza A viral replication, point mutations occur naturally in the viral neuraminidase gene which, following translation, do not permit the neuraminidase conformational change; and these become positively selected for in the presence of the drug. The commonest form of oseltamivir resistance is described as H274Y: a single nucleotide change which results in the amino acid histidine (H) being replaced by tyrosine (Y) at amino acid position 275. This confers high-level resistance to oseltamivir in N1-subtype influenza viruses, and to some extent, peramivir. Other important but less frequently encountered oseltamivir resistance mutations are R292K, N294S, and E119V; however all such resistant viruses remain fully sensitive to zanamivir since binding of this drug does not require the conformational change in the neuraminidase enzyme. Interestingly, influenza B remains fully sensitive to oseltamivir because the viral neuraminidase can accommodate oseltamivir, side chain and all, without the need for a conformational change.

In drug trials and clinical settings, oseltamivir resistant viruses are associated with the use of the drug in children and immunocompromised hosts; either as prophylaxis or treatment. Failure of the host immune response to fully control the viral replication offers an extended opportunity for the naturally-occurring viral mutations to be generated and hence selected for.

Place in therapy

Oral/nasogastric oseltamivir is the 1st line treatment of choice in critically ill patients with suspected or confirmed H1N1pdm infection.

In view of limited experience of its use, IV oseltamivir should be considered to treat critically ill adults and children older than 1 year having a life-threatening condition due to suspected or confirmed influenza A H1N1pdm, H3N2, or influenza B virus only when an alternative to IV zanamivir is required.

A patient-specific application must be made to Roche pharmaceuticals in order to obtain supplies.

Summary

- Oral/nasogastric oseltamivir is currently first line therapy for treating influenza in critically ill patients.
- The main adverse effects are headaches and vomiting which usually resolve after 1-2 days.
- Although a recent study suggests that standard dosing of 75mg twice daily is sufficient,¹ critical care physicians in the UK are accustomed to the use of high dose oseltamivir for a longer duration (150mg twice daily up to 10 days) in critically ill patients.²
- There is limited evidence on appropriate dosing for patients receiving haemofiltration; but 75mg once daily should be adequate though twice daily is often used in critical illness;.
- Unlicensed IV oseltamivir is available though there is very limited experience of its use. It should be considered when an alternative to IV zanamavir is required. In pregnancy, current safety data indicates that oseltamivir 75mg twice daily may be considered equally to inhaled zanamivir.
- In the clinical setting, resistance to oseltamivir has been associated with the use of the drug in both prophylaxis and treatment of the immunocompromised. However, for critically-ill immunocompromised patients, oral oseltamivir should still be the first-line treatment unless:
 - patients have laboratory-confirmed resistant virus
 - they are part of an outbreak involving known resistant virus
 - they deteriorate or fail to improve clinically with oseltamivir-sensitive virus

Therapy changes involving questions of drug resistance should be discussed with expert virology advice.

- There is little potential benefit of co-prescribing probenecid with oseltamivir in critically ill patients. Probenecid is associated with side effects and has not been proven to improve influenza outcomes when used in combination with oseltamivir. There are theoretical concerns that probenecid may reduce oseltamivir carboxylate (OC) penetration into respiratory secretions.

Zanamivir (Relenza®) Treatment

Background

Zanamivir is also a neuraminidase (NA) inhibitor which is licensed for the prophylaxis and treatment of influenza in adults and children (>5years).²¹ The licensed method of administration for zanamivir for treatment of H1N1pdm is via dry powder inhalation using a proprietary Diskhaler device and it is given at a dose of 10mg BD, which actually delivers 8mg. It has very poor oral bioavailability when administered via the gastrointestinal tract (GIT) and so can not be given by this route. The diskhaler may only be used in patients who are self ventilating. In mechanically ventilated patients it is not possible to administer the drug via Diskhaler. Despite initial interest in nebulised zanamivir for use in those unable to absorb oseltamivir, both the FDA and the Department of Health released warnings to state that zanamivir powder from the Diskhaler presentation should not be used via the nebulised route^{22, 23}. This emerged following an incident where nebulised zanamivir prepared from the licensed product caused a mechanical ventilator to block, which in turn led to the death of a patient. The zanamivir powder is formulated in lactose which was implicated as the causative factor in this event. There is inadequate data to establish safety or effectiveness of inhaled zanamivir in seriously ill influenza patients, especially those with pneumonia or bronchospasm

Zanamivir has a role in H1N1pdm patients who have failed to clear the virus (as evidenced by PCR analysis) despite treatment with oseltamivir, or suspected to be initially infected with an oseltamivir-resistant variant (e.g., failure of chemoprophylaxis in immunocompromised host). Genotypic resistance to oseltamivir is of course one potential cause of oseltamivir treatment failure, and should be investigated as a possibility. Oseltamivir resistance can occur rapidly in immunocompromised patients receiving oseltamivir treatment or prophylaxis. Early consideration for zanamivir therapy is needed for critically ill patients who are severely immunocompromised, especially where there has been prior exposure to oseltamivir.²⁴

Clinical Evidence

Intravenous Zanamivir

Studies of the unlicensed IV zanamivir preparation 600mg at a dose of 12-hourly have been sparse but high drug penetration has been demonstrated in the respiratory mucosa of human volunteers, following experimental human influenza A virus inoculation.²⁵ This route and dose were used successfully in a case of H1N1pdm that was refractory to a course of nebulised zanamivir²⁶ and there has been subsequent experience.²⁷ Unlicensed zanamivir aqueous solution which can be administered via inhaled nebulized and intravenous routes are available on a compassionate use basis²⁸. The IV product should be avoided in pregnancy, unless the expected benefit to the patient is thought to outweigh any possible risk to the fetus. The safety of zanamivir when used during pregnancy has not been established. Reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs. Studies in rats did not show any evidence of teratogenicity, impairment of fertility or clinically significant impairment of peri or post-natal development of offspring following administration of zanamivir. However, there is no information on placental transfer in humans.²⁸

Inhaled Zanamivir

The unlicensed zanamivir aqueous solution can also be administered via nebuliser. A double-blinded, randomized, placebo controlled trial was conducted in 41 hospitalized patients to assess the tolerability and efficacy of nebulised zanamivir (16mg four times a day) in combination with rimantadine.²⁹ The length of treatment for both treatment and control group (nebulised saline with rimantadine) arms was 5 days. The median time to viral shedding was 4 days in the rimantadine/placebo arm and 2 days in rimantadine/zanamivir arm. Only one of the patients had an adverse drug event (retrosternal burning with dyspnoea) thought to be attributable to the study

medication. Note that whilst the majority of the viruses in the study were sensitive to rimantadine, the current H1N1pdm influenza is rimantadine-resistant. This trial did show, however, that higher nebulised doses of zanamivir were well tolerated.

A placebo controlled pilot treatment study of adults (unpublished) was conducted to evaluate the safety and efficacy of zanamivir administered via nebuliser (16mg dose) and intranasally (6.4mg dose) twice daily for 7 days. Patients were divided into three groups: Group 1 received zanamivir (16mg) via nebuliser plus zanamivir (6.4mg) intranasally, Group 2 received zanamivir (16mg) via nebuliser plus placebo intranasally and Group 3 received both placebos via nebuliser and intranasally. Due to a low incidence of influenza, the targeted recruitment was not achieved. The study, therefore, did not have sufficient power to detect a specific treatment difference. Although the study lacked sufficient power, some useful data on safety and tolerability did emerge. The most frequently reported drug adverse events in the inhaled zanamivir (group 2) were dizziness (5%), nausea and vomiting (11%). Only one serious event (severe frontal headache and dizziness) was reported and deemed possibly related zanamivir. In summary, higher dose of nebulised zanamivir were well tolerated.³⁰

There is a case of treatment failure with inhaled zanamivir in an immunocompromised patient thought to be associated with poor lung delivery; the patient subsequently responded to oseltamivir.³¹

There appears to be inadequate data to establish safety or effectiveness of inhaled zanamivir in seriously ill influenza patients, especially those with pneumonia or bronchospasm.

Place in therapy

Zanamivir should be considered the treatment of choice in critically ill patients who

- are not absorbing from the GIT
- fail to clear oseltamivir-sensitive virus despite treatment
- have oseltamivir-resistant virus
- are pregnant with pneumonia and possible oseltamivir failure/resistance
- Are severely immunocompromised

Administration and dosing schedule

Presentation 5mg/dose, inhalation powder, Vials (unlicensed, 200mg/20ml) no refrigeration required.

Adults

A letter from the HPA outlining responsibilities and logistics for obtaining the unlicensed aqueous zanamivir solution (including authorisation of supply, the supply chain and return of follow up pharmacovigilance data) is appended at the end of this document (Appendix 1)

Nebulised

There is inadequate data of effectiveness and safety of inhaled zanamivir to recommend use, particularly in pneumonia or bronchospasm. The Diskhaler product should not be used for nebulisation.²³ There is unlicensed aqueous solution of the drug that does not contain lactose available from GlaxoSmithKline for compassionate use in severe influenza illness. This same product can be used either for nebulisation at a dose of 25mg 6-hourly (or intravenously at 600mg 12-hourly). If this formulation is used for nebulisation, each vial can be multi-used for up to 24 hours (i.e.4 doses), if refrigerated.²⁸

Intravenous

To prepare, withdraw the required zanamivir dose into a syringe. Remove the same volume from an infusion bag of sodium chloride 0.9%. Add the zanamivir to the infusion bag and mix gently by

hand and administer over 30 minutes. In cases of volume overload or paediatrics, the final concentration of zanamivir administered should NOT be lower than 0.2mg/mL. For patients on intermittent hemodialysis, the dose of zanamivir is administered after completion of haemodialysis.²⁸

Clinical Pharmacokinetics

Zanamivir is not protein bound and not hepatically metabolised or modified. It is excreted unchanged in the urine.²¹

Renal and Hepatic impairment

No dose adjustment is necessary, except for the IV regimen. Please read the dosing instructions below very carefully.

The table below shows the **twice daily** maintenance dose regimens of IV Zanamivir for adults and adolescents, which is administered following an initial dose of 600 mg.²⁸

Adults and Adolescents	CrCl (mL/min)				
	≥ 80	50 to <80	30 to <50	15 to <30 & CVVF	<15
	600 mg	400 mg	250 mg	150 mg	60 mg

Time interval between initial dose and maintenance dose

- The twice daily maintenance dose regimen should begin **12 hours** after starting the initial dose infusion, except for patients in the renal failure categories below:
- For patients with **CrCl of 15 to <30ml/min or haemofiltration (CVVF)**, the twice daily dose regimen should begin at **24hrs** after the start of the initial dose.
- For patients with **CrCl of <15ml/min**, the twice daily dose regimen should begin at **48hrs** after start of the initial dose.

For pregnant women, pre-pregnancy body weight should be used in the calculation of CrCl.

IV Zanamivir Dosage Determination for Children (≥ 6 months of age):

- Assess renal function by determination of creatinine clearance (CrCl, in mL/min/1.73m²), which may be calculated from height and serum creatinine, as follows:

For serum creatinine in units of mg/dL:

$$CL_{Cr}(mL/min/1.73m^2) = \frac{0.55 \cdot HT}{Scr}$$

where HT = height in cm and Scr = serum creatinine in mg/dL.

For serum creatinine in units of micromoles/liter:

$$CL_{Cr}(mL/min/1.73m^2) = \frac{48.6 \cdot HT}{Scr}$$

where HT = height in cm and Scr = serum creatinine in μM.

- Based on the CLcr determination and body weight, children should receive IV zanamivir doses (mg/kg) ranging from 1.5 to 24 mg/kg **twice daily**, as shown:

Paediatrics (≥6 months)	CLcr (mL/min/1.73m ²)				
	≥ 80	50 to <80	30 to <50	15 to <30	<15
Weight Range					
19 to 37 kg ¹	16 mg/kg	11 mg/kg	6.5 mg/kg	4 mg/kg	1.5 mg/kg
11 to <19 kg	20 mg/kg	13 mg/kg	8 mg/kg	5 mg/kg	2 mg/kg
<11 kg	24 mg/kg	16 mg/kg	10 mg/kg	6 mg/kg	2.5 mg/kg

¹ Children who are less than 13 years of age but who weigh >37kg should receive the recommended dose for adults and adolescents.

Side Effects

There have been rare reports of patients with previous history of respiratory disease (asthma, COPD) and very rare reports of patients without previous history of respiratory disease, who have experienced acute bronchospasm and/or serious decline in respiratory function after use of inhaled zanamivir.²¹

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

Immune system disorders: *Very rare:* allergic-type reaction including facial and oropharyngeal oedema

Respiratory, thoracic and mediastinal disorders: *Very rare:* bronchospasm, dyspnea, throat tightness or constriction

Skin and subcutaneous tissue disorders: *Very rare:* rash, urticaria

Psychiatric and nervous system disorders: Convulsions and psychiatric events such as depressed level of consciousness, abnormal behaviour, hallucinations and delirium have been reported during zanamivir administration in patients with influenza. The symptoms were mainly reported in children and adolescents. Convulsions and psychiatric symptoms have also been reported in patients with influenza not taking zanamivir.²⁵

Precautions

The licensed dry powder inhaler contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. This does not apply to the lactose free formulations available on a compassionate use basis.

Neuropsychiatric events have been reported during administration of zanamivir in patients with influenza, especially in children and adolescents. Therefore, patients should be closely monitored for behavioural changes and the benefits and risks of continuing treatment should be carefully evaluated for each patient.²¹

Drug Interactions

Zanamivir is not protein bound and not hepatically metabolised or modified. Clinically significant drug interactions are unlikely.²¹

Drug Resistance

Surveillance of seasonal influenza in Australia and south-east Asia during 2006-8 detected a small number of influenza A H1N1pdm strains which had a significantly reduced susceptibility to zanamivir and determined by an amino acid substitution Q136K. However this arose after passage of the viruses in culture and was not detectable in the original clinical specimens; therefore the true role of this mutation in human infection remains unknown, despite its effect being confirmed by reverse genetics. This mutation does not affect virus susceptibility to oseltamivir.

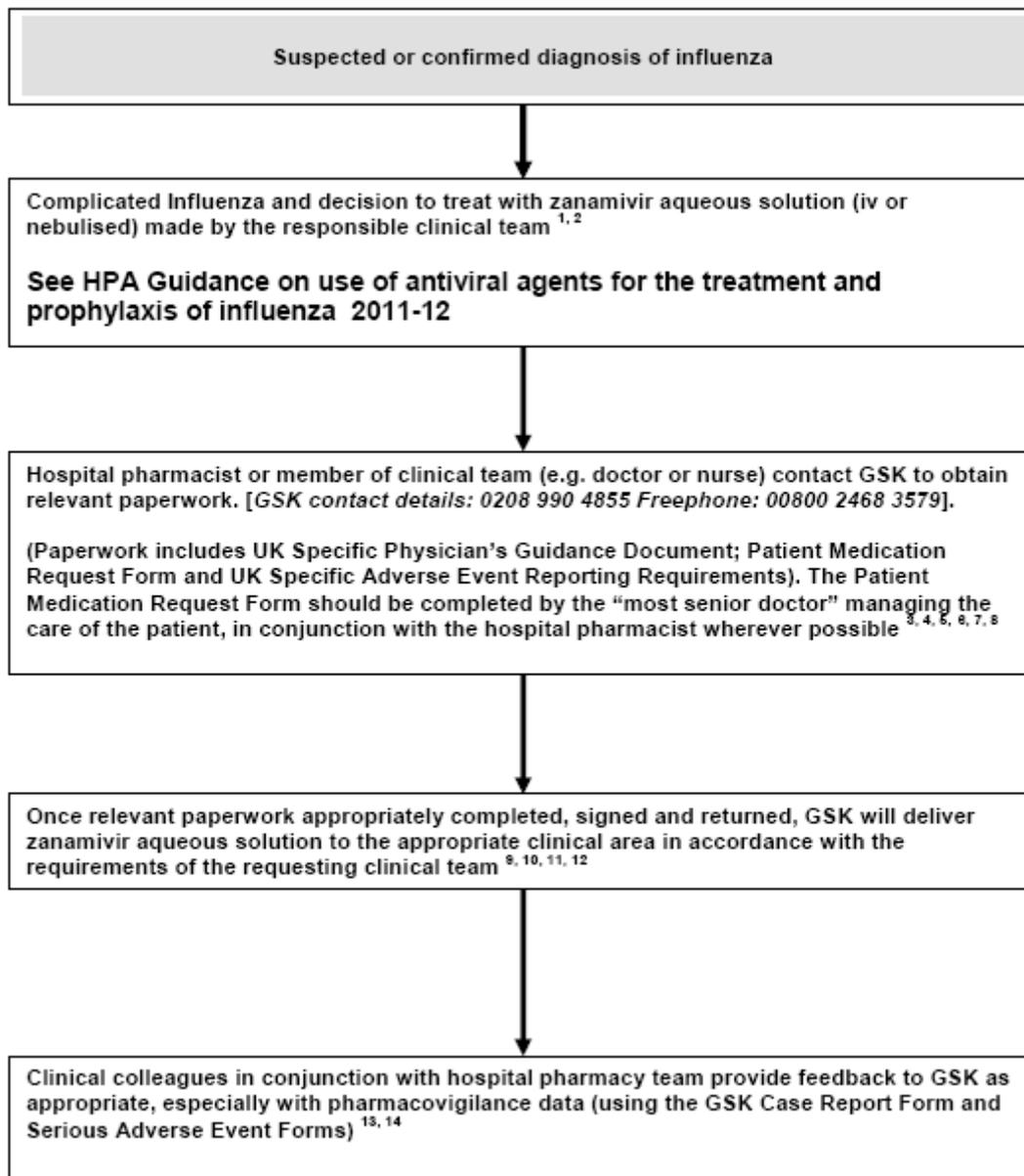
Monitoring treatment efficacy

This should be done according to the guidance described for oseltamivir (see page 5).

Summary

- There is inadequate data to establish the safety or effectiveness of inhaled zanamivir in seriously ill influenza patients, especially those with pneumonia or bronchospasm.
- Zanamivir powder from the Diskhaler device should not be given by nebulisation in mechanically ventilated patients as ventilator dysfunction may occur.
- Intravenous (IV) zanamivir should be considered the treatment of choice in critically ill influenza patients who:
 - are not absorbing from the gastrointestinal tract
 - known to have oseltamivir-resistant virus
 - have oseltamivir-sensitive virus but show poor clinical response after 5 days
 - Are severely immunocompromised
- In less severe cases nebulised aqueous zanamavir solution may be considered as an alternative to IV. Here the unlicensed IV product is used for nebulisation.

Supply of unlicensed zanamivir aqueous solution on a named patient, compassionate use basis from GlaxoSmithKline²⁴



Guidance Notes

General

1. 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 (see HPA Guidance on use of antiviral agents for the treatment and prophylaxis of influenza, 2011-12). **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.**

2. 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.

3. Wherever possible, ordering of zanamivir aqueous solution should follow "normal" medicines processes in Trusts, i.e. the hospital pharmacy should, if possible, order zanamivir aqueous solution.

4. GSK hours of despatch for zanamivir aqueous solution are **[See additionally, points 10 and 11 below]:**

a. Monday – Friday: 8am to 7pm

b. Saturday & Sunday: 8am to 3pm

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

Saturday 24 December 2011: 8am – 3pm

Sunday 25 December 2011: 8am – 3pm

Monday 26 December 2011 – Boxing Day (Bank Holiday): 8am – 3pm

Tuesday 27 December 2011 (Bank Holiday): 8am – 3pm

Wednesday 28 December 2011: 8am -7pm

Thursday 29 December 2011: 8am -7pm

Friday 30 December 2011: 8am -7pm

Saturday 31 December 2011: 8am – 3pm

Sunday 1 January 2012: 8am – 3pm

Monday 2 January 2012 (Bank Holiday): 8am – 3pm

Requesting a Named Patient Supply

5. When a decision to prescribe zanamivir aqueous solution is confirmed, contact should be made with **GSK on 0208 990 4855, Freephone: 00800 2468 3579**. 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 (i.e. senior nurse or doctor) **[See additionally, points 10 and 11 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].

6. Whilst GSK can be contacted 24 hours a day to discuss medical emergencies, GSK will not despatch outside of the hours 8am-7pm Monday-Friday or 8am-3pm Saturday/Sunday; therefore consideration should be given by the clinical team whether

GSK should be contacted after 7pm Monday-Friday /3pm Saturday/Sunday and before 7am in the morning.

7. GSK will email the relevant paperwork (i.e. UK Specific Physicians Guidance Document; Patient Medication Request Form; UK Specific Adverse Event Reporting Requirements) to the requestor and to the “most senior doctor”.

8. 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].

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

10. To guarantee same day despatch, hospitals are asked to allow up to 2 hours for processing of their request prior to close of despatch i.e. to send in their requests to GSK by

a. 5pm Monday – Friday or by

b. 1pm Saturday and Sunday

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

Despatch, Delivery and Receipt

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

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

b. 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.

c. 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.

13. Once despatched, 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.

Pharmacovigilance Information

14. 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.

Peramivir Treatment

Background

Peramivir is also a neuraminidase inhibitor, and has been made available in the US on an unlicensed basis as an intravenous formulation for emergency use for the treatment of certain hospitalized patients with known or suspected H1N1pdm influenza.³² This drug is still being evaluated in phase 3 clinical trials, though limited phase 2 and 3 safety and efficacy data for peramivir IV are available.³³ Intravenous peramivir was recently approved for use in Japan. At the time of writing, peramivir is not available in the UK but that may change. It is manufactured in the US by BioCryst.

Clinical Evidence

The FDA website states that in common with the other approved neuraminidase inhibitors, the efficacy and safety of IV peramivir has not been established in hospitalized patients with any type of influenza A or B virus including H1N1pdm virus. Two trials have been conducted using oseltamivir as the comparator, however the results did not indicate that peramivir was superior and, since a clinically meaningful non-inferiority margin has not been established, no conclusions can be drawn about the trial results. The fourth trial demonstrated no statistically significant distinctions between two different doses or single and multiple doses of peramivir.⁷

To date ~1,891 clinical trials subjects have received peramivir given IV or IM, including 478 who received a single dose of 600 mg IV. To date there have been no trials of peramivir in patients with specific H1N1pdm virus. The IM method of administration is not being developed. Data on multi-dose administration are limited; 33 adult clinical trial subjects have received approximately 600mg (or higher) intravenously once daily for five or more days.

There are currently no published reports of those < 18 years have received peramivir in clinical trials, though there are reports of use in this age group.³² No pharmacokinetic, safety or efficacy data are available in the paediatric population. Despite this, the FDA has permitted a limited use of peramivir IV in children under emergency conditions. Some safety data exists for peramivir IV 600 mg once daily for 5 to 10 days under emergency conditions. No pregnant women have received peramivir to date and no pharmacokinetic, safety or efficacy data are available in pregnancy.

Place in therapy

Peramivir is currently unavailable in the UK. But should this change, it potentially could have a role in those who:

- are not absorbing from the GIT
- fail to clear oseltamivir-sensitive virus despite treatment

Administration and dosing schedule

Presentation 200mg/20 ml vials (unlicensed). No refrigeration required.

Adults

Treatment dose The standard adult dose of peramivir is 600 mg IV in sodium chloride 0.9% over 30 minutes once a day, for 5 to 10 days. The maximum infusion rate is 40mg/min.

Paediatric Daily Dosage Recommendations^{*33}

Age	Dose (mg/kg)
Birth through 30 Days	6 mg/kg
31 Days through 90 Days	8 mg/kg
91 Days through 180 Days	10 mg/kg
181 Days through 5 Years	12 mg/kg
6 Years through 17 Years	10 mg/kg

*Maximum Daily Dose is 600 mg IV

Clinical Pharmacokinetics

The major route of elimination of unchanged peramivir is via the kidney. In normal renal function, the elimination half-life of IV product is 7.7 to 20.8 hour.

Renal and Liver impairment

Renal Impairment or Hemodialysis or Haemofiltration Creatinine Clearance	Daily Dose (IV) ³³
CrCl 50-80 mL/min	600 mg
CrCl 31-49 mL/min	150 mg
CrCl 10-30 mL/min	100 mg
Haemofiltration or CrCl <10 mL/min and not on haemodialysis	100 mg on day 1 followed by 15 mg daily thereafter
Hemodialysis or CrCl <10 mL/min	100 mg on day 1, then 100 mg given 2 hours after dialysis days only.

For dosing in paediatric renal function consult this FDA site.³³

As peramivir IV is not significantly metabolized by the liver, no dose adjustment is necessary in impaired hepatic function.³³

Side Effects

The most commonly reported adverse events in clinical trials of peramivir IV were diarrhoea, nausea, vomiting, and neutropenia. Although not seen in the trials to date peramivir IV may be associated with rare cases of anaphylaxis and serious skin reactions and a variety of neurological and behavioural symptoms that have been reported with other neuraminidase inhibitors.

From the available phase 1, 2 and 3 data the more common adverse events related to administration of peramivir are:

diarrhoea nausea vomiting neutrophil count decreased

From the available phase 1 and 2 data, other less common adverse events related to administration of peramivir are:

dizziness headache somnolence nervousness insomnia feeling agitated depression nightmares hyperglycemia	hyperbilirubinemia raised blood pressure cystitis ECG abnormalities (prolonged QTc interval observed in one patient in a phase 1 trial) anorexia proteinuria hematuria
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Drug Interactions

Limited data exists but peramivir is primarily renally eliminated so coadministration with drugs that reduce renal function or compete for active tubular secretion may increase plasma concentrations of peramivir and/or increase the concentrations of other renally eliminated drugs.

Drug Resistance

No clinical data are available on the development of resistance to peramivir at present.³³ However, in vitro peramivir selects for the same H275Y mutation that confers oseltamivir resistance, and peramivir is at least 80-fold less active for N1 viruses with the H275Y mutation.

Summary

Peramivir intravenous is not currently available in the UK. But should this change, it potentially could have a role as an unlicensed alternative to IV zanamivir in patients not absorbing from the gastrointestinal tract.

Because of cross-resistance, peramivir is likely to be ineffective in patients with documented or highly suspected oseltamivir resistance

Ribavirin Treatment

Background

Ribavirin is a guanosine analogue that likely exhibits multiple mechanisms of action, both direct and indirect.³⁴ It has a wide spectrum of activity against RNA and DNA viruses, with the oral and nebulised forms being licensed for the treatment of chronic hepatitis C in combination with other agents³⁵ and for respiratory syncytial virus (RSV) bronchiolitis in infants and children, respectively.³⁶ Ribavirin is known to have *in vitro* activity against influenza viruses and there is increased interest in the compound because of uncertainties surrounding H1N1pdm.³⁷

Clinical Evidence

There are numerous small scale studies of ribavirin to treat influenza, mainly via the oral or aerosolised route and these studies have recently been succinctly summarised.³⁷ The dose of ribavirin for oral therapy for active infection ranges from 100mg three times daily to a 3.6g loading followed by 1.2g twice daily. Trials utilising these doses have given mixed results. Doses of 1 gm per day were not effective clinically or virologically in a controlled trial involving uncomplicated influenza in adults.³⁸ Larger starting doses (1.2g hourly for three hours) followed by 1.2g twice daily dosing has improved signs and symptoms of influenza A and B in adults, without significantly affecting viral titres obtained from throat gargles / nasal washes.³⁹ Plasma bilirubin abnormalities were associated with the higher dose regimens (possibly reflecting haemolytic anaemia, a known side effect of the medication). Of note, combinations of oral ribavirin and oseltamivir show additive antiviral effects *in vitro* and in animal models of H5N1 infection.⁴⁰ Triple combinations of ribavirin with amantidine and oseltamivir have also been found to be effective against pre-pandemic H1N1, H3N2 and H1N1pdm *in vitro*, even against oseltamivir or amantidine resistant strains^{41,42}. The effectiveness of a triple antiviral combination to treat H1N1pdm has been examined in a retrospective Korean study, which found sole oseltamivir was as effective as triple therapy (oseltamivir, amantidine and ribavirin).⁴³ The ribavirin dose in the triple therapy cohort was small. Animal studies show that the effectiveness of ribavirin in H1N1pdm infection is related to the timing of initiation of therapy and the dose.⁴⁴

Several studies of aerosolised ribavirin with an average exposure of 2 to 6 grams over 3 or 4 days resulted in a more rapid reduction in fever and other clinical signs of influenza in the ribavirin groups, although others found no difference.³⁷

Information on the efficacy of intravenous ribavirin in influenza is even more sparse. One study gave a continuous infusion of ribavirin in three patients with either influenza or parainfluenza infections and noted reductions in viral shedding temporally related to the start of the infusion (5mg/kg/hr for 8 hours followed by 1.5mg/kg/hr for 2 to 6 days).⁴⁵ One case series reports on three patients with influenza associated myocarditis who were treated with intravenous ribavirin. Viral shedding was reported to abruptly stop on initiation of ribavirin therapy, however two of the patients died soon after and the third survived for 8 months on an artificial heart.⁴⁶

The use of Ribavirin in the treatment of influenza is controversial and unproven. The United States Food and Drug Administration have highlighted this and called for formal trials to evaluate safety and efficacy.³⁷

Place in therapy

Oral and nebulised ribavirin formulations are available in the UK. Intravenous ribavirin formulations are unlicensed but available at high cost through the manufacturer. Ribavirin in combination with a neuraminidase inhibitor and possibly an adamantine (e.g. amantadine) may have a role in those who:

- fail to clear zanamivir-sensitive virus despite zanamivir treatment
- have oseltamivir and suspected zanamivir resistant virus

Combination therapy with ribavirin should be discussed with the Health Protection Agency

Administration and dosing schedule

Presentation Ribavirin 200mg tablets / capsules, 400mg tablets, 40mg/ml oral solution, 6g lyophilisate / 100ml vial for aerosolisation, 1g/10ml ampoules for infusion (unlicensed).

Treatment dose in adults:

Enteral

In adult patients give 1.2g enterally every hour for three doses, followed by 1.2g every 12 hours for 48 hours (total ribavirin dose 8.4g in 2 days).³⁹

Aerosol / Nebulised

Greatest experience is with the use of a small particle aerosol generator (SPAG) or Aiolos nebuliser. Most studies that examine ribavirin therapy in influenza use this approach and the licensed product for ribavirin aerosol production for treatment of RSV uses the same method to generate 190microg/l air ribavirin concentration.

Dissolve the powder in a minimum of 75ml water for injections in the 100ml vial. The solution should be adequately mixed to ensure complete dissolution. Shake well. When using the SPAG generator, transfer the solution to the clean, sterilised 500ml flask and dilute to a final volume of 300ml with water for injections. When using the Aiolos nebuliser, transfer the solution into an infusion bag and dilute to a final volume of 300ml with water for injections. The final ribavirin concentration should be 20mg/ml.³⁶

Dosing frequencies vary by study. Typically the aerosol was initially delivered for 16 to 18 hours, then for three 4-hour blocks each day for three days. These patients were not receiving mechanical ventilation.^{47,48}

Intravenous

This therapy is unlicensed. There is currently one UK importer of intravenous ribavirin (Virazole): Creopharma (0844 879 3188). The required dose should be diluted in 5% glucose or 0.9% sodium chloride and administered over 30 to 60 minutes. There is no specific direction on the final concentration to use.

A continuous infusion 5mg/kg/hr for 8 hours followed by 1.5mg/kg/hr for 2 to 6 days has been used for influenza infection and generated plasma levels that far exceeded the MIC.

This dose is higher than the recognised dose for Haemorrhagic Fever with Renal Syndrome (33mg/kg initial loading dose followed six hours later by 16 mg/kg every 6 hr during 4 days (16 doses), then followed eight hours later by 8 mg/kg every 8 hr for a further 3 days).⁴⁹

Clinical Pharmacokinetics

Clearance of intravenous ribavirin is approx 28% via the renal route with the remainder through metabolism. There is a long terminal half-life due to phosphorylated ribavirin being sequestered intracellularly. Red blood cells do not degrade phosphorylated ribavirin and thus a proportion of the drug may remain in the system until red blood cells are destroyed.⁵⁰ There is a high volume of distribution.

Renal and Liver impairment

Data on drug clearance in renal or hepatic impairment is sparse. One small study showed a marked reduction in total plasma clearance in patient with renal impairment and a modest reduction in patients with liver impairment.³⁴ Patients with impaired renal function should be carefully monitored for signs and symptoms of toxicity, such as haemolytic anaemia. No specific dose adjustment recommendations can be made due to the paucity of information.

Renal replacement therapies are unlikely to contribute much to drug clearance due to high volumes of distribution.

Side Effects

Pooled safety data described are derived from 5 clinical trials (402 patients) with hemorrhagic fever with renal syndrome or Argentine Hemorrhagic Fever. The doses used were smaller than in case reports for influenza treatment.

Notable differences between the ribavirin and placebo groups respectively were for anaemia (12.1% and 6.1%), hyperbilirubinaemia (6.3% and 1.7%), coma (1.5% and 5.3%), shock (3.6% and 6.1%), renal failure (12.1% and 20.7%) and dialysis (2.5% and 9.9%).⁴⁹

Effects on electrolytes have been demonstrated in one retrospective study with 58% of patients exhibiting hypocalcaemia and 46% of patients exhibiting hypomagnesaemia.⁵¹

Product data sheets list other side effects though the data is for patients receiving *concomitant interferons*. These side effects include: Psychiatric / CNS effects (e.g. suicidal ideation, aggression, depression, emotional lability, and somnolence) growth retardation in children, haemolysis, cardiac arrhythmias, retinopathy, thyroid dysfunction, dental / periodontal disorders, gastro-intestinal effects, hepatomegaly and jaundice, pruritis, rash, dermatitis and other skin conditions, muscle, joint and bone pain and numerous other effects (see Product Summary of Product Characteristics for full information).^{35,52}

Carcinogenesis and Mutagenesis

In rodent studies there is some evidence that ribavirin can cause mutagenesis.⁵³

It rodent studies it was concluded that ribavirin was noncarcinogenic.⁵³

One manufacturer advises that carcinogenicity cannot be excluded³⁵

Reproduction Studies

Ribavirin was found to be teratogenic in several rodent studies although not in baboon studies. It is concluded that ribavirin may cause foetal harm in humans. Because of the long terminal half-life of the drug, the minimum interval following treatment with ribavirin before pregnancy can be safely initiated is estimated to be 7 months.⁵³

Precautions

Because of the reproductive risks associated with ribavirin, its use should be subject to formal risk assessment to protect health care workers and patients alike. Particular attention should be made to the Control of Substances Hazardous to Health (COSHH) regulations. Occupational exposure during nebulisation/aerosol formation limits the acceptance of these methods of delivery.

Drug Interactions

Results of *in vitro* studies indicated no cytochrome P450 enzyme mediated metabolism of ribavirin. Ribavirin does not inhibit cytochrome P450 enzymes and there is no evidence from toxicity studies that ribavirin induces liver enzymes^{35,52}

Antacids reduce the oral bioavailability of ribavirin^{35,52}

Nucleoside analogues: Ribavirin has been shown to inhibit phosphorylation of zidovudine and stavudine *in vitro*. The clinical significance of these findings is unknown, though manufacturers recommend that plasma HIV RNA levels be closely monitored in patients treated with ribavirin concomitantly with zidovudine or stavudine and a review carried out if HIV RNA levels rise.^{35,52}

Co-administration of ribavirin and didanosine is not recommended as *in vitro* data shows exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased. There have been reports of fatal hepatic failure as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactataemia/lactic acidosis.^{35,52}

Drug Resistance

No clinical data are available on the development of resistance to ribavirin at present.

Summary

The use of ribavirin by any route is controversial because of the lack of a robust evidence base. There are safety concerns regarding the potential to cause haemolytic anaemia and other metabolic abnormalities with oral or intravenous administration. Bronchospasm may occur when given by aerosol. There are reproductive risks for the patient. Health care workers may also be exposed to these risks, particularly when ribavirin is aerosolised. Enteral or intravenous ribavirin should only be considered in critically ill patients who:

- fail to clear zanamivir sensitive virus despite therapy with intravenous zanamivir (ribavirin should be added to intravenous zanamivir therapy)
- are suspected or known to have oseltamivir and zanamivir resistant virus (ribavirin should be added to oral oseltamivir / intravenous zanamivir therapy)

Combination therapy should first be discussed with the Health Protection Agency.

Corticosteroid Therapy

Background

The use of corticosteroid therapy in the management of adult respiratory distress syndrome (ARDS) and acute lung injury (ALI) has been the subject of much controversy for many years. This controversy extends to the use of corticosteroids in the management of H1N1pdm patients.^{54,55} Certain infective causes of lung inflammation are routinely treated with corticosteroid therapy, such as in the management of *pneumocystis carinii* pneumonia.⁵⁶ In some countries corticosteroids have been widely used in the management of H1N1pdm infection⁵⁷⁻⁵⁹ and retrospective cohort studies have begun to appear in the literature. The World Health Organisation does not recommend corticosteroid therapy for H1N1pdm pneumonitis¹⁴ and specifically counsel to avoid high-dose steroids unless indicated for another reason.

Clinical Evidence

A study of 13 patients with suspected H1N1pdm pneumonia and ALI-ARDS described patients response to a Meduri style methylprednisolone regimen.⁶⁰ The authors concluded that corticosteroid therapy was associated with significant improvements in lung function, organ dysfunction scores and hospital mortality, however the study had no control group.

A much larger retrospective study included 220 patients with suspected or proven H1N1pdm infection with respiratory failure requiring an ICU admission.⁶¹ Patients were said to have received steroid if the dose given was equivalent or greater to either 24mg/day methylprednisolone or 30mg/day prednisolone. Three groups of patients were described; those who never received steroids, those who received steroids 'early' (i.e. on ICU admission) and a 'no early corticosteroid therapy' group (i.e. received steroids during ICU stay, but not on admission). The 'early' group were significantly older, more likely to have asthma, COPD, use chronic steroids or be sicker as measured by SAPS3 scores than patients who never received steroids. The early group had a significantly higher mortality and hospital acquired pneumonia (HAP) rate. Multiregression analysis found that the mortality significance disappeared, but the increase in HAP remained statistically significant, leading the authors to conclude that early steroids had no effect on mortality, but increased HAP rates.

More recent studies have used propensity scores to correct for potential selection bias. A large French study enrolled 208 patients with respiratory failure and strongly suspected or proven H1N1pdm infection to examine the effect of steroids on outcome in critical care.⁶² Corticosteroid doses were converted to hydrocortisone equivalent, 39.9% of patients received corticosteroids (median daily dose equivalent to 370mg hydrocortisone, median duration 11 days). Mortality was significantly greater in the corticosteroid group (33.7% vs 16.8%). Further analysis using propensity scores and a sensitivity analysis found that mortality remained significantly greater in the corticosteroid group (adjusted Hazard Ratio 2.6; 95% CI 1.4-4.7, p=0.002). Because initiation of steroid therapy followed a bimodal model (within 3 days of mechanical ventilation, 'early' vs late), a further analysis was conducted and found that early administration with steroids was significantly associated with death (aHR 3.42; 95% CI 1.73-6.75, p=0.001), whilst later administration was not (aHR 1.93; 95% CI 0.84-4.43, p=0.12). Patients in the steroid group developed more ICU-acquired infection and pneumonia than patients in the non-steroid group and this was statistically significant, however this finding was not further subjected to propensity score analysis.

A similar study in 245 Korean patients also uses propensity scores.⁶³ Steroid doses were converted to prednisolone equivalent, patients receiving greater than 15mg equivalence were placed in the 'case subjects' group, patients not given corticosteroids were placed in the 'control

subjects' group. Crude mortality at 14 days was 27% vs 17% ($p=0.07$), at 60 days was 46% vs 23% ($p<0.001$) and at 90 days was 58% vs 27% ($p<0.001$) respectively. Multivariate analysis found that steroid use was associated with increased mortality (adjusted OR 2.2, 95% CI 1.03-4.71, $p=0.04$). When using propensity matching, the association persisted (90 day mortality, adjusted OR 2.63, 1.42-4.82, $p=0.002$). Superinfection rates were examined using a propensity matched case control study and found to be significantly greater in the steroid group (46% vs 28%, $p=0.03$)

These studies are retrospective and the data is heterogeneous. Exposure duration and timing of steroids is not standardised, doses are not consistent and the technique of converting the dose of different steroids to a standard reference steroid is particularly problematic given their different half-lives and durations of action. However, the largest, most rigorously statistically analysed studies to date find that the administration of corticosteroids in H1N1pdm infection is associated with increased mortality and secondary infections.

Summary

Corticosteroids should not be routinely used to treat acute lung injury or adult respiratory distress syndrome in critically ill patients with suspected or proven H1N1pdm infection.

'Low dose' corticosteroid therapy for refractory shock states should be used cautiously and in accordance with the Surviving Sepsis Campaign guidelines.³

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