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

Health Protection Agency

This guidance is intended to enable health protection units (HPUs) to address local queries about the treatment and prophylaxis of influenza A(H1N1). 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_077276

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 INFLUENZA A(H1N1)

Indications

Adults and children over the age of one year

Ideally treatment to be administered within 12-48 hours of onset of symptoms. Stop treatment if a negative laboratory result is obtained. Current cases should be defined as per the **HPA case definition** available from: www.hpa.org.uk

Under 1 year of age

Children under the age of one who have symptoms of influenza should be treated with oseltamivir 2mg/kg twice a day for 5 days. Children in this age group 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, and will have low threshold for referring children to hospital clinics for further management decisions if severe or complicated influenza, or adverse effects of treatment are suspected.

Note: The HPA recommends advising clinicians to seek extra advice when prescribing for children under **2 months old**.

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.

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. In normal circumstances, these drugs are not recommended for use in pregnancy unless the benefit to the mother justifies the theoretical risk to the fetus. In the current circumstances the balance of benefit to risk supports their use and they should be provided for pregnant women. Indeed appropriate treatment of pregnant women with oseltamivir or zanamivir will help to reduce symptoms such as fever and this may benefit the developing fetus.

Zanamivir is the recommended medicine, as it is inhaled and reaches low concentrations in the blood. However, if a pregnant women has a contraindication to zanamivir, or requires a medicine which is systemically active oseltamivir should be used.

References:
- Department of Health. *Pandemic Influenza: guidance of preparing maternity services. 2008*. Available from:www.dh.gov.uk/en/Publicationsandstatistics /Publications/PublicationsPolicyAndGuidance/DH_091737.
- 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.

The UK Teratology Information Service (UK-TIS)

The UK Teratology Information Service (UK-TIS, formerly NTIS), which is a service commissioned by the HPA, 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 for her permission for her contact details to be passed on to UK-TIS who can be contacted on 0844 892 0909.

Informed consent to pass on contact details to UK-TIS should be sought. UK-TIS have 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

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

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

We have provided an example checklist with available evidence on treatment for discussion with pregnant women - see Appendix 3.

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 breast fed 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 1 below:

Under 1 year of age

The recommended dose for children under one year of age is 2mg/kg twice daily for 5 days. The Department of Health has provided the tables below regarding volumes to be administered in the under ones for different weight ranges.

There are two different preparations which can be used in this age group: one is a suspension manufactured by Roche, Tamiflu® suspension; and the other a solution of oseltamivir, which will be prepared by designated licensed hospital pharmacy manufacturing units. They are of differing concentrations and volumes; oseltamivir suspension has a strength of 12mg in 1 ml and oseltamivir solution has a strength of 15mg in 1ml; see tables below.

Note: The syringe provided in the Tamiflu® suspensions package should be discarded and replaced with a 3ml oral syringe, provided separately, to allow for administration of small volumes.

Table 2 Department of Health recommended treatment doses of oseltamivir for children under the age of one year

OSELTAMIVIR Solution 15mg in 1 ml Dose calculation based on weight and dose of 2mg/Kg		OSELTAMIVIR Suspension 12mg in 1 ml Dose calculation based on weight and dose of 2mg/Kg	
Weight Range in kg	Dose to be given in ml	Weight Range in kg	Dose to be given in ml
3.0-3.6	0.4	3.0-3.5	0.5
3.7-4.3	0.5	3.6-4.1	0.6
4.4-5.0	0.6	4.2-4.7	0.7
5.1-5.7	0.7	4.8-5.3	0.8
5.8-6.4	0.8	5.4-5.9	0.9
6.5-7.1	0.9	6.0-6.5	1.0
7.2-7.8	1.0	6.6-7.1	1.1
7.9-8.5	1.1	7.2-7.7	1.2
8.6-9.2	1.2	7.8-8.3	1.3
9.3-9.9	1.3	8.4-8.9	1.4
10-10.6	1.4	9.0-9.5	1.5
10.7-11.3	1.5	9.6-10.1	1.6
11.4-12.0	1.6	10.2-10.7	1.7
		10.8-11.3	1.8
		11.4-11.9	1.9
		12.0-12.5	2.0

(1) This dose should be given TWICE a day for five days. Please dispense only ONE of these alternative preparations.
(2) The HPA recommends advising clinicians to seek extra advice when prescribing for children under 2 months old.

Table 1 Department of Health recommended treatment doses of oseltamivir for adults and children over the age of one year

Age of patient	Weight in kg	Capsule size	Dose
Over 1 and under 3 years	Less than 15 kg	30 mg capsules	30mg twice daily for five (5) days (ONE 30mg capsule to be taken twice a day for five days)
Over 3 and under 7 years	15 to 23 kg	45 mg capsules	45mg twice daily for five (5) days (ONE 45mg capsule to be taken twice a day for five days)
Over 7 and under 13 years	23-40 kg	30 mg capsules	60mg twice daily for five (5) days (TWO 30mg capsules (total of 60mg) to be taken twice a day for five days)
Over 13 years ADULT DOSE	Over 40 kg	75 mg capsules	75mg twice daily for five (5) days (ONE 75mg capsule to be taken twice a day for five days)

(1) Ideally dose should be calculated based upon the weight of the patient, however, during a pandemic this may not be practical and the use of the age based table above is appropriate.
(2) See appendices for accompanying vouchers and labels

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

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 poorly systemically absorbed. Please also refer to zanamivir section.

Table 3 Department of Health recommended treatment dose of oseltamivir for adults with renal impairment

GFR (ml/min)	Recommended dose for oseltamivir treatment
> 30 (ml/min)	75 mg twice daily
> 10 to 30 (ml/min)	75 mg once daily, or 30 mg 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 1. 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 (1 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 have advised that **the suspension must be reserved for under 1 year olds only.**

Oseltamivir solution

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

Oseltamivir solution has a bitter taste and may require the addition of a small volume (less than 10ml) of a strongly flavoured sugary drink eg black current 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.

Note: The suspension and the solution are of differing concentrations and therefore different volumes by child's weight are required for the two preparations. Always use the correct table to determine the volume for the preparation used (Table 2).

Table 4 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.

Reference: *British National Formulary*, March 2009.

Table 5 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.

Reference: *British National Formulary for Children*, March 2009.
(1) Any adverse effect should be reported using the yellow card system.

ZANAMIVIR (Relenza®) TREATMENT

Administration, dosage and formulation

Adults and children over 5 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.

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

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

Renal impairment or patients on renal replacement therapies

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

- 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/

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

Table 6 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.

PROPHYLAXIS OF INFLUENZA A (H1N1)

Indications

Adults and children over the age of one year

Currently **the HPA algorithm should be followed to determine who needs prophylaxis,** available from: www.hpa.org.uk

Note: Stop treatment if a negative laboratory result is obtained in the suspected case.

Under 1 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.

Pregnancy

In the context of a novel influenza virus in a pandemic situation the European Medicines Agency (EMEA) suggest 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 EMEA suggest 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.
- 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

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

OSELTAMIVIR (Tamiflu®) PROPHYLAXIS

Administration and dosage schedule

See Table 7 below. The Committee for Medicinal Products for Human Use (CHMP), EMEA has reviewed the evidence for under 1 year olds and 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.

Reference:
- EMEA. *Guidance on use of antiviral medicines in the event of an influenza A/H1N1 pandemic*: www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/27353509en.pdf

Interim guidance on the use of oseltamivir prophylaxis in secondary schools

The current Department of Health guidance on dosage of oseltamivir in secondary school age children (academic years 7-11 / age 11-16 years) is covered by two recommendations:

- If child is over 7 years and under 13 years of age (expected to be in the body weight range of 23-40kg) dose is 60mg once daily for 10 days.
- If child is over 13 years (expected to be over 40kg body weight) dose is 75mg once daily for 10 days (adult dose).

This may be amended in the case of large scale prophylaxis for secondary schools in children aged 11 years and above; provided that 30mg capsules are not available, or, there is a need to enable simpler logistic arrangements to:

- All children in secondary education (national academic year 7 and above) 75 mg once daily for 10 days provided that body weight is above 23kg. If body weight is 23kg, or less, then an individually calculated dose based upon weight and age should be used.

As this is interim guidance, whenever an HPU wishes to use this amended protocol they must contact the Deputy National Incident Director (Medical) at the NECC to ensure that it is still current and that the circumstances warrant its use.

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

Table 8 Department of Health recommended prophylaxis dose of oseltamivir for adults with renal impairment

GFR (ml/min)	Recommended dose for prevention
> 30 (ml/min)	75 mg once daily
> 10 to 30 (ml/min)	75 mg every second day, or 30 mg 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 above.

Side effects

Covered in treatment section above.

ZANAMIVIR (Relenza®) PROPHYLAXIS

Administration, dosage and formulation

Inhalation of powder, adult and child over 5 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 above.

Table 7 Department of Health recommended prophylaxis doses of oseltamivir for adults and children over the age of one year

Age of patient	Weight in kg	Capsule size	Dose for treatment
Over 1 and under 3 years	Less than 15 kg	30 mg capsules	30mg once daily for ten (10) days (ONE 30mg capsule to be taken once a day for ten days)
Over 3 and under 7 years	15 to 23 kg	45 mg capsules	45mg once daily for ten (10) days (ONE 45mg capsule to be taken once a day for ten days)
Over 7 and under 13 years	23-40 kg	30 mg capsules	60mg once daily for ten (10) days (TWO 30mg capsules (total 60mg) to be taken once a day for ten days)
Over 13 years ADULT DOSE	Over 40 kg	75 mg capsules	75mg once daily for ten (10) days (ONE capsule to be taken once a day for ten days)

(1) Ideally dose should be calculated based upon the weight of the patient, however, during a pandemic this may not be practical and the use of the age based table above is appropriate.
(2) See appendices for accompanying vouchers and labels.

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

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 Comdpendium (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: Evidence relating to children aged under 1

Appendix 2: Drug interactions in the treatment of HIV infection

Appendix 3: Background information for discussion with pregnant women

Appendix 4: Supportive measures

Appendix 5: Flu response centres in England

Appendix 6: Version control statements

Appendix 1

EVIDENCE RELATING TO CHILDREN AGED UNDER 1 YEAR

During influenza seasons it is recognised that children younger than 24 months are consistently at substantially higher risk of hospitalisation than are 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 & Child health have 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. Their full statement is available on their website. Their 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 (2 mg 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 the 8th May 2009 that:

> *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 2 to 3 mg per kg body weight.*

Internal review of some of the original papers

Oseltamivir is not licensed in children under 1 year. However, Okamoto et al from Japan published a retrospective study of 103 children less than one year following an alert from Roche.

The alert:
www.fda.gov/medwatch/SAFETY/2003/tamiflu_deardoc.pdf)

The alert highlights the company's concern following preclinical trials involving deaths in immature rats. The 7-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 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.

The review by Whitley and Monto, 2006 refer to three clinical toxicology studies which had identified neurotoxicity in newborn rats administered oseltamivir. They point out that the dosage used was higher that that used for humans and that the metabolism of oseltamivir in rats differs to that of humans.

References:

1. The RCPCH consensus statement available from: www.rcpch.ac.uk/Research/CE/Guidelines-frontpage/Guideline-Appraisals-by-Topic/practice-statements
2. 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
3. Committee on Infectious Diseases. *Prevention of Influenza: Recommendations for Influenza Immunization of Children*, 2007–2008. Pediatrics 2008;121;e1016-e1031,
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
5. Okamoto, S, Kamiya, I, *et al. Experience with Oseltamivir for Infants Younger Than 1 Year Old in Japan.* The Pediatric Infectious Diseases Journal June 2005; Vol 24 (issue 6):575-5
6. Roche Pharmaceuticals. Alert letter December 2003. Available from: www.fda.gov/medwatch/SAFETY/2003/tamiflu-deardoc.pdf

Appendix 2

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 stand on the 19th 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 ~2-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)
- 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.

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

Appendix 3

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 are 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 occuring 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 Influenza A(H1N1)?

Refer to the pregnancy section above.

- The currently circulating influenza A(H1N1) 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 Influenza A(H1N1)?

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 3 continued

Risk to the fetus

- There are 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 the adverse foetal 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.

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Appendix 4

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 CSM 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 breast feeding.

Reference: *British National Formulary*, March 2009.

Management of gastro-intestinal symptoms associated with oseltamivir

The occurrence of gastro-intestinal symptoms in association with the use of oseltamivir in prophylaxis and treatment schedules is a well recognised problem which 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 1-2 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 1. Available from: http://thorax.bmj.com/content/vol62/suppl_1/

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/

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 2 mg/kg bid (n = 515)	Placebo (n = 517	30 to 75 mgb Oseltamivir 30 to 75 mgb (n = 158)	Oseltamivir 30 to 75 mgb (n = 99)
Gastrointestinal disorder				
Very Common:				
Vomiting	15 %	9 %	20 %	10 %
Diarrhoea	10 %	11 %	3 %	1 %
Common:				
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.

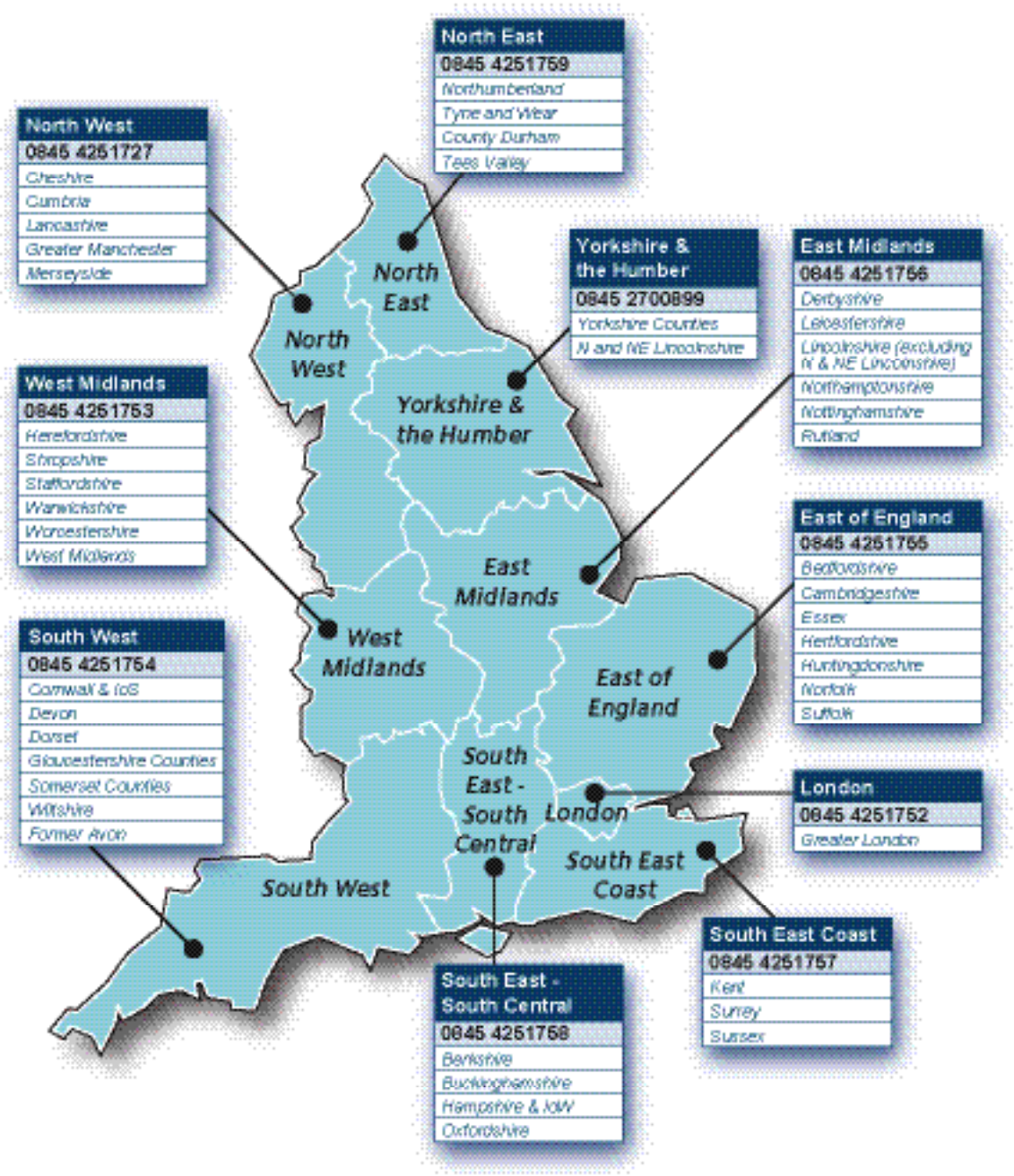
Appendix 5

FLU RESONSE CENTRES IN ENGLAND

Flu response centres (FRCs) have been established in each region of England to receive calls from health professionals regarding patients with flu-like illness and their contacts.

FRCs undertake the assessment of patients, arrange with GPs and others for samples to be taken for laboratory diagnosis, identify and follow up contacts and arrange for prophylaxis to be given where appropriate.

Regional FRC name	Contact number
North West Flu Response Centre	0845 4251727
London Flu Response Centre	0845 4251752
West Midlands Flu Response Centre	0845 4251753
South West Flu Response Centre	0845 4251754
East of England Flu Response Centre	0845 4251755
East Midlands Flu Response Centre	0845 4251756
Yorkshire and the Humber Flu Response Centre	0845 2700899
North East Flu Response Centre	0845 4251759
South East Coast Flu Response Centre	0845 4251757
South East - South Central Flu Response Centre	0845 4251758



Appendix 6

VERSION CONTROL STATEMENTS

Version Control Statement 22/5/9. Version 1.0-Version 1.1

1. Name of UK-TIS (UK Teratology Information Service) abbreviated consistently as *UK-TIS* rather than UK TIS.

2. Spelling standardised from foetus to fetus throughout document.

3. Additional paragraph added to Appendix 7 from the Oseltamivir Summary of Product Characteristics reflecting a change in their wording: *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 1-2 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.

   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/

   This replaces previous text: *The official Summary of Product Characteristics for Tamiflu® clearly recognises nausea and vomiting as a "very common" side-effect in adults and in children and vomiting abdominal pain, diarrhoea and dyspepsia as common side effects, supported by data from the clinical trials database. The tables below shows the most frequently reported ADRs from clinical trials (abridged to show only GI disorder.*

   To control these side-effects the manufacturer recommends that although Oseltamivir can be taken without food, it is recommended that it is taken with food to reduce the chance of nausea and vomiting occurring.

4. Wording changed in Appendix 5 to more accurately reflect its contents: 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

5. Spelling changed of Nucleoside Reverse Transcriptase Inhibitor (NRTI) in Appendix 5.

6. On page 7, in list of appendices, title of Appendix 5 changed from: *Drug interactions with antiretrovirals* to Drug interaction in the treatment of HIV infection.

7. Title of Appendix 4 changed from Pharmacy labels for *oseltamivir capsules* to Pharmacy Labels for treatment dosing.

8. Title of Appendix 8 *Summary of recommendations for treatment/prophylaxis in all groups* deleted as this Appendix no longer present.

9. New Appendix 8 created with title of *Version Control Statements.*

10 In Appendix 5 statement *Refer to patient information leaflet and or SPC* made bold on request of manufacturer.

11. In Appendix 5 in sentence *patient information leaflet and or SPC, patient information leaflet* abbreviated to PIL for consistency throughout document and wording changed to and rather than and or

12. Trade names removed from Page 4 and table on Page 6 to ensure consistent generic pharmaceutical naming.

13. Table on page 6 ammended with references to correct table numbers for doses (Should read: Table 7-prophylaxis for adults and children over the age of 1, Table 8- prophylaxis for those with renal impairment)

14. Appendix 4, page 11 given new title: *Pharmacy Labels for treatment dosing.*

Version Control Statement 28/5/9 Version 1.1-Version 1.2

1. Page 1, section 'Under 1 year of age', added the dose to the treatment indication to read '... Children under the age of one who have symptoms of influenza should be treated with oseltamivir 2mg/kg twice a day for 5 days.'

2. Page 2, section 'OSELTAMIVIR (Tamiflu(r)) TREATMENT', subsection 'Under 1 year of age', sentence in first paragraph expanded to read '...The Department of Health has provided the tables below regarding volumes to be administered in the under ones for different weight ranges.'

3. Page 2, section 'OSELTAMIVIR (Tamiflu(r)) TREATMENT', subsection 'Under 1 year of age', second paragraph

Appendix 6 continued

ammended to read '...There are two different preparations which can be used in this age group: one is a suspension manufactured by Roche, Tamiflu® suspension; and the other a solution of oseltamivir, which will be prepared by designated hospital pharmacy licensed manufacturing units. They are of differing concentrations and volumes; oseltamivir suspension has a strength of 12mg in 1 ml and oseltamivir solution has a strength of 15mg in 1ml; see tables below.

4. Page 3, section 'Formulations', subsection 'Osletamivir solution', paragraph ammended to read '... A solution of oseltamivir 15mg in one ml is being prepared by designated licensed hospital pharmacy manufacturing units...' and '... Oseltamivir solution has a bitter taste and may require the addition of a small volume (less than 10ml) of a strongly flavoured sugary drink e.g. blackcurrant squash, to help very young children to tolerate the medicine.

5. Section 'ZANAMAVIR (Relenza(r)) TREATMENT', subtitle changed to read '...Adults and children over 5 years...'

6. Page 4, section 'Renal impairment or patients on renal replacement therpaies', note ammended to read '... Note: Paediatric patients with severe renal impairment are not covered by this guidance. Seek specialist advice in all cases.'

7. Page 4, section 'Indications', subsection 'Under 1 year of age', ammended to read '... A decision on whether prophylaxis with oseltamivir should be recommended should be taken by an expert in the care of young children.'

8. Appendix 2, 'General practitioner/delegated healthcare professional authorisation voucher for adults and children aged 1 year and older' removed.

9. Appendix 3, 'General practitioner/delegated healthcare professional authorisation voucher for children aged less than 1 year' removed.

10. Appendix 4, 'PHARMACY LABELS FOR TREATMENT DOSING' removed.

11. Appendices 5-8 renumbered following removal of appendixes 2 and 3.

12. Appendix 6, section 'Risk to the fetus', paragraph 5 ammended for readability to '... During the first trimester of pregnancy the risk of congenital anomalies occuring may be reduced by the administration of antipyretics.'

13. Added appendix, above version control statements, with description of the purpose of, and contact details for flu response centres in England.

14. Change of name and removal of prescribing table to reflect end of containment phase.