

Summary of prescribing guidance for the treatment and prophylaxis of influenza-like illness



This guidance is intended to enable health protection units (HPUs) to address local queries about the treatment and prophylaxis of pandemic (H1N1) 2009 influenza. It is not a substitute for the Summary of Product Characteristics (SPC) and the Patient Information Leaflet (PIL) which must accompany the drug package provided.

Further information is also available on the HPA website: www.hpa.org.uk

Current guidelines are based on the Department of Health document *Use of antiviral drugs in an influenza pandemic - scientific evidence base*. Available from:

www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107133

Note: NICE guidance on triggering prescription of antiviral medications does **not** apply during a flu pandemic. This guidance will be regularly reviewed and updated. Please refer to the HPA or Department of Health website.

Treatment of suspected pandemic (H1N1) 2009 influenza

Indications

Adults and children over the age of one year

Ideally treatment to be administered within 12-48 hours of onset of symptoms. Current cases should be defined as per the **HPA case definition** available from: www.hpa.org.uk/swineflu

Under one year of age

Children under the age of one year who have symptoms of influenza should be treated with oseltamivir. The recommended doses of oseltamivir are:

- Children up to one month of age is 2mg/kg body weight twice a day for five days.
- Children over one month and up to three months of age is 2.5mg/kg body weight twice a day for five days.
- Children aged over three months and up to one year of age is 3mg/kg body weight twice a day for five days.

Children in these age groups with influenza symptoms will be assessed by a GP or other healthcare worker experienced in assessing children. At this assessment, the correct dose of antiviral medicine will be determined and any other medical management requirements will be identified.

GPs will be available to review these children in the community. GPs will have a low threshold for seeking the advice of a specialist for further management decisions if severe or complicated influenza, or adverse effects of treatment are suspected.

In the UK, two preparations of oseltamivir are available for treating children under one year of age: oseltamivir (Tamiflu) suspension 12mg in 1ml (manufactured by Roche and licensed for use in children over one year of age); and oseltamivir solution 15mg in 1ml. The raw ingredient powder of pharmaceutical grade has been purchased from Roche to manufacture into a solution by designated

licensed hospital pharmacy manufacturing units. New dosage guidance is based on 15mg in 1ml of oseltamivir oral solution. Primary care trusts have been asked to quarantine the 12mg in 1ml oseltamivir suspension.

Reference:

- Department of Health. *Recommendations on the use of antiviral medicines for pregnant women, women who are breastfeeding and children under the age of one year*. 2009.

People who are immunocompromised

People who have influenza-like illness who are in hospital and immunocompromised should have either zanamivir alone or zanamivir and oseltamivir. Detailed guidance is available at: www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1259152289698

Pregnancy

As with many medicines, oseltamivir and zanamivir have not been specifically tested in pregnancy and breastfeeding and, therefore, are not licensed for this use. However, use in several hundred women during pregnancy has not provided any evidence of harm to the fetus, and no harm has been shown in pregnant animals treated with oseltamivir.

Early initiation of antiviral treatment for pregnant women with influenza is recommended.

Pregnant women presenting with uncomplicated illness due to influenza, and who have no evidence of systemic disease, can be offered either zanamivir (Relenza) or oseltamivir (Tamiflu). In view of the lower systemic exposure, zanamivir is recommended as first choice although either drug can be used. If the patient suffers with conditions such as asthma or chronic pulmonary disease, or may have difficulty with an inhaled preparation, oseltamivir should be used.

Pregnant women developing severe, systemic or complicated disease due to influenza will typically be

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treated as an inpatient and should be offered treatment with oseltamivir.

The UK Teratology Information Service (UK-TIS)

The UK Teratology Information Service (UK-TIS, formerly NTIS), which is a service commissioned by the HPA who have agreed to undertake the surveillance of pregnancy outcomes where women are prescribed oseltamivir or zanamivir.

Any woman who is pregnant and is confirmed as having been exposed to an antiviral should be asked to give permission for her contact details to be passed on to UK-TIS, which can be contacted on 0844 892 0909.

Informed consent to pass on contact details to UK-TIS should be sought. UK-TIS has prepared a suitable script for seeking this information; the form of words recommended is:

'It is important to collect information on the effects of flu and its treatment on people in special groups, including those who are pregnant, as this helps us provide advice in the future. To allow us to do this, would you mind if we passed on your details and those of your GP to UK-TIS to allow them to do this as part of their routine health surveillance?'

Further details about the UK-TIS service are available from: www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1217835684939

The HPA has provided an example checklist with available evidence on treatment for discussion with pregnant women – see [Appendix 4](#).

Breastfeeding

Oseltamivir and its active metabolite, oseltamivir carboxylate, are excreted into human breast milk in very small amounts. Limited data suggest that clinical sequelae from maternal treatment would not be expected in a breastfed infant.

There are no data on zanamivir use during lactation but based on limited bioavailability the systemic exposure of a breastfed infant from maternal treatment is expected to be insignificant.

Women who are breastfeeding who have symptoms of influenza should be treated with an antiviral medicine. The preferred medicine is oseltamivir, as for other adults. However if a woman's baby is born and breastfeeding is started while the woman is taking zanamivir, she should complete the course of zanamivir. It is not necessary to switch to oseltamivir.

References:

- UK Medicines Information (www.ukmi.nhs.uk/)
- Department of Health. *Recommendations on the use of antiviral medicines for pregnant women, women who are breastfeeding and children under the age of one year*. 2009

OSELTAMIVIR (Tamiflu)

TREATMENT

Administration and dosage schedule

For adults and children over the age of one year

Oseltamivir capsules should be used as indicated in Table 6.

Under one year of age

Children up to one month of age is 2mg/kg body weight twice a day for five days.

Children over one month and up to three months of age is 2.5mg/kg body weight twice a day for five days.

Children aged over three months and up to one year of age is 3mg/kg body weight twice a day for five days.

Practitioners should refer to the guidance on the new antiviral authorisation vouchers issued by the Department of Health. See

www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_108873

In the UK, two preparations of oseltamivir are available for treating children under one year of age: oseltamivir (Tamiflu) suspension 12mg in 1ml (manufactured by Roche and licensed for use in children over one year of age); and oseltamivir solution 15mg in 1ml.

The raw ingredient powder of pharmaceutical grade has been purchased from Roche to manufacture into a solution by designated licensed hospital pharmacy manufacturing units. New dosage guidance is based on 15mg in 1ml of oseltamivir oral solution. PCTs have been asked to quarantine the 12mg in 1ml oseltamivir suspension.

Table 1 TREATMENT doses of oseltamivir (Tamiflu)

Up to one month of age	2mg per kg twice a day for five days
Over one month and up to three months	2.5mg per kg twice a day for five days
Over three months and under one year	3mg per kg twice a day for five days
From one year to under three years (< 15kg*)	ONE 30mg capsule twice a day for five days
From three years to under seven years (15–23kg*)	ONE 45mg capsule twice a day for five days
From seven years to under 13 years (23–40kg*)	TWO 30mg capsules twice a day for five days
From 13 years and over (including adults)	ONE 75mg capsule twice a day for five days

* if patient is not within the weight range expected for the age band in the prescribing table, then use the dose appropriate for the weight band, not the age band. e.g. if a six-year-old child is known to be >23kg, use the dose for the 23-40kg body weight band (seven-13 years of age).

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Renal impairment or patients on renal replacement therapies

The advice of experts in renal medicine is that patients who regularly attend a specialist renal clinic for management of renal failure should have their dose considered by their usual renal team.

Zanamivir may be preferable in a patient with renal failure as it is not well absorbed systemically. Please also refer to zanamivir section.

Table 2 Department of Health recommended treatment dose of oseltamivir for adults with renal impairment

GFR (ml/min)	Recommended dose for oseltamivir treatment
> 30 (ml/min)	75mg twice daily
> 10 to 30 (ml/min)	75mg once daily, or 30mg twice daily,
10 (ml/min)	See Renal Handbook and discuss with renal team
dialysis patients	See Renal Handbook and discuss with renal team

Reference: SPC & Renal Handbook, 3rd edition.

Formulations

Capsules

30mg capsules (yellow), 10 cap pack
45mg capsules (grey), 10 cap pack
75mg capsules (grey-yellow), 10 cap pack

The capsules should be administered as per Table 6. If adults, adolescents or children are unable to swallow capsules they may receive appropriate doses of Tamiflu by opening capsules and pouring the contents of capsules into a suitable, small amount (one teaspoon maximum) of sweetened food product such as regular or sugar-free chocolate syrup, honey (only for children two years or older), light brown or table sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce or yogurt to mask the bitter taste.

The mixture should be stirred and the entire contents given to the patient. The mixture must be given immediately after its preparation. It is not necessary to administer any undissolved white powder as this is inert material.

Suspension – Tamiflu

Sugar-free, tutti-frutti flavoured oseltamivir (as phosphate) for reconstitution with water, 12mg/1ml. The Department of Health has advised that PCTs should quarantine the suspension.

Oseltamivir solution

A solution of oseltamivir 15mg in 1ml is being prepared by designated licensed hospital pharmacy manufacturing units. The same 3ml syringe as for the Tamiflu suspension will be provided for measuring the volume.

Oseltamivir solution has a bitter taste and may require the addition of a small volume (less than 10ml) of a strongly-flavoured sugary drink such as blackcurrant squash to help very young children to tolerate the medicine. If the medicine is added to a drink then the parents should be told to make sure that the whole volume of the drink is taken.

Table 3 Side-effects of oseltamivir listed in the British National Formulary (BNF)

Side-effects	Nausea, vomiting, abdominal pain, diarrhoea, headache, conjunctivitis
Less commonly	Rash
Also reported	Hepatitis, arrhythmias, neuropsychiatric disorders (in children and adolescents), visual disturbances, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Table 4 Side-effects of oseltamivir listed in the British National Formulary for Children (BNFC)

Side-effects	Nausea, vomiting, abdominal pain, dyspepsia, diarrhoea, headache, fatigue, insomnia, dizziness, conjunctivitis, epistaxis, rash
Very rarely	Hepatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, neuropsychiatric disorders also reported

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ZANAMIVIR (Relenza) TREATMENT

Administration, dosage and formulation

Adults and children over five years

TWO 5mg blisters to be inhaled (using the 'Diskhaler') twice a day for five days (equivalent to 10mg twice a day for five days).

Caution: Asthma and chronic pulmonary disease (risk of bronchospasm); a short-acting bronchodilator should be available. Avoid in severe asthma unless close monitoring possible and appropriate facilities available to treat bronchospasm), uncontrolled chronic illness. Other inhaled drugs should be administered before zanamivir.

Table 5 Side-effects of zanamivir listed in the BNF/BNFC

British National Formulary	Very rarely: bronchospasm, respiratory impairment, angioedema, urticaria, and rash; also reported, neuropsychiatric disorders (especially in children and adolescents)
British National Formulary for Children	Very rarely: bronchospasm, respiratory impairment, angioedema, urticaria and rash

Reference: British National Formulary/British National Formulary for Children, March 2009.

Renal impairment or patients on renal replacement therapies

Zanamivir may be the preferred drug of choice in renal failure.

Paediatric patients with severe renal impairment are not covered by this guidance. Seek specialist advice in all cases.

- Inhaled zanamivir results in approximately 10%-20% of the inhaled dose being absorbed. Following inhalation, zanamivir is entirely excreted unchanged in the urine.
- The half-life of zanamivir is prolonged in patients with renal impairment.
- Given the importance of local concentrations, the low systemic exposure and the previous tolerance of much higher exposures, the manufacturers recommend that no dose adjustment is required in patients with renal impairment.
- There is no published data about the use of zanamivir in patients undergoing renal replacement therapies, however for the above reasons, it has been suggested that the normal dose is used in these patients.

Reference: UK Medicines Information (UKMI): www.ukmi.nhs.uk/

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PROPHYLAXIS OF PANDEMIC (H1N1) 2009 INFLUENZA

Indications

Adults and children over the age of one year

Currently the Department of Health guidance as summarised in Appendix 1 should be followed. The full guidance is available at the following link: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107133 and is summarised in Appendix 1.

Under one year of age

The balance of benefit and risk for using oseltamivir for the prophylaxis of influenza in children under one year who are not currently suffering from influenza symptoms is not clear. A decision on whether prophylaxis with oseltamivir should be recommended should be taken by an expert in the care of young children.

Reference:

- Department of Health. *Recommendations on the use of antiviral medicines for pregnant women, women who are breastfeeding and children under the age of one year.* 2009.

People who have been in contact with a case of oseltamivir-resistant pandemic (H1N1) 2009 influenza

Contacts of people with oseltamivir-resistant influenza requiring prophylaxis should be prescribed zanamivir. Detailed guidance is available at: www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1259152327913

People who are in hospital and immunocompromised

Contacts who are in hospital and immunocompromised and require prophylaxis should be prescribed zanamivir. Detailed guidance is available at: www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1259152327913

Pregnancy

In the context of a novel influenza virus in a pandemic situation, the European Medicines Agency (EMA) suggests the benefit of using antiviral medicines outweighs the risk, for both treatment and prophylaxis.

If it is decided that a pregnant women requires prophylaxis because of family or other contact with a novel pandemic virus strain, the preferred antiviral medicine is zanamivir.

Breastfeeding

In the context of a novel influenza virus in a pandemic situation the EMA suggests the benefit of using antiviral medicines outweighs the risk, for both treatment and prophylaxis.

If it is decided that a women who is breastfeeding requires prophylaxis because of family or other contact with a novel pandemic virus strain, the preferred antiviral medicine is oseltamivir. However, if a woman's baby is born and breastfeeding is started while the woman is taking zanamivir, she should complete the course of zanamivir; it is not necessary to switch to oseltamivir.

References:

- Department of Health. *Recommendations on the use of antiviral medicines for pregnant women, women who are breastfeeding and children under the age of one year.* 2009.
- EMA. *Guidance on use of antiviral medicines in the event of an influenza A/H1N1 pandemic.* Available from: www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/27353509en.pdf

OSELTAMIVIR (Tamiflu) PROPHYLAXIS

Administration and dosage schedule

Table 6 PROPHYLAXIS doses of oseltamivir (Tamiflu)

Up to one month of age	2mg per kg once a day for 10 days
Over one month and up to three months	2.5mg per kg once a day for 10 days
Over three months and under one year	3mg per kg once a day for 10 days
From one year to under three years (<15kg*)	ONE 30mg capsule once a day for 10 days
From three years to under seven years (15–23kg*)	ONE 45mg capsule once a day for 10 days
From seven years to under 13 years (23–40kg*)	TWO 30mg capsules once a day for 10 days
From 13 years and over (including adults)	ONE 75mg capsule once a day for 10 days

* if the patient is not within the weight range expected for the age band in the prescribing table, then use the dose appropriate for the weight band, not the age band. e.g. if a six-year-old child is known to be >23kg, use the dose for the 23-40kg body weight band (7-13 years of age).

Renal impairment or patients on renal replacement therapies

The advice of experts in renal medicine is that patients who regularly attend a specialist renal clinic for management of renal failure should have their dose considered by their usual renal team.

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GFR (ml/min)	Recommended dose for prevention
> 30 (ml/min)	75mg once daily
> 10 to 30 (ml/min)	75mg every second day, or 30mg once daily,
10 (ml/min)	See Renal Handbook and discuss with renal team
dialysis patients	See Renal Handbook and discuss with renal team

Reference: SPC & Renal Handbook, 3rd edition.

(1) Paediatric patients with renal impairment are not covered by this guidance. Seek specialist advice in all cases.

(2) Zanamivir may be preferable in a patient with renal failure as it is poorly systemically absorbed. Please refer to zanamivir section.

Formulations

Covered in treatment section.

Side-effects

Covered in treatment section.

ZANAMIVIR (Relenza) PROPHYLAXIS

Administration, dosage and formulation

Inhalation of powder, adult and child over five years.
TWO 5mg blisters to be inhaled (using the 'Diskhaler') once a day for ten days (equivalent to 10mg once a day for ten days).

Renal impairment or patients on renal replacement therapies

No dose adjustment necessary. See treatment section.

References:

- Department of Health. *Use of antiviral drugs in an influenza pandemic - scientific evidence base*.2006. Available from: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_077276
- Department of Health. *Pandemic Influenza, Guidance of preparing maternity services*. Available from: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_091737
- British National Formulary (BNF), March 2009.
- UK Medicines Information (UKMI) www.ukmi.nhs.uk
- The electronic Medicines Compendium (eMC). Oseltamivir SPC. Available from: <http://emc.medicines.org.uk/document.aspx?documentId=10446>
- Renal Handbook, 3rd edition. Caroline Ashley and Aileen Currie, editors.
- Health Protection Agency algorithms. Available from: www.hpa.org.uk
- RCPCH consensus statement available from: www.rcpch.ac.uk/Research/CE/Guidelines-frontpage/Guideline-Appraisals-by-Topic/practice-statements
- EMEA. *Guidance on use of antiviral medicines in the event of an influenza A/H1N1 pandemic*. Available from: www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/27353509en.pdf
- *Draft briefing and guidance for adult renal units in the UK during an influenza pandemic*. Prepared for the Renal Association of Clinical Affairs Board. 2007.
- Robson R, Buttimore A, Lynn K, et al. *The pharmacokinetics and tolerability of oseltamivir suspension on haemodialysis and continuous ambulatory peritoneal dialysis*. *Nephrol Dial Transplant*. 2006;21(9):2556-62
- Department of health. *Recommendations on the use of antiviral medicines for pregnant women, women who are breastfeeding and children under the age of one year*. 2009.

Appendices

Appendix 1:	Guidance on use of prophylaxis in the treatment phase of Pandemic (H1N1) 2009 Influenza
Appendix 2:	Evidence relating to children aged under one
Appendix 3:	Drug interactions in the treatment of HIV infection
Appendix 4:	Background information for discussion with pregnant women
Appendix 5:	Supportive measures
Appendix 6:	Version control statements

Appendix 1

GUIDANCE ON USE OF PROPHYLAXIS IN THE TREATMENT PHASE OF THE PANDEMIC (H1N1) 2009 INFLUENZA.

Full Department of Health guidance is available at: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107133

Indications

Prophylaxis should not ordinarily be given to the contact of a case of pandemic flu. However, clinical judgement should be used where risk is identified to particularly vulnerable individuals. In particular prophylaxis may be considered in the following circumstances:

- **Prophylaxis in household settings**

Prophylaxis for someone with a serious underlying condition where there is close prolonged contact with case of pandemic flu in a household setting.

- **Prophylaxis in institutional settings**

Prophylaxis for the prevention or control of infection in an institutional setting where people live in close proximity to each other, such as nursing homes, may be considered, where at least some of the people who share the facility have a serious underlying condition.

Prophylaxis in household settings

The decision to provide prophylaxis to a close contact of a case of pandemic flu in a household setting should be considered if the contact is at particularly high risk of complications from pandemic flu and the likelihood of exposure to the case while infectious is high. The decision should be taken by the primary care clinician, with the assistance of another appropriate expert clinician where necessary (e.g. paediatrician, renal physician, specialist caring for a patient with immunodeficiency).

Close prolonged contact

Examples of close prolonged contact would be persons living and/or sleeping in the same household, pupils in the same dormitory, and boy/girlfriends.

Higher-risk groups

The people with a serious underlying condition listed in Table 8 overleaf should be considered for prophylaxis if they are a close prolonged contact in a household setting with a case of pandemic flu.

Prophylaxis in institutional settings

Prophylaxis for the prevention or control of infection in an institutional setting where people live in close proximity to each other sharing common facilities, such as a nursing homes, may be considered, where at least some of the people who share the facility belong to one, or more, of the higher-risk groups.

The decision to provide prophylaxis for control of disease in an institutional setting should be made on a case-by-case basis and should usually be made by the local health protection unit (HPU).

Children in special schools may be at higher risk of an adverse outcome from pandemic flu due to their underlying conditions. When cases of pandemic flu occur in a special school, particular consideration should be given to the risk to the other children attending that school. This assessment should be undertaken in association with the local HPU.

Individuals with a serious underlying condition will usually be in known at-risk groups who will be particularly vulnerable to developing a severe illness, with potential rapid decline, leading to serious or life-threatening complications. Almost all of these patients will be receiving frequent secondary and tertiary care and some will live in institutions.

These individuals will fall into one of the groups shown in Table 8 overleaf.

Prophylaxis in children under one year of age

Doctors should carefully consider the benefits and risks of using prophylaxis in children under one year of age.

The Committee for Medicinal Products for Human Use (CHMP) has agreed that there is enough evidence to support the use of the oseltamivir for the treatment in children younger than one year of age. However, CHMP noted that there is less evidence to support the use of oseltamivir for the prevention of influenza.

It is, therefore, recommended that prophylaxis should only be given to a child under one year of age when another significant health condition is also present.

Appendix 1

Table 8 Prophylaxis of people with serious underlying conditions

Group A: Those with depleted immunity who will be less able to cope with secondary bacterial infection after pandemic flu.

This will include adults and children who:

- Are immunosuppressed secondary to chemotherapy for cancers.
- Are on steroids:
 - for [children](#) at a dose of 1mg/kg body weight per day or more; or more than 20mg absolute dose if body weight greater than 20kg; whichever is the lesser.
 - for [adults](#) receiving greater than 20mg prednisolone daily.
- Are on multiple immunosuppressants such as cyclosporin, tacrolimus and sirolimus.
- Are on biological therapies such as infliximab, etanercept, anakinra or similar agents.
- Are on antiproliferative immunosuppressants such as azathioprine and mycophenolate mofetil.
- Are on transplant immunosuppression.
- Have hypogammaglobulinaemia, although this is rare and should be treated already with immunoglobulin.
- Have neutrophil abnormalities, although these are rare and patients will be under specialist care.
- Have serious illness related to being HIV positive.
- Have primary immunodeficiency (all types).

Group B: Those identified following clinical assessment as having advanced chronic illness, which would be destabilised by a severe viral illness.

This will include adults and children identified within the following groups as being particularly vulnerable. The following [examples](#) are to assist decision-making, but the ultimate decision remains with the clinician following an individual assessment as the list cannot cover every eventuality:

- **Chronic hepatic failure**
 - Awaiting transplantation.
 - Recent hospital admissions with hepatic failure.
- **Renal conditions**
 - Nephrotic syndrome or on immunosuppression.
- **Cardiac conditions**
 - Chronic congestive cardiac failure: anyone with current New York Heart Association (NYHA) class III or IV symptoms resulting from a cardiac problem.
 - Current severe impairment of left ventricular function (LV ejection fraction less than 35%) from any cause.
 - Current severe structural heart disease (eg severe non-operated valvular disease, cardiomyopathy).
 - Severe congenital heart disease in adults.
 - Cyanotic congenital heart disease in children.
 - Previous history of severe viral myocarditis.
- **Respiratory conditions**
 - Cystic fibrosis.
 - Difficult-to-manage asthma (e.g. >2 exacerbations requiring additional treatment per year or regular hospital admission).
 - Difficult-to-manage COPD (e.g. >2 exacerbations requiring additional treatment per year or regular hospital admission or FEV1<50% predicted).
 - Difficult-to-manage bronchiectasis (e.g. >2 exacerbations requiring additional treatment per year).
 - Lung cancer on treatment.
 - Interstitial lung disease under hospital follow up.
- **Neurological conditions**
 - Unstable epilepsy.
 - Severe neurodegenerative diseases, or severe neurodisability, predisposing to aspiration or failure to clear respiratory secretions.
- **Child-specific conditions**
 - Chronic lung disease of prematurity.
 - Complex neurodisability/cerebral palsy.

Group C: Patients recently discharged from hospital, having been treated for a serious illness, whose recovery would be destabilised by a severe viral illness.

Appendix 2

EVIDENCE RELATING TO CHILDREN AGED UNDER ONE YEAR

During influenza seasons it is recognised that children younger than 24 months are consistently at substantially higher risk of hospitalisation than older children, and the risk of hospitalisation attributable to influenza infection is highest in the youngest children.

The Science and Research Department of the UK Royal College of Paediatrics and Child Health has produced a consensus statement on the use of oseltamivir in infants under one year of age during a flu pandemic which took account of expert opinion and information available as of May 2009. The full statement is available on the website www.rcpch.ac.uk/Research/CE/Guidelines-frontpage/Guideline-Appraisals-by-Topic/practice-statements. The RCPCH summary recommendation is that:

'Clinicians should weigh up the potential risks and possibility of ineffective treatment versus the potential benefit of treatment in each case and ensure there has been discussion with parents to enable them to make an informed choice. If treatment with oseltamivir is considered for symptom relief in infants less than one year, the dose used in the published Japanese studies (2mg per kg twice daily) for five days would currently seem a reasonable choice.'

This is consistent with the advice given by the European Medicines Agency on 8 May 2009¹:

'In case of a pandemic, the Committee for Medicinal Products for Human Use (CHMP) agreed that there is enough evidence to support the use of the Tamiflu [oseltamivir] for the treatment in children younger than one year of age. The committee noted that there is less evidence to support the use of Tamiflu for the prevention of influenza. Therefore doctors should carefully consider the benefits and risks for each infant. Should Tamiflu be prescribed to children under the age of one, the recommended dosage is 2mg to 3mg per kg body weight.'

Internal review of some of the original papers

Oseltamivir is not licensed in children under one year. However, Okamoto et al from Japan published a retrospective study of 103 children less than one year following an alert from Roche.^{2,3}

The alert is at:
www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107133

The alert highlights the company's concern following preclinical trials involving deaths in immature rats. The seven-day rats that died were associated with unusually high exposure to both oseltamivir and oseltamivir phosphate. Further studies were carried out following this.

The alert goes on to state that the clinical significance of these preclinical data to human infants is uncertain. However, due to concerns over immature blood brain barriers in children under one year, Roche recommended that Tamiflu not be administered to children of less than one year.

The Japanese group did not find any cases of fatality or encephalopathy in 102 children (one lost to follow-up). The authors did this study because of clinical concerns regarding influenza encephalopathy in this age group and the fact that they would usually use oseltamivir to treat such cases.

A 2006 review by Whitley and Monto referred to three clinical toxicology studies that had identified neurotoxicity in newborn rats administered oseltamivir.⁴ They pointed out that the dosage used was higher than that used for humans and that the metabolism of oseltamivir in rats differs to that of humans.

References:

1. EMEA, *Guidance on use of antiviral medicines in the event of an influenza A/H1N1 pandemic*, available from: www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/27353509en.pdf
2. Okamoto, S, Kamiya, I, et al. Experience with Oseltamivir for Infants Younger Than one year old in Japan. *The Pediatric Infectious Diseases Journal* June 2005; Vol 24 (issue 6):575-5
3. Roche Pharmaceuticals. Alert letter December 2003. Available from: www.fda.gov/medwatch/SAFETY/2003/tamiflu-deardoc.pdf
4. Richard J. Whitley, Arnold S. Monto. *Prevention and Treatment of Influenza in High-Risk Groups: Children, Pregnant Women, Immunocompromised Hosts and Nursing Home Residents.* *JID* 2006;104 (Suppl 2): s133-138.

Appendix 3

DRUG INTERACTION IN THE TREATMENT OF HIV INFECTION

Refer to PIL and SPC.

There are potential interactions between antiviral treatment and anti-HIV therapy. This information is based on the best available knowledge of theoretical interactions and has been summarised by Liverpool University at www.hiv-druginteractions.org

With the permission of Liverpool University the information below describes these interactions as they stood on 19 May 2009.

Oseltamivir

- Not metabolised by, nor an inhibitor of, CYP450 or glucuronyltransferase enzymes.
- Oseltamivir is metabolised to oseltamivir carboxylate by hepatic esterases. The carboxylate undergoes renal excretion by glomerular filtration and tubular secretion.
- Transported by P-glycoprotein (P-gp), limiting brain uptake.

Interaction potential

- No interaction anticipated at the level of hepatic metabolism. Oseltamivir has been linked tentatively with neuropsychiatric reactions and, if so, inhibition of brain P-gp by boosted protease inhibitors (PI) could increase risk of neurotoxicity. Although it is more likely that influenza itself is responsible for CNS symptoms, we suggest vigilance when oseltamivir and boosted PIs are coadministered.
- Need to consider potential for interaction at level of renal secretion (i.e. lamivudine, emtricitabine, tenofovir).
- Coadministration of probenecid (an inhibitor of renal secretion) increases oseltamivir carboxylate concentrations by approximately two-fold (Wattanagoon Y, et al, 2009, *Antimicrob Agents Chemother*, 53: 945-952).
- Until there are further data on the magnitude of any interaction between oseltamivir and renally excreted Nucleoside Reverse Transcriptase Inhibitor (NRTI) we suggest caution in patients with any degree of renal impairment.

Zanamivir

- Inhaled zanamivir results in 10-20% of the inhaled dose being absorbed.

Interaction potential

- Does not undergo any appreciable metabolism.
- Does not inhibit or induce CYP450 enzymes (in vitro data).

Note: This advice will be revised as more data emerges. The most up-to-date information is available from: www.hiv-druginteractions.org

- Renally cleared unchanged, but since systemic exposure is low, we consider there to be a very low potential for any interaction with renally cleared antiretrovirals.

Appendix 4

BACKGROUND INFORMATION FOR DISCUSSION WITH PREGNANT WOMEN

Please remember to refer to the most up to date information on the Department of Health website, the relevant Royal Colleges, UKTIS and the EMEA.

What are the risks of influenza in pregnancy?

Maternal risk

- Pregnant women do not seem to be at an increased risk of contracting influenza than the general population. However, pregnant women, particularly in the third trimester of pregnancy, appear to be at a higher risk of developing influenza-associated pneumonia and cardio-respiratory complications.^{1,2} In keeping with this, the incidence of acute cardio-respiratory hospitalisations during influenza season increases throughout pregnancy, the highest incidence being during the third trimester.
- An increase in influenza-associated mortality among pregnant women was documented during the influenza pandemics of 1918-1919 and 1957-1958, although a similar increase has not been noted during the inter-pandemic periods.^{2,3}

Risk to the fetus

- There is inconsistent data to suggest that maternal influenza may be associated with an increased risk of some congenital anomalies, including oesophageal atresia,⁴ or anophthalmos/microphthalmos;⁵ an increased risk of anencephaly was also reported following epidemics of Asian influenza.^{6,7,8}
- The Hungarian Case-Control Surveillance of Congenital Abnormalities reported an association between maternal influenza during the second and third month of pregnancy and congenital anomalies in the offspring, including cleft lip or palate, neural tube defects, and cardiovascular abnormalities.⁹ The use of antipyretics reduced the risk of congenital anomalies, suggesting that they were due to fever. Use of folic acid supplements reduced or eliminated the apparent risk associated with influenza during pregnancy.
- A further case-control study involving 363 infants with neural tube defects (NTD) and 523 normal newborns indicated an increased risk of NTDs associated with maternal influenza. In this study, risk was enhanced when antipyretics were used.¹⁰

- There are, however, a number of studies that have not found any increased risk of congenital anomalies in association with maternal influenza.^{6, 11-13} Maternal influenza has not been associated with an increased risk of spontaneous abortion and intrauterine death.
- An association has been reported between high-fever-related maternal diseases (including influenza) and an increased risk of congenital anomalies in a case control study.^{9, 14, 15} During the first trimester of pregnancy the risk of congenital anomalies occurring may be reduced by the administration of antipyretics. Fever associated with influenza can be reduced in pregnancy with the use of paracetamol; this antipyretic is suitable for use in all stages of pregnancy.

What is the treatment for Pandemic (H1N1) 2009 Influenza?

Refer to the pregnancy section above.

- The currently circulating Pandemic (H1N1) 2009 Influenza virus has been shown to be sensitive to the neuraminidase inhibitor antiviral medications zanamivir and oseltamivir, but is resistant to amantadine and rimantadine.
- The neuraminidase inhibitors oseltamivir (Tamiflu, oral) and zanamivir (Relenza, inhaled) are effective for prophylaxis and treatment of influenza.

What are the risks of treatment for Pandemic (H1N1) 2009 Influenza?

Maternal risk

- Side-effects as documented in the treatment section above.
- Zanamivir is administered by inhalation and is deposited at high concentrations throughout the respiratory tract with less systemic absorption;¹⁸ for that reason it is the preferred drug for use in pregnant patients for treatment unless there is a clinical contraindication.
- However, due to its route of administration, zanamivir may be associated with adverse respiratory effects, such as bronchospasm and dyspnoea, which may be a concern in patients at risk of respiratory problems.

Appendix 4 continued

Risk to the fetus

- There is limited data available on the safety of oseltamivir and zanamivir in pregnancy, but the animal studies and human exposure details that are available have not demonstrated harm.

Other practical advice

Risks of adverse fetal outcomes following influenza in pregnancy may be reduced by appropriate use of folic acid supplementation. Appropriate use of antipyretics (e.g. paracetamol) may also reduce risk of the adverse fetal outcomes associated with fever.

Adapted from *Management of Pregnant Women during an influenza A(H1N1) Pandemic*, UK Teratology Information Service. www.toxbase.org. May 2009.

References:

1. Kort B. A., Cefalo R. C., Baker V. V. *Fatal influenza A pneumonia in pregnancy*. Am J Perinatol 1986, 3(3):179-182.
2. Neuzil K. M., Reed G. W., Mitchel E. F., Simonsen L., Griffin M. R. *Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women*. Am J Epidemiol 1998, 148(11): 1094-1102.
3. Greenberg M, Jacobziner H, Pakter J. *Maternal mortality in the epidemic of Asian influenza, New York City, 1957*. Am J Obstet Gynecol 1958, 76:897-902.
4. Leck I. *Incidence of malformations following influenza epidemics*. Br J Prev Soc Med 1963, 17:70-80.
5. Busby A., Dolk H., Armstrong B. *Eye anomalies: seasonal variation and maternal viral infections*. Epidemiology 2005, 16(3):317-322.
6. Doll R., Hill A. B., Sakula J. *Asian influenza in pregnancy and congenital defects*. Br J Prev Soc Med 1960, 14:167-172.
7. Coffey V. P., Jessop W. J. *Maternal influenza and congenital deformities: a prospective study*. Lancet 1959, 2(7109):935-938.
8. Hakosalo J., Saxen L. *Influenza epidemic and congenital defects*. Lancet 1971, two(7738):1346-1347.
9. Acs N., Banhidly F., Puho E., Czeizel A. E. *Maternal influenza during pregnancy and risk of congenital abnormalities in offspring*. Birth Defects Res A Clin Mol Teratol 2005, 73(12):989-996.
10. Li Z., Ren A., Liu J., Pei L., Zhang L., Guo Z., Li Z. *Maternal flu or fever, medication use, and neural tube defects: a population-based case-control study in Northern China*. Birth Defects Res A Clin Mol Teratol 2007, 79(4):295-300.
11. Wilson M. G., Stein A. M. *Teratogenic effects of asian influenza. A n extended study*. Jama 1969, 210(2):336-337.
12. Walker W. M., Mc Kee Ap. *Asian influenza in pregnancy; relationship to foetal anomalies*. Obstet Gynecol 1959, 13(4):394-398.
13. Korones S. B., Todaro J., Roane J. A., Sever J. L. *Maternal virus infection after the first trimester of pregnancy and status of offspring to four years of age in a predominantly Negro population*. J Pediatr 1970, 77(two):245-251.
14. Acs N., Banhidly F., Horvath-Puho E., Czeizel A. E. *Population-based case-control study of the common cold during pregnancy and congenital abnormalities*. Eur J Epidemiol 2006, 21(1):65-75.
15. Czeizel A. E., Puho E. H., Acs N., Banhidly F. *High fever-related maternal diseases as possible causes of multiple congenital abnormalities: a population-based case-control study*. Birth Defects Res A Clin Mol Teratol 2007, 79(7):544-551.
16. National Institute for Health and Clinical Excellence (NICE). *NICE technology appraisal TA168 Amantadine, oseltamivir and zanamivir for the treatment of influenza*. 2009.
17. National Institute for Health and Clinical Excellence (NICE). *NICE technology appraisal TA158 Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza*. 2008.
18. The electronic Medicines Compendium (eMC). *Relenza*. Available from: <http://emc.medicines.org.uk>.
19. Advisory Committee on Immunisation Practices (ACIP). *Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008*. Available from: www.cdc.gov/mmwr/preview/mmwrhtml/rr57e717a1.htm

Appendix 5

SUPPORTIVE MEASURES

Antipyretics

Paracetamol is indicated for the treatment of pyrexia and mild to moderate pain. Caution should be used in hepatic impairment, renal impairment and alcohol dependence. Side-effects are rare.

Ibuprofen is indicated for pain and fever in children and available as syrup. Caution should be used in the elderly, allergic disorders (including history of hypersensitivity to aspirin or any other NSAID, which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID), during pregnancy and breastfeeding and in coagulation defects. **Clearly this list is not exhaustive. Please refer to the British National Formulary (BNF).**

Note: Owing to an association with Reye's syndrome, the Committee on Safety of Medicines has advised that aspirin-containing preparations should not be given to children under 16 years, unless specifically indicated, e.g. for Kawasaki syndrome. Aspirin and aspirin-containing products are also contraindicated in breastfeeding.

Reference: *British National Formulary*, March 2009.

Management of gastrointestinal symptoms associated with oseltamivir

The occurrence of gastrointestinal symptoms in association with the use of oseltamivir in prophylaxis and treatment schedules is a well-recognised problem that may adversely affect patient compliance.

According to the manufacturer, 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 one to two days. In children, the most commonly reported adverse drug reaction was vomiting.

The manufacturer's PIL for the 30/45/75mg capsules and solution gives the following advice: The most common side effects of Tamiflu are nausea, vomiting, diarrhoea, stomach ache and headache. These side-effects mostly occur only after the first dose of the medicine and will usually stop as treatment continues. The frequency of these effects is reduced if the medicinal product is taken with food.

Antibiotics

For further information please see: *Clinical management of patients with an influenza-like illness during an influenza pandemic*. Thorax, January 2007. Volume 62, supplement one. www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pneumonia/Guidelines/CAPGuideline-full.pdf

References:

PIL:

<http://emc.medicines.org.uk/medicine/10474/PIL/Tamiflu+12mg+ml+powder+for+oral+suspension/>

<http://emc.medicines.org.uk/medicine/20372/PIL/Tamiflu+30mg+and+45mg+Hard+Capsules/>

<http://emc.medicines.org.uk/medicine/10467/PIL/Tamiflu+Capsules+75mg/>

SPC:

<http://emc.medicines.org.uk/medicine/10446/SPC/Tamiflu+75mg+hard+capsule/>

Table 9 Gastrointestinal Adverse Drug Reactions (ADRs) in the oseltamivir treatment studies and in the oseltamivir prophylaxis study in children published by the manufacturer

System Organ Class (SOC) Frequency category Adverse Drug Reaction	Percentage of Patients Experiencing the ADR			
	Treatment		Treatment	Prevention
	Oseltamivir 2mg/kg bid (n = 515)	Placebo (n = 517)	Oseltamivir 30 to 75mg (n = 158)	Oseltamivir 30 to 75mg (n = 99)
Gastrointestinal disorder				
<i>Very common:</i>				
Vomiting	15%	9%	20%	10%
Diarrhoea	10%	11%	3%	1%
<i>Common:</i>				
Nausea	3%	4%	6%	4%
Abdominal pain	5%	4%	2%	1%

Reference: Abstracted from the manufacturers data published on the electronic Medicines Compendium (eMC) accessed on 19 May 2009 at <http://emc.medicines.org.uk/document.aspx?documentId=10446>.

Appendix 6

VERSION CONTROL STATEMENTS

Version Control Statement 18/12/09 *Version 5.0*

1. New guidance on use of antivirals for oseltamivir-resistant pandemic (H1N1) 2009 influenza and people in hospital who are immunocompromised.

Version Control Statement 23/11/09 *Version 4.0*

1. A change in dosage regimen for treatment as per EMEA/DH guidance:
Children up to one month of age is 2mg/kg body weight twice a day for five days.
Children over one month and up to three months of age is 2.5mg/kg body weight twice a day for five days.
Children aged over three months and up to one year of age is 3mg/kg body weight twice a day for five days.

2. Change in dosage regimen for prophylaxis in Table 6 as per EMEA/DH guidance:
Children up to one month of age is 2mg/kg body weight once a day for 10 days.
Children over one month and up to three months of age is 2.5mg/kg body weight once a day for 10 days.
Children aged over three months and up to one year of age is 3mg/kg body weight once a day for five days.

3. Added text outlining that PCTs have been asked to quarantine the 12mg in 1ml oseltamivir suspension.

4. Added text regarding issuing of new guidance on antiviral authorisation vouchers.

Version Control Statement 26/10/09 *Version 3.1*

1. Editorial consistency and house style amendments.

Version Control Statement 19/10/09 *Version 2.1 - Version 3.0*

1. Removed table on prophylaxis for higher risk groups from Appendix 1 and replaced with Table 8: Prophylaxis of people with serious underlying conditions. These changes are in line with DH policy on week commencing 12 October 2009.

Version Control Statement 5/9/09 *Version 1.2 - Version 2.0*

1. Removed advice regarding stopping treatment/prophylaxis if a negative laboratory result is obtained, as most care now based upon symptomatic diagnosis.

2. Changed treatment and prophylaxis doses of oseltamivir for children aged six months and over and under one year of age changed to 3mg/kg as per EMEA/DH recommendations in text and tables.

3. Added text outlining the DH policy of stockpiling raw ingredient powder for manufacturing of oseltamivir solution in licensed hospital pharmacy units.

4. Added references to use of DH/NHS antiviral authorisation vouchers for prescribing oseltamivir for treatment of children up to 13 years of age. Amended advice on the management of pregnant women to reflect latest DH advice.

5. Removed interim guidance on the use of oseltamivir prophylaxis in secondary schools using a fixed dose of 75mg/day as no longer required.