

**PROPOSAL FOR THE INCLUSION OF OSELTAMIVIR PHOSPHATE FOR THE
PREVENTION AND TREATMENT OF AVIAN INFLUENZA (H5N1) IN THE WHO
MODEL LIST OF ESENTIAL MEDICINES**

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1 Summary statement of the proposal

Oseltamivir phosphate is proposed for inclusion in the World Health Organisation (WHO) Model List of Essential Medicines (EML) for the prevention and treatment of avian influenza (H5N1).

2 Name of focal point in WHO submitting or supporting the application

3 Name of the organisation consulted and/or supporting the application

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4 International Nonpropriety Name (INN, generic name) of the medicine

INN: Oseltamivir phosphate

Chemical name: Ethyl (3R,4R,5S)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate phosphate (1:1)

5 Formulation proposed for inclusion

Capsules: 75 mg (10 pack)

Oral Suspension: 12 mg / 1ml – 100 ml (powder for reconstitution)

6 International availability – sources, if possible manufactures (Appendix A)

Oseltamivir phosphate is marketed by the Pharmaceutical Division of Hoffmann-La Roche and its international subsidiary companies as part of the Roche Group (Roche Holding Ltd). A detailed list of manufacturers and distributors is presented in Appendix A.

7 Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested on the Model List of Essential Medicines (EML) as an individual medicine.

8 Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

8.1 Global burden of disease

The World Health Organisation (WHO) estimates that epidemics of influenza result in 3-5 million cases of severe illness and between 250,000 to 500,000 deaths every year.¹ In the United States (US) alone influenza viruses are responsible for 20,000 to 50,000 deaths and up to 300,000 hospitalisations each year.^{2,3} In the United Kingdom (UK) it is estimated that yearly influenza epidemics cause between 12,000 to 13,800 deaths.⁴ Studies conducted across Europe have shown the influenza-associated seasonal excess mortality to be 16 per 100,000 of the population in Germany, 14 per 100,000 of the population in the Netherlands, and 21.6 per 100,000 of the population in Switzerland.⁵ However, in the developing world much less is known about the impact of influenza.¹

In contrast to influenza epidemics, influenza pandemics are rare events that occur every 10 to 50 years.⁶ Pandemics originate with the emergence of a new subtype of influenza virus which is able to cause disease, replicate in humans, and spread efficiently from person to person.⁷ The first influenza pandemic was described in 1580 and since then at least 31 influenza pandemics have been recorded. During the last century, three influenza pandemics occurred –

the ‘Spanish flu’ pandemic of 1918-19 was responsible for 20-40 million deaths, while the ‘Asian flu’ pandemic in 1957 and the ‘Hong Kong flu’ in 1968 each caused an estimated 1-4 million deaths.⁷ Although the next influenza pandemic is expected to cause clinical disease in two billion people estimates of the death toll and the number of people that will require hospitalisation are less precise.⁶ However, it has been estimated that a pandemic similar to the 1918 pandemic may lead to 10 million hospitalisations and 1.7 million deaths in the United States alone.⁸ Scenarios modelled on the mild pandemic of 1968, anticipate that there will be between 2 million and 7.4 million cases of influenza. However, if the death toll associated with the 1918 influenza virus is translated to the current world population of 6.5 billion, there could be 180 million to 360 million deaths globally (Table 8.1.1).³

Table 8.1.1: Death toll in the 20th century pandemics and future projections

Year	Population	Death toll	per 100,000 people
1918	1.8 billion	50 million	2,777
1957	3.8 billion	1 million	26
1968	4.5 billion	1 million	27
Next	6.5 billion	1.7 - 180 million	26 - 2,777

Source: Kamps *et al.*(2006)⁶ – Influenza Report 2006 (www.InfluenzaReport.com).

Human influenza viruses are members of the Orthomyoviridae family.⁶ Influenza A, B, and C are the most important genera of the Orthomyoviridae family, and are responsible for causing pandemic and seasonal disease in humans.⁹ The currently circulating influenza viruses that cause human disease are influenza A and B – the former (influenza A) being the most virulent of the two.^{1,10} The main antigenic determinants of influenza A and B viruses are the transmembrane glycoproteins: haemagglutinin (H or HA) and neuraminidase (N or NA).⁶ Haemagglutinin is a lectin that mediates the binding of the virus to target cells and entry of the viral genome into the target cell. Neuraminidase is an enzyme involved in the release of progeny virus from infected cells, by cleaving sugars that bind the mature viral particles.¹⁰ Based on the antigenicity of these glycoproteins, influenza A viruses are further subdivided into sixteen H (H1 – H16) and nine N (N1 – N9) subtypes. The full nomenclature for influenza virus isolates requires connotation of the influenza virus type (A or B), the host species (omitted if human in origin), the geographical site, serial number, year of isolation, and lastly, the H and N variants in brackets (e.g. A/goose/Guangdong/1/96 (H5N1)).⁶

Influenza A viruses are enveloped, single-stranded RNA viruses with a segmented genome.⁹ The eight RNA segments of the influenza A virus genome encode 11 viral proteins: the polymerase proteins (PB1, PB2, PA, PB1-F2), nucleocapsid protein, haemagglutinin, neuraminidase, matrix proteins (M1, M2), and non-structural proteins (NS1, NS2).¹¹ Molecular changes in the RNA genome occur via two main mechanisms: point mutation (antigenic drift) and RNA segment reassortment (antigenic shift).^{9,10} Point mutations cause minor changes in the antigenic character of viruses, whereas reassortment occurs when a host cell is infected with two or more influenza A viruses, leading to the creation of a novel subtype.⁹ Animal viruses can improve their transmissibility in humans by adaptive mutation or genetic reassortment (i.e. the mixing of animal and human viruses).⁷ Recent studies have confirmed that the 1918-19 pandemic was caused by a H1N1 virus which is believed to have originated from the reassortment of avian and human viruses. However, it has been proposed that 1918-19 influenza virus was not a reassortant virus but more likely an entirely avian-like virus that adapted to humans.¹² The pandemic strains, H2N2 in 1957 (‘Asian flu’) and H3N2 in 1968 (‘Hong Kong flu’), were reassortant viruses containing genes from avian viruses (Table 8.1.2): three in 1957 (haemagglutinin, neuraminidase, and the RNA polymerase PB1) and two (haemagglutinin and PB1) in 1968.⁶

Table 8.1.2: Antigenic shifts and the impact of past pandemics

Year	Designation	Resulting pandemic	Death toll
1889	H3N2	Moderate	?
1918	H1N1 ('Spanish flu')	Devastating	50 million
1957	H2N2 ('Asian flu')	Moderate	1 million
1968	H3N2 ('Hong Kong flu')	Mild	1 million

Source: Kamps *et al.* (2006)⁶ – Influenza Report 2006 (www.InfluenzaReport.com).

Avian influenza (H5N1) virus poses the most likely pandemic threat.¹³ The avian H5N1 strain has become endemic in wild waterfowl and in domestic poultry in many parts of Southeast Asia, and is spreading across Asia into Europe and Africa.⁶ Recent research has revealed that just 10 amino acid alterations in the polymerase proteins differentiate the 1918-19 influenza virus sequences from that of avian viruses, and that a number of the same changes have been identified in recently circulating, highly pathogenic H5N1 viruses.¹² However, to date the H5N1 avian influenza remains largely a disease of birds. This is evident in the fact that despite the infection of tens of millions of poultry over large geographical areas for more than two years, fewer than 200 human cases have been confirmed by a laboratory.¹⁴ The first human cases of avian influenza in Hong Kong in 1997 coincided with outbreaks of highly pathogenic H5N1 avian influenza in poultry.¹⁵ Of the 18 people identified with H5N1 disease, six died.⁸ Although H5 antibodies were detected in healthcare workers and family members with contact, indicating infection with the virus, no cases of severe disease occurred.⁶ To date, episodes of avian influenza have occurred in individuals or communities with close links with poultry, but none has occurred where human-to-human transmission was implicated beyond doubt.¹⁵

As of April 11, 2007, 317 human cases of H5N1 infection had been reported to the WHO (Table 8.1.3), mostly as a result of close contact between humans and infected birds.¹⁶ To date, the disease has predominantly affected children and young adults.¹⁴ Of 116 patients for whom demographical data had been published by the WHO (December 2003 until 9 February 2006), 50% were 16 years old or younger, 75% were younger than 30 years, and 90% were younger than 40 years old. Whether, and to what extent, genetic composition plays a role in the susceptibility and resistance to infection with H5N1 influenza virus remains unknown.⁶

To date, the majority of human H5N1 cases have been reported in Asian countries, in particular, Cambodia, China, Indonesia, Thailand, and Viet Nam (Fig.8.1.1). Extensive studies and investigations have identified direct contact with infected birds as the most likely source of exposure of all the most recently confirmed human cases of H5N1, in China, Indonesia, and Turkey.¹⁴ The cumulative number of confirmed human cases of avian influenza A (H5N1) reported to WHO (to 11 April 2007) is summarised in Table 8.1.3. The number of confirmed cases of H5N1 infected poultry (to 30 April 2007) is presented in Figure 8.1.2.

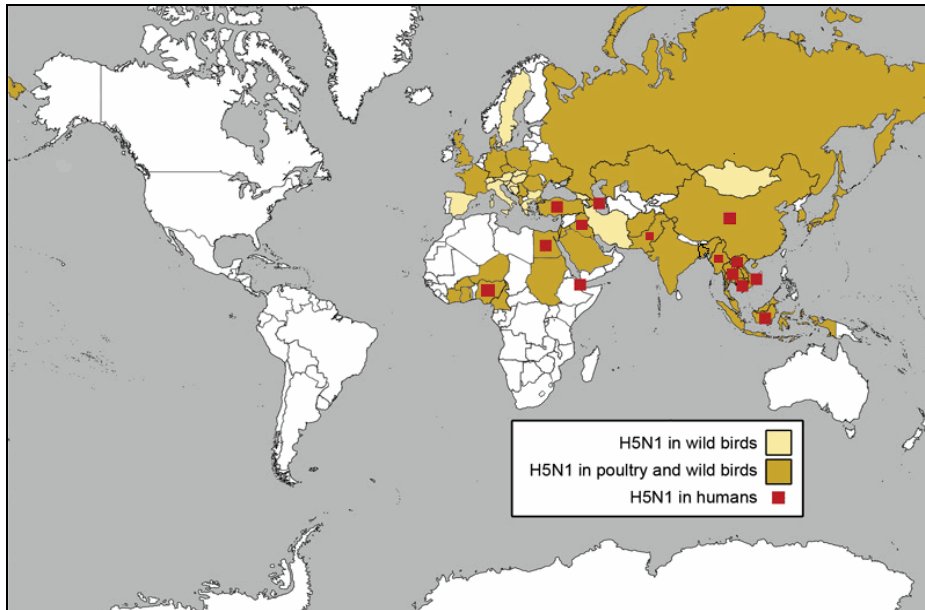


Figure 8.1.1 Nations with confirmed cases of avian influenza (H5N1).

Source: <http://www.pandemicflu.gov/>

Table 8.1.3: Cumulative number of confirmed human cases of avian influenza A (H5N1) reported to WHO (11 April 2007)

Country	2003		2004		2005		2006		2007		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Azərbayjan	0	0	0	0	0	0	8	5	0	0	8	5
Cambodia	0	0	0	0	4	4	2	2	1	1	7	7
China	1	1	0	0	8	5	13	8	3	2	25	16
Djibout	0	0	0	0	0	0	1	0	0	0	1	0
Egypt	0	0	0	0	0	0	18	10	19	5	37	15
Indonesia	0	0	0	0	20	13	55	45	26	22	101	60
Iraq	0	0	0	0	0	0	3	2	0	0	3	2
Lao PDR	0	0	0	0	0	0	0	0	2	2	2	2
Nigeria	0	0	0	0	0	0	0	0	1	1	1	1
Thailand	0	0	17	12	5	2	3	3	0	0	25	17
Turkey	0	0	0	0	0	0	12	4	0	0	12	4
Viet Nam	3	3	29	20	61	19	0	0	0	0	95	42
Total	4	4	46	32	98	43	115	79	54	33	317	191

Total number of cases includes number of deaths. WHO reports only laboratory-confirmed cases. All dates refer to onset of illness.

Source: McFee (2007)¹⁷

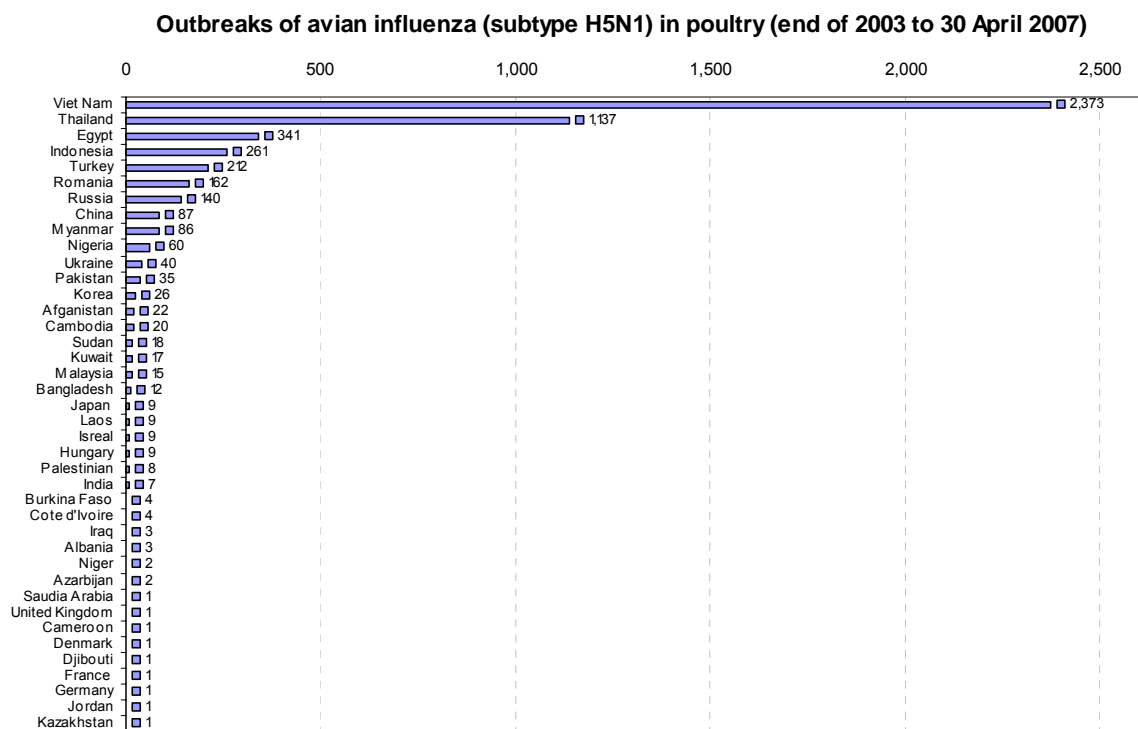


Figure 8.1.2 Worldwide outbreaks of avian influenza (H5N1).

Source: McFee (2007)¹⁷

8.2 Clinical features of avian influenza (H5N1) in humans

The H5N1 serotype, first diagnosed in Hong Kong in 1997, is the only avian influenza strain to cause repeatedly severe disease in humans. Although the number of human cases to date has been relatively low, the case-fatality rate is high (~60%).¹⁶ The clinical manifestations of avian influenza (H5N1) infection in humans ranges from asymptomatic to fatal pneumonitis and multi-organ failure.⁶

The WHO avian influenza fact sheet (February 2006)¹⁴ states that the incubation period for H5N1 avian influenza may be longer than that of normal seasonal influenza (i.e. 2-3 days), with current data for H5N1 infection indicating an incubation period ranging from 2-8 days and possibly as long as 17 days. However, the WHO currently recommends that an incubation period of seven days be used for field investigators and the monitoring of patient contacts.¹⁴ The initial symptoms of avian influenza include a high fever, frequently with a temperature higher than 38°C, and general influenza-like symptoms, such as cough, sore throat, rhinitis, malaise, fatigue, headache, and myalgia. However, fever and cough were found to be the most common presenting initial symptoms in human cases of H5N1 infection during the more recent outbreaks in Hong Kong, Viet Nam, Thailand, and Cambodia.¹⁷ The WHO reports that diarrhoea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums can also present as early symptoms of avian influenza.¹⁴ Watery diarrhoea without the presence blood is also more common in H5N1 avian influenza than in normal seasonal influenza. Avian influenza can also affect the central nervous system, causing seizures or acute encephalitis.^{14,17}

The WHO avian influenza fact sheet (February 2006)¹⁴ states that not all confirmed cases of H5N1 infection have presented with respiratory symptoms. However, on present evidence, difficulty in breathing develops around five days following the first symptoms. Respiratory

distress, a hoarse voice, and a crackling sound when inhaling are common findings. Sputum production is variable and occasionally bloody, with almost all patients developing pneumonia. Laboratory findings of cases with severe avian influenza H5N1 include leucopenia, lymphopenia, mild-to-moderate thrombocytopenia, impaired liver function with elevated liver enzymes, prolonged clotting times, and renal impairment.^{6,14} Chest radiographs are abnormal with the presence of interstitial infiltration, and patchy lobar infiltrates in a variety of patterns (i.e. single lobe, multiple lobes, unilateral or bilateral distributions). As the illness progresses clinical features compatible with Adult Respiratory Distress Syndrome (ARDS) are evident.⁶ A summary of the key differentiating symptoms of avian influenza compared with seasonal influenza are presented in Figure 8.2.1.

Is it? Number of "+" indicates strength of association	Avian Flu (H5N1)	Seasonal Influenza (Flu)	Upper Respiratory Infection	Common Cold
Elevated temp	+++ /++++	++	++	+/-
Fever/chills	++++	++++	++++	
Cough	+++	+++	+++	+++
Shortness of breath	++++	+/-	+/-	
Chest discomfort	+++	++	++	
Sore throat	+/-	+++	+++	++
Vomiting/nausea	++	+	+	-
Diarrhea	++	+ (young children)	+/-	-
CNS/encephalopathy/seizures	++	-	-	-
Malaise/fatigue	+++	+++	+	+/-
Runny nose/watery eyes	+/-	+	++	+++
Headache/muscle ache	+++	+++	++	+/-
Young healthy at risk for serious illness	+++	+/-	+/-	-

Figure 8.2.1 Summary of the key differentiating symptoms of avian influenza compared with seasonal influenza.

Source: McFee (2007)¹⁷

8.3 Economic impact of avian influenza

The CDC (United States Centers for Disease Control) estimated that the economic impact of an avian influenza pandemic could exceed US\$160 billion.¹⁷ A study conducted by the US Congressional Budget Office (CBO), and published on the 8th December 2005, examined the possible macroeconomic effects that an influenza pandemic would have on the United States.¹⁸ Under assumptions based on the 1918-19 influenza pandemic, this study estimated that the consequences of a severe pandemic in the United States could include 200 million infected people, 90 million clinically ill, and two million dead. To calculate the supply impact of a severe pandemic, this study assumed that 30% of all workers would become ill and 2.5% would die, with 30% of workers missing an average of three weeks of work, resulting in a 5% decrease in the gross domestic product (GDP). With an estimated 18-45 million people requiring outpatient care, the economic costs could total US\$675 billion.^{13,18} In general terms, McFee (2007)¹⁷ claims that an avian influenza pandemic would cause incalculable losses in life, animal and human, economic burdens ranging from losses in tourism to severe deprivation resulting from the impact on food supplies, commerce, trade, and worker availability.

8.4 Prophylaxis and treatment of avian influenza (H5N1)

The most effective interventions reported to reduce influenza morbidity and mortality are vaccination and the use of antiviral drugs.⁷ Although vaccines are the most effective way to reduce the impact of a pandemic, human H5N1 vaccines are a relatively new development and information on their safety, immunogenicity, and their protective effects is relatively limited.¹⁹ However, on 21 February 2008, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending to grant marketing authorisation for the pre-pandemic, split virion, inactivated, influenza vaccination Prepandrix™ (ATC Code J07BB02).²⁰ This decision by the European Medicines Agency (EMA) means that the GlaxoSmithKline (GSK) Prepandrix™ is the first vaccine to receive a licence for pre-pandemic use in all 27-member European states.²¹ The approved indication for Prepandrix™ is: active immunisation against H5N1 subtype of influenza A virus.²⁰

In the case of the antiviral drugs, there are two classes available to treat avian influenza: neuraminidase inhibitors (oseltamivir and zanamivir), and adamantanes (M-blockers - amantadine and rimantadine). Although these antiviral agents were developed for the treatment and prophylaxis of seasonal influenza, oseltamivir is claimed to reduce the duration of viral replication and improve prospects of survival in cases of avian influenza.¹⁴ However, the recent emergence of oseltamivir-resistant variants is a matter of concern.^{22,23} Therefore, it is important and timely, to examine the efficacy, safety, and cost-effectiveness of oseltamivir phosphate in the treatment and prophylaxis of avian influenza in adults and children.

8.5 Oseltamivir phosphate – neuraminidase inhibitor

Oseltamivir phosphate is approved for use in 80 countries worldwide.²⁴ Oseltamivir phosphate is FDA approved for the treatment and prophylaxis of influenza A and B.²⁵

Pharmacodynamics

The PI for oseltamivir phosphate (Tamiflu®)²⁶ states:

Oseltamivir phosphate is a pro-drug of the active metabolite, oseltamivir carboxylate. The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase is essential for the release of recently formed virus particles from infected cells and the further spread of infectious virus in the body. A study in cultured tracheobronchial epithelial cells and primary nasal epithelial cells has shown that oseltamivir may also suppress virus entry to cells. The active metabolite inhibits neuraminidases of influenza viruses of both types A and B. Inhibitory concentrations *in vitro* are in the low nanomolar range. The 50% inhibitory concentration (IC₅₀) was in the range of 0.1 to 2.6 nM. The relationship between the *in vitro* antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established. The active metabolite also inhibits influenza virus infection and replication *in vitro* and inhibits influenza virus replication and pathogenicity in animal models.

Pharmacokinetics

The PI for oseltamivir phosphate (Tamiflu®)²⁶ states:

Oseltamivir is absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is converted predominantly by hepatic esterases to the active metabolite. In multiple dose studies the peak concentration of the active metabolite occurs 2 to 3 hours after dosing. Following an oral dose of 75 mg twice daily the peak concentration (C_{max}) of the active metabolite is approximately 350 - 400 ng/mL. At least 75% of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5% relative to the active metabolite. Plasma concentrations of the active metabolite are unaffected by co-administration with food. The active metabolite reaches all key sites of influenza infection as shown by studies in the ferret, rat and rabbit. In these studies, anti-viral concentrations of the active metabolite were seen in the lung, broncho-alveolar lavage, nasal mucosa, middle ear and trachea, following oral administration of oseltamivir phosphate. The mean volume of distribution

(V_{ss}) of the active metabolite is approximately 23 L in humans. The binding of the active metabolite to human plasma protein is negligible (approximately 3%). Oseltamivir is extensively converted to the active metabolite by esterases located predominantly in the liver. Neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. Thus interactions mediated by competition for these enzymes are unlikely. Absorbed oseltamivir is primarily (>90%) eliminated by conversion to the active metabolite. Peak plasma concentrations of the active metabolite decline with a half-life of 6 hours to 10 hours in most subjects. The active metabolite is not further metabolised and is eliminated entirely (>99%) by renal excretion. Renal clearance (18.8 L/hr) exceeds glomerular filtration rate (7.5 L/hr) indicating that tubular secretion (via the anionic pathway) in addition to glomerular filtration occurs. Less than 20% of an oral radio-labelled dose is eliminated in faeces.

9 Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

9.1 Indications for use

Oseltamivir phosphate (Tamiflu[®]) has regulatory approval for the treatment and prophylaxis of influenza viruses Types A and B (United States FDA approved,²⁵ and Australia TGA approved²⁷). Oseltamivir phosphate received US FDA approval in November 2000. Oseltamivir phosphate has not gained FDA approval for use in avian influenza. The National Institute for Clinical Excellence (NICE) guidance for the prophylaxis and treatment of influenza with oseltamivir phosphate of influenza A or influenza B is presented in Table 9.1.1.

Table 9.1.1: NICE guidance for the prophylaxis and treatment of influenza with oseltamivir

NICE guidance (February and September 2003)

- Oseltamivir is not recommended for seasonal prophylaxis against influenza;
- Oseltamivir is not recommended for post-exposure prophylaxis, or treatment of otherwise healthy individuals with influenza;
- Oseltamivir is recommended for post-exposure prophylaxis in at-risk adults and adolescents over 13 years who are not effectively protected by influenza vaccine and who can commence oseltamivir within 48 hours of close contact with someone suffering from influenza-like illness ; prophylaxis is also recommended for residents in care establishments (regardless of influenza vaccination) who can commence oseltamivir within 48 hours if influenza-like illness is present in the establishment;
- Oseltamivir is recommended (in accordance with UK licensing) to treat at-risk adults who can start treatment within 48 hours of the onset of symptoms; oseltamivir is recommended for at-risk children who can start treatment within 48 hours of the onset of symptoms.

At-risk patients include those aged over 65 years or those who have one or more of the following conditions:

- Chronic respiratory disease (including chronic obstructive pulmonary disease and asthma);
- Significant cardiovascular disease (excluding hypertension);
- Chronic renal disease;
- Immunosuppression;
- Diabetes mellitus.

Source: British National Formulary, 55th edition (2008)²⁸

As stated in the Product Information (Roche, 20 February, 2008),²⁶ Tamiflu[®] (oseltamivir phosphate – capsules and oral suspension) is indicated for the treatment of infections due to influenza A and B viruses in adults and children aged 1 year and older. Treatment should commence as soon as possible, but no later than 48 hours after the onset of the initial symptoms of infection. Tamiflu[®] (oseltamivir phosphate – capsules and oral suspension) is

also indicated for the prevention of influenza in adults and children aged 1 year and older. The PI for Tamiflu[®] states that vaccination is the preferred method of routine prophylaxis against infection with influenza virus.²⁶

9.2 Dosage regimens

Treatment of influenza – Adults and adolescents

The Product Information (Roche, 20 February, 2008),²⁶ for Tamiflu[®] (oseltamivir phosphate – capsules and oral suspension) recommends treatment should begin within the first or second day of onset of symptoms of influenza. The recommended oral dose of Tamiflu[®] capsules in adults and adolescents 13 years of age and older is 75 mg twice daily, for 5 days. Adults and adolescents 13 years of age and older who are unable to swallow capsules may receive a dose of 75 mg Tamiflu[®] suspension twice daily for five days.²⁶

Treatment of influenza – Paediatrics

The recommended oral dose of Tamiflu[®] oral suspension for paediatric patients one year and older or adult patients who cannot swallow a capsule is presented in Table 9.2.1.

Table 9.2.1: Recommended paediatric dosages – influenza treatment

Body weight in kg	Recommended dose for 5 days
≤15 kg	30 mg twice daily
>15 to 23 kg	45 mg twice daily
>23 to 40 kg	60 mg twice daily
>40 kg	75 mg twice daily

Source: Product Information (Roche, 20 February, 2008)²⁶

An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg doses. The Product Information (Roche, 20 February, 2008)²⁶ for Tamiflu[®] recommends that patients use this dispenser. Paediatric patients weighing > 40 kg who are able to swallow capsules, may also receive treatment with a 75 mg capsule twice daily as an alternative to the recommended dose of Tamiflu[®] suspension.²⁶

Prophylaxis of influenza - Adults and adolescents

The Product Information (Roche, 20 February, 2008)²⁶ for Tamiflu[®] (oseltamivir phosphate – capsules and oral suspension) recommends an oral dose of 75 mg once daily for 10 days of Tamiflu[®] for prevention of influenza following close contact with an infected individual. Therapy should begin within two days of exposure. The recommended dose for prevention during a community outbreak of influenza is 75 mg once daily. The Product Information (PI) claims that the safety and efficacy of Tamiflu[®] have been demonstrated for up to six weeks, and that the duration of protection lasts for as long as dosing is continued.²⁶

Prophylaxis of influenza - Paediatrics

The Product Information (Roche, 20 February, 2008)²⁶ for Tamiflu[®] recommends that children weighing > 40 kg, who are able to swallow capsules, may also receive prophylaxis with a 75 mg capsule once daily for 10 days as an alternative to the recommended dose of Tamiflu[®] suspension. The recommended prophylactic oral dose of Tamiflu[®] suspension for children ≥1 year of age is presented in Table 9.2.2.

Table 9.2.2: Recommended paediatric dosages – influenza prophylaxis

Body weight in kg	Recommended dose for 10 days
≤15 kg	30 mg once daily
>15 to 23 kg	45 mg once daily
>23 to 40 kg	60 mg once daily
>40 kg	75 mg once daily

Source: Product Information (Roche, 20 February, 2008)²⁶

A dosing syringe marked with 30 mg, 45 mg and 60 mg dosing levels is provided. The PI recommends that Tamiflu[®] powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient.²⁶

9.2.1 Dose adjustments

The PI for Tamiflu[®] states that no dose adjustment is required for patients with hepatic dysfunction in the treatment or prevention of influenza (Child-Pugh score ≤9). In the treatment of influenza the PI states that no dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. However, in patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose be reduced to 75 mg of Tamiflu[®] once daily, for 5 days. Tamiflu[®] should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤10 mL/min.²⁶

In the case of influenza prophylaxis, the PI for Tamiflu[®] states that no dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. However, in patients with creatinine clearance between 10 and 30 mL/min receiving Tamiflu[®] it is recommended that the dose be reduced to 75 mg of Tamiflu[®] every other day. Tamiflu[®] should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤10 mL/min.²⁶

The PI states that, as the safety and efficacy of prophylactic Tamiflu[®] have not been established in children aged less than 1 year of age, Tamiflu[®] should not be used in children under 1 year of age.²⁶ No dose adjustment is required for geriatric patients in the treatment or prevention of influenza unless there is co-existent renal impairment (aged ≥ 65 years).²⁶

9.3 Patient monitoring

Patients should be advised to report any adverse event when using Tamiflu[®]. The following adverse events have been identified during post-marketing use of Tamiflu[®] (oseltamivir phosphate):

- Swelling of the face or tongue, allergy, anaphylactic/anaphylactoid reactions;
- Dermatitis, rash, eczema, urticaria, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN);
- Hepatitis, abnormal liver function tests;
- Cardiac arrhythmias;
- Gastrointestinal bleeding, haemorrhagic colitis;
- Seizures, delirium, including altered levels of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares;
- Aggravation of diabetes mellitus.

9.4 Reference to existing WHO and other clinical guidelines

The WHO and NICE recommend the use of oseltamivir phosphate in the treatment and prophylaxis of influenza using the doses recommended in the product information.^{14,28}

However, in the case of avian influenza (H5N1) the WHO suggests that clinicians should consider increasing the duration of treatment with oseltamivir phosphate to 7-10 days in patients who do not show a clinical response.¹⁴ The WHO also suggests that in cases of severe H5N1 infection, clinicians may need to increase the recommended daily dose or the duration of treatment, being mindful that doses of oseltamivir phosphate above 300 mg per day are associated with increased side effects.¹⁴

9.5 Need for special diagnostic or treatment facilities and skills

As Tamiflu[®] (oseltamivir phosphate) is self-administered by the patient (oral capsule or liquid suspension) no special treatment facilities or skills are needed for the purposes of drug administration.

In the case of avian influenza the WHO suggests that consideration should be given to the taking of serial clinical samples of all treated patients where there are appropriate measures for infection control, to monitor for changes in viral load, to assess drug susceptibility, and to assess drug levels.¹⁴ However, such measures may not be feasible or practical in the case of a pandemic (e.g. logistical and financial constraints).

10 Summary of comparative effectiveness in a variety of clinical settings

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

MEDLINE (via PubMed: 1950 to June 2007) and the Cochrane Library (Issue 2, 2007) were searched to identify systematic, critical, and narrative reviews, randomised clinical trials, health technology assessments (HTA), economic evaluations, *in vitro* studies, animal studies, and case series/reports in which oseltamivir phosphate was the antiviral drug studied (either as a single agent or in combination with another antiviral therapy). The reference lists of identified trials, reviews, reports and guidelines were thoroughly searched for any potentially relevant studies. Experts in the field were also contacted to identify any unpublished studies or reports.

Information from any influenza strain believed to be potentially relevant to H5N1 in the animal and *in vitro* studies was included (i.e. the studies provided information on the likelihood of H5N1 resistance to antivirals). Studies employing computer-modelling techniques were not included because these types of studies were considered beyond the scope of this project. Where genetic analysis studies were identified from *in vitro* or animal searches, they were included only if the studies documented actual drug-resistance mutations in H5N1 virus. We limited inclusion of clinical trials to randomised controlled trials only.

To maximise the sensitivity for the retrieval of all potentially relevant studies, the electronic databases were initially searched using an unrestricted search strategy employing the exploded MeSH terms (exp Influenza, Human/; exp Oseltamivir/) and specific text-word terms including 'oseltamivir', 'H5N1', and 'avian influenza.' To restrict and improve the specificity of these searches the following terms were used: 'systematic[sb]', 'economic', 'in vitro', 'animal', and 'case series.' In the case of antiviral combination therapy, a summary of the search terms used to identify relevant studies is presented in Table 10.1.1.

Table 10.1.1: Treatment of H5N1 with antiviral combination therapy search strategy

Source	Study type	Search terms
PubMed	SR	(oseltamivir OR zanamivir OR neuraminidase inhibitors) AND (amantadine OR rimantadine OR adamantane) AND (combined OR combination) AND (influenza) AND systematic [sb]
PubMed	RCT	(oseltamivir OR zanamivir OR neuraminidase inhibitors) AND (amantadine OR rimantadine OR adamantane) AND (combined OR combination) AND (influenza) AND ((Clinical Trial[ptyp]))
PubMed	in vitro	(oseltamivir OR zanamivir OR neuraminidase inhibitors) AND (amantadine OR rimantadine OR adamantane) AND (combined OR combination) AND (influenza) AND in vitro
PubMed	animal	(oseltamivir OR zanamivir OR neuraminidase inhibitors) AND (amantadine OR rimantadine OR adamantane) AND (combined OR combination) AND (influenza) (Animals[Mesh:noexp])
PubMed	case	(oseltamivir OR zanamivir OR neuraminidase inhibitors) AND (amantadine OR rimantadine OR adamantane) AND (combined OR combination) AND (influenza) AND ((Humans[Mesh]) AND (Case Reports[ptyp]))
PubMed	general	(oseltamivir OR zanamivir OR neuraminidase inhibitors) AND (amantadine OR rimantadine OR adamantane) AND (combined OR combination) AND (influenza)
Cochrane	SR	(oseltamivir or zanamivir) AND (amantadine or rimantadine) in Title, Abstract or Keywords Study types: Cochrane reviews, Other reviews
Cochrane	CCT	(oseltamivir or zanamivir) AND (amantadine or rimantadine) in Title, Abstract or Keywords. Study type: clinical trials

Abbreviations: SR = systematic review; RCT = randomised controlled trial; CCT = controlled clinical trial.

10.2 Summary of available data (appraisal of quality, outcome measures, summary of results)

Five systematic reviews²⁹⁻³³ of oseltamivir phosphate in the treatment and prophylaxis of seasonal influenza were identified by the literature searches. Two of these reviews were Cochrane reviews,^{29,32} two were Health Technology Assessment Reports (HTA)^{30,31} and one was a Belgium Health Care Knowledge Centre (KCE) report.³³ The Cochrane review by Jefferson *et al.*(2006)²⁹ superseded the previous Cochrane review by Jefferson *et al.*(2004) and the review published by the same authors in The Lancet in 2006.³⁴ Although the review conducted by Van de Vyver *et al.*(2006)³³ was published more recently, with a more recent search, the meta-analyses included for oseltamivir phosphate were based on those presented in the review by Turner *et al.*(2003).³⁰ Therefore, the data published in the review by Turner *et al.*(2003)³⁰ is cited in this report in preference to that data published by Van de Vyver *et al.*(2006).³³ In aggregate, the results of these five systematic reviews form the basis of this report. More recent studies not included in the systematic reviews are assessed separately in this report.

10.2.1 Oseltamivir phosphate in the treatment of seasonal influenza – adults

The meta-analysis conducted by Jefferson *et al.*(2006)²⁹ showed that the use of oseltamivir phosphate resulted in a 20% reduction in the time to alleviation of symptoms compared to placebo (Hazard ratio [HR] 1.20, 95% CI 1.06 to 1.35) in the ITT (intention-to-treat) population. The use of oseltamivir phosphate also resulted in a statistically significant reduction in the time to alleviation of symptoms in influenza-positive patients (HR 1.30, 95% CI 1.13 to 1.50). However, for the latter outcome, there was some evidence of heterogeneity in treatment effect ($P = 0.19$, $I^2 = 37.5\%$). Only one trial reported data for the time to return to normal activities. For this trial, the use of oseltamivir phosphate in the ITT population

appeared to be only marginally more effective than placebo (HR 1.23, 95% CI 1.02 to 1.48). In the case of influenza-positive patients, the use of oseltamivir phosphate resulted in a statistically significant reduction in the time to return to normal activities (HR 1.34, 95% CI 1.07 to 1.67).

Two trials assessed the effect that oseltamivir phosphate administration (75-150 mg daily) had on viral load (as estimated by mean nasal titres of excreted viruses at 24 and 48 hours post-randomisation). Although the results showed that in patients treated with oseltamivir the viral load was significantly reduced (WMD -0.73, 95% CI -0.99 to -0.47) treatment with oseltamivir did not suppress viral excretion, irrespective of dose.

Jefferson *et al.*(2006)²⁹ found that oseltamivir phosphate was effective in preventing lower respiratory tract complications in influenza cases (Odds ratio [OR] 0.32, 95% CI 0.18 to 0.57), bronchitis (OR 0.40, 95% CI 0.21 to 0.76), and pneumonia (OR 0.15, 95% CI 0.03 to 0.69). However, oseltamivir phosphate was not effective in preventing cases of influenza-like illness (OR 0.21, 95% CI 0.02 to 2.04). Only one trial reported data on hospitalisation rates. For this trial, the event rates were rather small with only eight reported hospitalisations across both trial arms (oseltamivir 3/982 versus placebo 5/662). The odds of requiring hospitalisation in influenza cases only was not reduced by the use of oseltamivir (OR 0.40, 95% CI 0.10 to 1.69).

10.2.2 Oseltamivir phosphate in the prophylaxis of seasonal influenza – adults

The systematic review conducted by Jefferson *et al.*(2006)²⁹ only identified two trials of influenza prophylaxis in healthy adult subjects. The results of the meta-analysis showed that the prophylactic use of oseltamivir phosphate had no effect against influenza-like illness (ILI) when patients were treated at a daily dose of 75 mg (RR 1.28, 95% CI 0.45 to 3.66) or a dose of 150 mg daily (RR 1.00, 95% CI 0.25 to 3.95). Jefferson *et al.* found that both oral oseltamivir phosphate doses (75 mg and 150 mg daily) were effective against symptomatic influenza (RR 0.39, 95% CI 0.18 to 0.85; RR 0.27, 95% CI 0.11 to 0.67, respectively). Both the 75 mg and 150 mg oseltamivir phosphate daily doses appeared to protect against symptomatic and asymptomatic influenza (RR 0.46, 95% CI 0.31 to 0.68; RR 0.48, 95% CI 0.29 to 0.80, respectively). In the case of asymptomatic influenza, neither dose of oseltamivir phosphate appeared to be effective (oseltamivir 75 mg daily RR 0.73, 95% CI 0.43 to 1.26; oseltamivir 150 mg daily RR 0.67, 95% CI 0.35 to 1.28). However, the data for each of these outcomes for the higher dose regimen (150 mg daily) were based on the results of a single study.

In the case of post-exposure prophylaxis, Jefferson *et al.*(2006) identified just two studies. The results of the first of these two studies showed that post-exposure prophylaxis with oseltamivir phosphate provided an efficacy of 58.5% (15.6% to 79.6%) for households and of 68% (34.9% to 84.2%) for individual contacts. Jefferson *et al.* suggested that given the high circulation of virus (184 out of 298 index cases had influenza, 66% of which had influenza A H1N1 strain) the effectiveness was high (62.7%: 26% to 81%). The results of the second of the two studies found that oseltamivir phosphate provided 89% (67% to 97%) protective efficacy in contacts of index cases with influenza and 84% (45% to 95%) for index cases.

Summary of the evidence for adults

Although the systematic review conducted by Jefferson *et al.*(2006)²⁹ examined the evidence of the efficacy of oseltamivir phosphate in the treatment and prophylaxis of seasonal influenza in healthy adults, Jefferson *et al.* identified no comparative evidence of the role of

oseltamivir phosphate in avian influenza. Therefore, there is major uncertainty regarding the applicability of the evidence to avian influenza.

10.2.3 Oseltamivir phosphate in the treatment of seasonal influenza – children

Two systematic reviews^{30,32} of oseltamivir phosphate in the treatment of seasonal influenza in children were identified by the literature searches. One of these reviews was a Cochrane review³² whilst the other was a Health Technology Assessment Report (HTA).³⁰ Given the Cochrane review conducted by Matheson *et al.* (2006)³² represents the most recent source of evidence, the results of this review form the basis of this report.

Matheson *et al.* (2006)³² conducted searches of CENTRAL (*The Cochrane Library* Issue 1, 2005), MEDLINE (1966 to April 2005), EMBASE (January 1980 to December 2004), the on-line GlaxoSmithKline Clinical Trials Register, the on-line Roche Clinical Trial Protocol Register and Clinical Trials Results Database (August 2005), internet web sites, and reference lists of articles. Studies were included for review if they were double-blind, randomised, controlled trials and compared the efficacy of neuraminidase inhibitors (oseltamivir and zanamivir) with placebo or other antiviral drugs in children (less than 12 years of age). Matheson *et al.* identified a total of six controlled trials of neuraminidase inhibitors for the treatment of influenza in children and five controlled trials of neuraminidase inhibitors for the prevention of influenza in children. Of the 11 trials identified, only three studied oseltamivir phosphate and fulfilled the inclusion criteria. These consisted of two treatment trials and one prevention trial. The results of the prevention trial will be addressed in Section 10.2.4 of this report.

The first of the treatment trials (WV15758) was a double-blind RCT assessing the efficacy and safety and tolerability of a five day course of twice daily oral oseltamivir (or placebo) in the treatment of naturally acquired, symptomatic influenza infection in 695 children aged 1 to 12 years. The second of the treatment trials (WV15759/WV15871) was a double-blind RCT assessing the efficacy and safety and tolerability of a five day course of twice daily oral oseltamivir (or placebo) in the treatment of naturally acquired, symptomatic influenza infection in 334 children with asthma aged 6 to 12 years.³²

The results of WV15758 showed that in children aged 1 to 12 years oseltamivir phosphate treatment statistically significantly reduced the median duration of illness by 26% (36 hours) in children with laboratory-confirmed influenza ($P < 0.0001$) and by 17% (21 hours) in the intention-to-treat population ($P = 0.0002$).³² Although oseltamivir treatment reduced the median duration of illness in all age groups (i.e. ≤ 2 years, 3-5 years, > 5 years) only the older age group achieved a statistically significant reduction compared to control (median time to resolution of illness: 90 hours, 95% CI 76 to 109 hours; 125 hours 95% CI 114 to 141 hours, respectively). Oseltamivir treatment statistically significantly reduced the median time to resolution of illness by 34% ($P < 0.0001$) in children with influenza A but not in children with influenza B ($P = 0.27$). In children with laboratory-confirmed influenza, oseltamivir significantly reduced the median time to return to normal activity by 40% (44.6 hours; $P < 0.0001$). In children aged one to five years, oseltamivir shortened the median time to return to normal activity from 121.3 hours in the control group to 63.5 hours in the treatment group (48%; $P = 0.003$). In children with laboratory-confirmed influenza oseltamivir reduced the incidence of physician diagnosed complications requiring antibiotic use by 40% ($P = 0.005$) and overall antibiotic use by 24% ($P = 0.03$). Over the 28-day follow-up period oseltamivir reduced the incidence of physician diagnosed acute otitis media by 44% in children aged 1 to 12 years with laboratory-confirmed influenza without otitis media at enrolment and by 56% in children aged 1 to 5 years. Oseltamivir treatment did not significantly reduce the rates of

bronchitis (1% vs. 3%), pneumonia (1% vs. 2%), or sinusitis (3% vs. 4%). The results of WV15758 indicated that there were no reported deaths during the study period and only two reported cases of hospitalisation (both from the control arm).³²

For the primary study outcome (time to resolution of illness) the results for WV15759/WV15871 were inconclusive. Although there appeared to be a trend toward a reduction in the median duration of illness in asthmatic children with laboratory-confirmed influenza of 7.7% (10 hours) the result failed to reach statistical significance ($P = 0.54$). A similar non-significant result was observed for the median time to return to normal activity (12.6 hours; $P = 0.46$). Matheson *et al.*(2006) noted that amongst children who started treatment with oseltamivir less than 24 hours after the onset of symptoms, there was greater, but not a statistically significant reduction in the median duration of illness (39.8 hours; 25%; $P = 0.078$) compared with children who commenced treatment more than 24 hours after the onset of symptoms (3.9 hours). The results of WV15759/WV15871 also showed that pulmonary function (median FEV₁) improved by 10.8% by day 6 in children with laboratory-confirmed influenza treated with oseltamivir phosphate, compared with 4.7% of children treated with placebo ($P = 0.015$). There were no reported deaths during the study period.³²

10.2.4 Oseltamivir phosphate in the prophylaxis of seasonal influenza – children

The systematic review conducted by Matheson *et al.*(2006)³² identified only one trial of oseltamivir phosphate in the prophylaxis of seasonal influenza in children. This trial (WV16193) was an open-label, parallel group RCT conducted in Europe and North America during the 2000 to 2001 influenza season. WV16193 assessed the efficacy, safety and tolerability of oral oseltamivir phosphate in the prophylaxis of influenza infection in household contacts of index cases with influenza-like illness. Study participants included contacts of index cases with influenza-like illness (temperature $\geq 37.8^{\circ}\text{C}$ plus cough and/or coryza) during a documented community influenza outbreak. Both contacts and index cases included children aged 1 to 12 years. Index cases received a 5-day course of twice-daily oral oseltamivir 30 to 75 mg (age-adjusted dose). Household contacts received either placebo or a 10-day course of once-daily oral oseltamivir using an age-adjusted dose. Households were randomised by cluster, so that all contacts in the same household received the same treatment. Study follow-up was 30 days.³²

The results of WV16193 showed that oseltamivir phosphate prophylaxis statistically significantly reduced the incidence of laboratory-confirmed, symptomatic influenza by 64% ($P = 0.019$) in all paediatric contacts. However, in paediatric contacts of index cases with laboratory-confirmed the observed reduction (55%) failed to reach statistical significance ($P = 0.089$). Matheson *et al.*(2006)³² claimed that this lack of effect appeared to be due to some contacts already being positive for sub-clinical influenza infection (diagnosed by viral culture of throat and nose swabs) and that in a retrospective analysis of paediatric contacts who were confirmed to be influenza negative at baseline, the protective efficacy rose to 80% ($P = 0.021$).

Matheson *et al.*(2006)³² concluded that oseltamivir phosphate may be considered for the treatment of children aged 1 to 12 years with influenza infection if near-patient testing is available and economic resources permit, and provided that therapy can be commenced within 48 hours of the onset of symptoms. Matheson *et al.* claim that for children aged 1 to 12 years in the household (when another member of family is affected), oseltamivir may be considered for post-exposure prophylaxis. However, the evidence supporting this approach is weak. Based on the current evidence, Matheson *et al.* suggest that neuraminidase inhibitors

should not be targeted specifically for ‘at-risk’ children (those with pre-existing chronic medical conditions) as benefit has not been shown in this population.

Summary of the evidence for children

Although the systematic review conducted by Matheson *et al.* (2006)³² examined the evidence of the efficacy of oseltamivir phosphate in the treatment and prophylaxis of seasonal influenza in children, Matheson *et al.* identified no comparative evidence of the role of oseltamivir phosphate in avian influenza. Therefore, there is major uncertainty regarding the applicability of the evidence to avian influenza.

10.2.5 Treatment of avian influenza (H5N1) in humans

Studies were included for review if they were case series of one or more patients treated with oseltamivir phosphate. Three studies of oseltamivir treatment of avian influenza (H5N1) in humans fulfilled the inclusion criteria.³⁵⁻³⁷ The results of these studies are summarised in Table 10.2.5.1.

Table 10.2.5.1: Summary of oseltamivir treatment of avian influenza (H5N1) in humans

Study (Year)	Place (Year)	Number treated	Dose/regimen	Corticosteroid use	Outcome
Hien (2004) ³⁶	Vietnam (2003-2004)	5*	35 – 75 mg twice daily up to 5 days. Started on day 5, 6, 11 or 12 of illness	In those treated with oseltamivir: 3/5 In those not treated with oseltamivir: 4/4	Death: 3/5 in those treated with oseltamivir Death: 4/4 in those not treated with oseltamivir
Chotpitayasunondh (2005) ³⁵	Thailand (2004)	7†	Dose not reported. Started on day 4,5,6,9,18 or 22 of illness	In those treated with oseltamivir: 6/7 In those not treated with oseltamivir: 2/5	Death: 5/7 in those treated with oseltamivir Death: 3/5 in those not treated with oseltamivir (Comment: there is some inconsistency in the way this is described)
Kandun (2006) ³⁷	Indonesia (2005)	1‡	75 mg twice daily. Started on day 10 of illness – received one of treatment.	In those treated with oseltamivir: 1/1 In those not treated with oseltamivir: 0/1	Death: 1/1 treated with oseltamivir Death: 0/1 not treated with oseltamivir
Kandun (2006) ³⁷	Indonesia (2005)	2¶	35 or 75 mg twice daily for 5 days. Started on day 5 or 7 of illness	In those treated with oseltamivir: 1/2 In those not treated with oseltamivir: 0/1	Death: 0/2 treated with oseltamivir Death: 0/1 not treated with oseltamivir

All 5 were treated with antibiotics. Dose of methylprednisolone was 1-5 mg/kg/day. Description of ill series at presentation (N = 10): median age = 13.7; fever = 100%; diarrhea = 70%; myalgia = 0%; cough = 100%; shortness of breath = 100%; pulmonary infiltrates = 100%; lymphopenia = NA; thrombocytopenia = NA; increased aminotransferase levels = 83%. (Beigel 2005)³⁸

† All 7 were treated with antibiotics. Dose of corticosteroid not reported. Description of ill series at presentation (N = 17): Median age = 14.0 years; fever = 100%; diarrhea = 41%; myalgia = 53%; cough = 94%; shortness of breath = 76%; pulmonary infiltrates = 100%; lymphopenia = 58%; thrombocytopenia = 33%; increased aminotransferase levels = 67%. (Beigel 2005)³⁸

‡ The oseltamivir treated case received methylprednisolone and antibiotics (regimens not reported); the second case recovered without antiviral, antibiotic or corticosteroid treatment. Treated case aged 37 years, fever 7 days, rhinorrhoea, cough, shortness of breath, hypotension, bilateral pulmonary infiltrates. Untreated case aged 9 years, fever 9 days, sore throat.

§ Virus isolates were available for one patient in each of the two clusters: molecular sequence analyses determined that the isolates were clade 2 H5N1 viruses of avian origin and fully sensitive to both adamantanes and neuraminidase inhibitors.

[¶] Both oseltamivir treated cases received antibiotics and one received corticosteroids (regimens not reported); the third case in this cluster recovered without treatment. Treated cases: aged 21 years, fever, cough 5 days, bilateral pulmonary infiltrates; aged 4 years, fever, rhinorrhoea, cough 2 days, mild bilateral pulmonary infiltrates. Untreated case aged 5 years, fever rhinorrhoea, cough headache 5 days.

Comments

In the study conducted by Hien *et al.*(2004)³⁶ treatment may have started too late to be effective. However, the patient that commenced treatment on day 12 survived. The study conducted Chotpitayasunondh *et al.*(2005)³⁵ indicated that two patients who were treated and survived tended to have been treated with oseltamivir earlier in the course of disease (median of 4.5 days from onset vs. 9.0 days in those who died). The two survivors received the full 5-day course of treatment. Of the five patients that died and received treatment, two had received the full 5-day course of oseltamivir. The effects of late oseltamivir treatment could not be determined in the study conducted by Kandun *et al.*(2006).³⁷

10.2.6 Treatment of avian influenza (H5N1) in animals – single agent therapy

Survival after treatment with oseltamivir

Five studies of oseltamivir phosphate/carboxylate treatment in animals fulfilled the inclusion criteria. These studies administered oseltamivir phosphate/carboxylate by oral-gavage. The results of these five studies is summarised in Table 10.2.6.1 (Appendix B).

The study by Leneva *et al.*(2000)³⁹ examined the efficacy of orally administered oseltamivir phosphate (GS4104) and oseltamivir carboxylate (GS4071) in mice infected with H5N1 and H9N2 influenza viruses. Oseltamivir exerted a significant dose-dependent antiviral effect in mice infected with A/HK/156/97 (H5N1) virus. Mice given doses of 1 and 10 mg/kg per day did not die whilst mice given doses of 0.1 mg/kg per day survived longer and the number of survivors was also increased. In mice infected with undiluted human influenza A/HK/1074/99 (H9N2) virus there were no deaths in mice orally administered oseltamivir at doses of 1 and 10 mg/kg/day. The number of survivors and the survival were greater among infected mice treated with 0.1 mg/kg per day than among the infected and untreated mice. However, the differences in survival were not statistically significant. Since the A/HK/1074/99 virus isolated from humans did not kill all of the mice in the control group, Leneva *et al.*(2000) studied the effect of oseltamivir on A/Qa/HK/G1/97 (P₃) virus, which is genetically related to the A/HK/1074/99 virus and causes death in 100% of infected mice. Mice infected with 10 MLD₅₀ of A/Qa/HK/G1/97 (P₃) virus and treated with orally administered oseltamivir were fully protected from death at doses of 1, 10 and 100 mg/kg per day of oseltamivir. Comparison of the results from the control group and the group treated with a dose of 0.1 mg/kg per day oseltamivir showed that the number of survivors and the MSD (mean survival days) were greater in the oseltamivir group.

Govorkova *et al.*(2001)⁴⁰ evaluated the efficacy of orally administered oseltamivir phosphate/carboxylate administered at 0.01, 0.1, 1.0, and 10 mg/kg/day to BALB/c mice. Four hours after initiation of treatment, the mice were infected with 5 MLD_{50s} of highly pathogenic influenza A/HK/156/97 (H5N1) or mouse-adapted A/quail/HK/G1/97 (H9N2) viruses. There were no signs of toxicity in control uninfected animals after treatment with as much as 100 mg of drug/kg/day. All control animals died 4 to 9 days after infection with H5N1 and 7 to 10 days after infection with H9N2 influenza virus. Treatment of H5N1-infected mice with oseltamivir provided complete protection (100% survival) against H5N1 virus at a dosage of only 0.1-1.0 mg/kg/day, whereas treatment with 0.01 mg/kg/day of

oseltamivir provided partial protection (33.3% survival). Govorkova *et al.*(2001)⁴⁰ also examined the efficacy of the oseltamivir when given late in the infection. Mice infected with 10 MLD₅₀s of A/HK/156/97 virus began receiving oseltamivir at 10 mg/kg/day 24, 36, 48, or 60 hours after infection. All untreated control animals died between days 8 and 10 after infection. Oral administration of oseltamivir increased the survival rates of mice in all treatment groups. No deaths were observed until day 8 after infection in mice treated with oseltamivir. When treatment with oseltamivir was given 24 hours after inoculation, 90% of mice survived. Even when given as late as 60 hours after infection, oseltamivir protected more than 65% of mice from lethal infection with H5N1 virus.

Yen *et al.*(2005)⁴¹ evaluated the efficacy of orally administered oseltamivir carboxylate administered at 0.1, 1.0, and 10 mg/kg twice daily to BALB/c mice infected with H5N1 A/Vietnam/1203/04 (VN1203/04) virus. To evaluate the pathogenicity of the VN1203/04 virus mice were inoculated with 10-fold dilutions of the virus and observed for clinical symptoms and survival. The virus was highly pathogenic in mice without prior adaptation; a virus dose as low as 101.2 EID₅₀ caused the deaths of all 5 infected mice. Yen *et al.*(2005) evaluated the prophylactic efficacy of 5 and 8 days of oseltamivir treatment of mice against challenge with 5 MLD₅₀ of VN1203/04 virus.

The 5-day regimen at a dosage of 0.1 mg/kg/day did not show any significant antiviral effect, compared with that shown with the placebo. Only mice that received the 5-day regimen at 10 mg/kg/day survived the challenge (50% survival rate) whereas mice that received other 5-day regimens died during the observation period. Yen *et al.*(2005)⁴¹ noted that death occurred at later days after inoculation for the mice that received 1 and 10 mg/kg/day of oseltamivir compared with the groups that received placebo and 0.1 mg/kg/day of oseltamivir. The administration of oseltamivir for 8 days improved survival rates in all treatment groups. A dose-dependent survival outcome was observed: the highest survival rate was achieved at 10 mg/kg/day (80%), followed by 1mg/kg/day (60%) and 0.1 mg/kg/day (10%). The results also suggested that weight change is prognostic of mouse survival. In the 8-day regimens, mice that received 1 or 10 mg/kg/day of oseltamivir had higher survival rates and less weight loss (<6%) than those that received 0.1 mg/kg/day or placebo (>15%). Furthermore, treatment with 10 mg/kg/day of oseltamivir for 8 days, rather than 5 days, resulted in decreased weight loss, from 13.5% to only 5%, and an increased survival rate, from 50% to 80%. Extending the duration of oseltamivir treatment from 5 to 8 days significantly enhanced survival. In the proportional hazards model, mice that received the 5-day regimens had a 2.7-fold greater risk of death than did mice that received the 8-day regimens ($P < 0.01$). However, the 8-day oseltamivir treatment regimen did not completely protect mice challenged with the VN1203/04 virus.

Govorkova *et al.*(2007)⁴² evaluated the use of oseltamivir phosphate/carboxylate for early post-exposure prophylaxis (PEP) and for treatment in ferrets exposed to representatives of two clades of H5N1 virus with markedly different pathogenicities in ferrets. In tests of post-exposure prophylaxis, groups of five ferrets were inoculated with A/Vietnam/1203/04 (H5N1) virus at a dose of either 10 or 10² EID₅₀. Three animals were observed for survival and clinical signs of infection, and two were sacrificed to determine virus titres in the internal organs. Oseltamivir treatment (5 mg/kg of body weight/day given as two daily doses of 2.5 mg/kg for 5 days) began 4 hours after virus inoculation. The efficacy of delayed treatment with oseltamivir was studied in groups of five ferrets inoculated with 10² EID₅₀ of A/Vietnam/1203/04 or 10⁶ EID₅₀ of A/Turkey/15/06 virus. Three animals were observed for survival and clinical signs of infection, and two were sacrificed to determine virus titres in the

internal organs. Oseltamivir treatment (10 or 25 mg/kg/day in twice-daily doses for 5 days) was initiated 24 hours after virus inoculation, and the animals were observed.

Challenge with 10 EID₅₀ (A/Vietnam/1203/04) caused death in two of three control ferrets on day 10 post inoculation and challenge with 10² EID₅₀ caused the deaths of all inoculated control animals between days 7 and 10 post-inoculation. All ferrets that received 5 mg/kg/day of oseltamivir 4 hours after inoculation survived virus challenge, although disease was not prevented.

To evaluate the activity of oseltamivir against established H5N1 influenza infection ferrets were inoculated with a lethal dose of A/Vietnam/1203/04 (H5N1) virus (10² EID₅₀) and treated with 10 or 25 mg/kg/day of oseltamivir starting 24 hours later. All animals treated with 10 mg/kg/day starting on day 2 post-inoculation, experienced fever and weight loss comparable to that in control ferrets. They were extremely lethargic, and two of three animals showed severe neurological signs (uncontrolled movements and hind limb paresis). All of these ferrets died between days 7 and 8 post inoculation. Treatment with 25 mg/kg/day of oseltamivir resulted in 100% survival.

Sidwell *et al.*(2007)⁴³ studied the efficacy of oral oseltamivir carboxylate (20 mg/kg/day twice daily for 5 days) in BALB/c mice infected with A/Duck/MN/1525/81 (H5N1) virus. Oseltamivir carboxylate prevented deaths in only 10 to 20% of infected mice, although the treatment significantly delayed the mean day to death compared to control ($P < 0.001$).

Virus titre in the lung of animals treated with oseltamivir

Five studies reported virus titre levels in the lung of animals treated with oseltamivir. The results of these five studies is summarised in Table 10.2.6.2 (Appendix B).

The study by Leneva *et al.*(2000)³⁹ found that the titres of A/HK/156/97 (H5N1) or A/Qa/HK/G1/97 (P₃) viruses in the lungs of mice treated with oseltamivir phosphate decreased in a dose-dependent fashion with the lowest effective dose being 0.1 mg/kg per day in both cases. In mice infected with A/HK/156/97 (H5N1), oseltamivir phosphate significantly decreased the titre of virus in the lungs, but at doses of 1 and 10 mg/kg per day, the reduction in virus titre was approximately the same as that of mice treated with 100 mg/kg per day; residual virus at titres of 3–4 log₁₀ EID₅₀ was detected in the lungs of these animals. In mice infected with A/Qa/HK/G1/97 (P₃), doses of 1 and 10 mg/kg per day reduced the virus titre in lungs significantly and a dose of 100 mg/kg per day completely inhibited replication.

Govorkova *et al.*(2001)⁴⁰ found that virus titres in the lungs of mice infected with A/HK/156/97 virus and treated with oseltamivir at the dosage of 0.01 mg/kg/day did not differ from those of controls. In mice infected with H9N2 virus, oseltamivir at 0.01 mg/kg/day failed to reduce virus titres in the lung. At 0.1, 1.0, and 10 mg/kg/day, oseltamivir markedly reduced virus titres in the lungs of mice infected with H9N2 virus.

The study by Yen *et al.*(2005)⁴¹ showed that the administration of 1 and 10 mg/kg/day of oseltamivir carboxylate for 5 days significantly inhibited virus replication in the lungs of mice at days 3 and 6 after inoculation ($P < 0.05$) but not at day 9 after inoculation with H5N1 A/Vietnam/1203/04 (VN1203/04) virus.

Govorkova *et al.*(2007)⁴² reported that viral replication was completely inhibited in ferrets inoculated with A/Vietnam/1203/04 virus and treated with oseltamivir 5 mg/kg/day twice daily for 5 days (first dose administered simultaneously to infection). A similar result was observed when ferrets were treated with oseltamivir 5 and 25 mg/kg/day twice daily for 5 days commencing 4 hours and 24 hours post infection, respectively. In ferrets treated with oseltamivir 10 mg/kg/day twice daily for 5 days, administered 24 hours post infection, viral replication was significantly inhibited compared to control ($P < 0.05$). Viral replication was also completely inhibited in ferrets inoculated with A/Turkey/15/06 virus and treated with oseltamivir 10 mg/kg/day twice daily for 5 days (administered 24 hours post infection).

Sidwell *et al.*(2007)⁴³ found there was no statistically significant difference in virus (A/Duck/MN/1525/81) titre levels in the lungs of mice treated with 20 mg/kg/day of oseltamivir compared to control ($P > 0.05$).

Virus titre in the brain tissue of animals treated with oseltamivir

Four studies reported virus titre levels in the brain tissue of animals treated with oseltamivir. The results of these four studies is summarised in Table 10.2.6.3 (Appendix B).

The study by Leneva *et al.*(2000) reported that the H5N1 and H9N2 viruses were undetectable in the brain of mice after treatment with doses of oseltamivir phosphate as low as 0.1 mg/kg per day. When the mice were treated with 0.01 mg/kg per day, the level of virus on days 3 and 4 were lower than those of the control animals.

Govorkova *et al.*(2001)⁴⁰ found that in the brains of untreated mice, virus titres on days 3, 4, and 7 after infection with A/HK/156/97 or A/quail/HK/G1/97 influenza virus ranged from 0.7 to 2.5 log₁₀ EID₅₀s. On days 3 and 4 after infection with H5N1 virus, virus titres were reduced 10-fold in the brains of mice treated with oseltamivir at 0.01 mg/kg/day ($P = 0.011$). The A/HK/156/97 (H5N1) virus was undetectable in the brains of mice after treatment with oseltamivir at a dosage of 0.1 mg/kg/day or more. The spread of A/quail/HK/G1/97 (H9N2) influenza virus to the brains of infected mice was reduced 32-fold at a dosage of 0.1 mg/kg/day ($P < 0.0001$) and was eliminated at a dosage of 1.0 mg/kg/day.

Yen *et al.*(2005)⁴¹ observed that all mice (placebo and oseltamivir doses of 0.1 and 1 mg/kg/day) except those that received 10 mg/kg/day of oseltamivir, had detectable brain virus titres at days 3, 6, and 9 after inoculation with A/Vietnam/1203/04 virus.

Govorkova *et al.*(2007)⁴² reported that on day 6 post inoculation, virus was detected in the brains of both control ferrets challenged with both 10 EID₅₀ and 10² EID₅₀ of A/Vietnam/1203/04 (H5N1) virus. Although oseltamivir treatment (5 mg/kg/day of oseltamivir 4 hours after inoculation) completely inhibited virus replication in the lungs and small intestine, virus was detected in the brain of one of two animals inoculated with 10² EID₅₀. At the lower infectious dose, virus titres were significantly lower in all organs ($P < 0.05$), except in one sample from the brain. Immuno-staining of histological sections of brain tissue from control ferrets showed a wide distribution of virus-positive cells. Ferrets that received oseltamivir prophylaxis had a narrower distribution of virus in the brain and fewer virus-positive cells than those that did not receive the treatment. Ferrets inoculated with A/Turkey/15/06 (H5N1) influenza virus had a lower level of spread to the brain.

When delayed treatment with 10 mg/kg/day of oseltamivir was applied (24 hours post infection) A/Vietnam/1203/04 (H5N1) virus was detected in multiple organs. Although this

drug regimen significantly inhibited virus replication in the lungs, liver, and spleen ($P < 0.05$) it did not significantly inhibited virus replication in the brain. Treatment with 25 mg/kg/day of oseltamivir completely inhibited virus replication in the internal organs of one of the two animals. In the other, virus was detected only in the brain (in two of two samples). In ferrets that received delayed treatment (24 hours post infection) A/Turkey/15/06 (H5N1) virus was not detected in the brains of ferrets treated with 10 mg/kg/day (5 days) of oseltamivir either by virus titration in embryonated chicken eggs or by specific staining of the brain sections.

Virus titre levels in the spleen of animals treated with oseltamivir

One study reported virus titre levels in the spleen of animals treated with oseltamivir. Govorkova *et al.*(2007)⁴² found that virus was detected in the spleens of both control ferrets challenged with both 10 EID₅₀ and 10² EID₅₀ of A/Vietnam/1203/04 (H5N1) virus. Although oseltamivir treatment (5 mg/kg/day of oseltamivir 4 hours after inoculation) completely inhibited virus replication in the lungs and small intestine, virus was detected in the spleen of one of two animals inoculated with 10² EID₅₀. Delayed treatment with 10 mg/kg/day of oseltamivir (24 hours post infection) significantly inhibited virus replication in the spleen ($P < 0.05$). Delayed treatment with 25 mg/kg/day of oseltamivir (24 hours post infection) completely inhibited virus replication. The results of this study is summarised in Table 10.2.6.4 (Appendix B).

Virus titre levels in the liver of animals treated with oseltamivir

One study reported virus titre levels in the liver of animals treated with oseltamivir. Govorkova *et al.*(2007)⁴² reported that virus was detected in the livers of both control ferrets challenged with both 10 EID₅₀ and 10² EID₅₀ of A/Vietnam/1203/04 (H5N1) virus. Although oseltamivir treatment (5 mg/kg/day of oseltamivir 4 hours after inoculation) completely inhibited virus replication in the lungs and small intestine, virus was detected in the liver of one of two animals inoculated with 10² EID₅₀. Delayed treatment with 10 mg/kg/day of oseltamivir (24 hours post infection) significantly inhibited virus replication in the liver ($P < 0.05$). Delayed treatment with 25 mg/kg/day of oseltamivir (24 hours post infection) completely inhibited virus replication. The results of this study is summarised in Table 10.2.6.5 (Appendix B).

Virus titre levels in the small intestine of animals treated with oseltamivir

One study reported virus titre levels in the small intestine of animals treated with oseltamivir. Govorkova *et al.*(2007)⁴² reported that oseltamivir treatment (5 mg/kg/day of oseltamivir 4 hours after inoculation with 10 EID₅₀ or 10² EID₅₀ of A/Vietnam/1203/04 (H5N1) virus) completely inhibited virus replication in the small intestine. The results of this study is summarised in Table 10.2.6.6 (Appendix B).

Virus titre levels obtained from nasal wash samples of animals treated with oseltamivir

Two studies reported virus titre levels obtained from nasal wash samples of animals treated with oseltamivir. The results of these two studies is summarised in Table 10.2.6.7 (Appendix B).

Le *et al.*(2005)⁴⁴ assessed the growth of a highly oseltamivir-resistant viral clone of A/Hanoi/30408/2005 (H274Y, clone 9) and of an oseltamivir-sensitive clone (H274, clone 7) in ferrets. Viral titres were higher in animals infected with the oseltamivir-sensitive virus ($P = 0.000099$). Oseltamivir treatment reduced viral titres in animals infected with the drug sensitive virus ($P = 0.048$), but not in animals infected with the resistant virus ($P = 0.23$). However, all of the viral clones, including those highly resistant to oseltamivir, were sensitive

to zanamivir (IC₅₀, 0.5–3.1 nM). Le *et al.* found that zanamivir treatment reduced viral titres in animals infected with virus that was oseltamivir-sensitive ($P = 0.0000019$) or oseltamivir-resistant ($P = 0.018$).

Govorkova *et al.* (2007)⁴² collected nasal washes on days 3, 5, and 7 after inoculation. Control animals inoculated with 10² EID₅₀ of A/Vietnam/1203/04 (H5N1) shed virus at mean titres of 4.4 and 5.5 log₁₀ EID₅₀/ml on days 3 and 5 post inoculation, respectively. On day 7 post inoculation, only one ferret survived in this group and shed virus at a titre of 6.5 log₁₀ EID₅₀/ml. Control ferrets inoculated with 10 EID₅₀ shed virus at a lower titres. Post-exposure prophylaxis with oseltamivir 5 mg/kg/day significantly ($P < 0.05$) inhibited virus replication in the upper respiratory tract; no virus was detected in the nasal washes on days 3, 5, and 7 post inoculation. Delayed treatment with 10 mg/kg/day of oseltamivir did not inhibit virus replication in the upper respiratory tract: nasal wash titres were comparable in treated and control ferrets. Although ferrets treated with 25 mg/kg/day of oseltamivir shed virus on days 3, 5, and 7 post inoculation, the mean titre on day 7 post inoculation was significantly lower than that in untreated animals ($P < 0.05$). Govorkova *et al.* (2007)⁴² reported that in ferrets inoculated with 10⁶ EID₅₀ of A/Turkey/15/06 virus and began treatment with 10 mg/kg/day of oseltamivir 24 hours later, the peak nasal inflammatory cell counts in nasal washes were significantly lower in treated than in control animals on days 5 and 7 post inoculation ($P < 0.05$). Moreover, cell counts remained at the same level in the control animals on days 3, 5, and 7 post inoculation, whereas they had returned to nearly normal levels in the treatment group on day 5 post inoculation. Comparison of the protein concentrations in the nasal washes confirmed that there was significantly less upper respiratory tract inflammation in the treatment group.

Virus resistance in animals treated with oseltamivir

Three studies reported virus resistance in animals treated with oseltamivir. The results of these three studies is summarised in Table 10.2.6.8 (Appendix B).

Govorkova *et al.* (2001)⁴⁰ investigated whether the A/HK/156/97 and A/quail/ HK/G1/97 influenza viruses became resistant to oseltamivir during the treatment of BALB/c mice by comparing the drug sensitivity of the challenge viruses with that of viruses obtained from murine lungs after treatment. Govorkova *et al.* used cell ELISA to test the viruses used to infect the mice and the viruses obtained on the seventh day after infection and treatment with 1.0 mg/kg per day of oseltamivir. After treatment, the mean EC₅₀s required to inhibit replication of A/HK/156/97 in MDCK cells were 7.3 µM for oseltamivir carboxylate. Replication of A/quail/HK/G1/97 influenza virus was inhibited at 8.2 µM. The mean EC₅₀s of the challenge viruses differ by 0.2 to 0.5 µM from those obtained after treatment. Thus, the viruses isolated after administration of oseltamivir carboxylate were as sensitive to the drug as were the viruses used to infect animals.

Yen *et al.* (2005)⁴¹ sequenced the NA genes of viruses isolated from mouse lungs, to identify the emergence of possible drug-resistance mutants during treatment. No amino-acid changes were identified in the conserved NA residues in the 7 viruses obtained on days 6 and 9 after inoculation from mice treated with different dosages of oseltamivir for 5 or 8 days. Yen *et al.* sequenced the HA1 region of 4 viruses isolated on days 6 and 9 after inoculation from mice treated for 5 days, and did not identify any amino-acid changes. Therefore, no NA or HA mutations that might decrease the sensitivity of the virus to oseltamivir emerged during treatment.

Govorkova *et al.*(2007)⁴² extracted viral RNA directly from the nasal washes and internal organs of ferrets and sequenced the NA and HA (HA1 subunit) genes to detect the emergence of oseltamivir-resistant mutants during treatment. Direct sequence analysis was first used to identify the dominant virus population. Sequencing of the samples obtained on days 5 to 7 post inoculation from ferrets treated prophylactically with 5 mg/kg/day of oseltamivir revealed only one amino acid substitution (I418M) in a virus isolated from the brain of a single animal inoculated with 10 EID₅₀ of A/Vietnam/1203/04 (H5N1) virus. Govorkova *et al.* report that residue 418 is not known to be associated with resistance to NA inhibitors, and that no changes were detected in the HA1 subunit. Plaque reduction assay in MDCK cells showed no change in the susceptibility of this sample to oseltamivir carboxylate. To detect the emergence of resistant variants of the less pathogenic A/Turkey/15/06 (H5N1) virus, Govorkova *et al.* directly extracted RNA from 10 samples obtained on days 5 to 6 post inoculation from nasal washes, lungs, and brains. Govorkova *et al.*(2007) detected one mutation in the nasal wash sample of one ferret. This mutation, R193K in the HA1 region, did not result in a reduction of susceptibility to the NA inhibitor *in vitro*.

10.2.7 Treatment of avian influenza (H5N1) in animals – combination therapy

Survival after treatment with oseltamivir and rimantadine combination therapy

Two studies of oseltamivir and rimantadine oral combination therapy reported survival as a study outcome. The results of these studies are summarised in Table 10.2.7.1 (Appendix B).

To determine the efficacy of orally administered oseltamivir phosphate and rimantadine combination therapy, Leneva *et al.* (2000)³⁹ used high (i.e. 100 MLD₅₀) and low (i.e. 5 MLD₅₀) doses of H9N2 virus in mice. Leneva *et al.* found that the group of mice that received 10 mg/kg per day of oseltamivir and 10 mg/kg per day of rimantadine demonstrated the best survival rate and the highest length of mean survival (days). However, when the high dose of virus (100 MLD₅₀) was used, the combination of drugs did not completely protect mice from weight loss or death. In mice infected with low dose of H9N2 virus, combinations of the two agents (0.01 mg/kg per day oseltamivir and 1 mg/kg per day rimantadine; 0.1 mg/kg per day oseltamivir and 10 mg/kg per day rimantadine) resulted in an increase in survival. Combinations of the inhibitors at other doses fully protected the mice from death.

Galabov *et al.*(2006)⁴⁵ studied the combination effect of rimantadine hydrochloride and oseltamivir phosphate on mice infected with influenza A/Aichi/2/68 (H3N2) virus. Combination therapy was administered simultaneously twice daily in a 5-day treatment course, starting 4 hours before intranasal inoculation with 0.05 ml/mouse of diluted virus containing 10 or 20 MLD₅₀. Each experimental group consisted of 11-24 mice per drug dosage and 15-35 mice in the placebo group. Galabov *et al.* reported that mean survival time in combination-treated groups was lengthened by 3.1-6.9 days. At a viral dose of 20 MLD₅₀ the mortality rate was 27.3% for the oseltamivir-rimantadine combination (0.05 mg/kg/day and 5.0 mg/kg/day, respectively) and 45.5% for the oseltamivir-rimantadine combination (0.05 mg/kg/day and 7.5 mg/kg/day, respectively), compared to 78.9% the mortality in the placebo group. At a viral dose of 10 MLD₅₀ the mortality rate was 45.5% for the oseltamivir-rimantadine combination (0.05 mg/kg/day and 5.0 mg/kg/day, respectively) and 10% for the oseltamivir-rimantadine combination (0.05 mg/kg/day and 7.5 mg/kg/day, respectively).

Virus titre levels in the lung of animals treated with oseltamivir and rimantadine

One study reported virus titre levels in the lung of animals treated with rimantadine and oseltamivir oral combination therapy. The results of this study is summarised in Table 10.2.7.2 (Appendix B).

Galabov *et al.* (2006)⁴⁵ studied the titres of influenza virus A/Aichi/2/68 (H3N2) in the lungs of infected mice (10 MLD₅₀) subjected to a 5-day combined treatment of 0.05 mg/kg of oseltamivir and 5 mg/kg of rimantadine daily. Galabov *et al.* found that compared to the placebo group a decrease of the infectious virus content was observed in the group of mice treated with the combination therapy by 1 log₁₀ CCID₅₀ at 24 hours, by 2 log₁₀ at 36 hours, and by 2.8 log at 48 and 60 hours post inoculation.

Survival after treatment with oseltamivir and amantadine combination therapy

One study of oseltamivir and amantadine oral gavage combination treatment reported survival as a study outcome. The results of this study is summarised in Table 10.2.7.3 (Appendix B).

Ilyushina *et al.* (2007)⁴⁶ treated BALB/c mice by oral gavage for 5 days with amantadine (1.5, 15 or 30 mg/kg/day) and oseltamivir (1 or 10 mg/kg/day) separately or in combination. Mice were challenged 24 hours after initiation of treatment with 10 mouse 50% lethal doses of either amantadine-sensitive (rgVN-1203_{sens}) or amantadine-resistant (rgVN-1203_{resist}) recombinant A/Vietnam/1203/04 (H5N1) virus. When inoculated with rgVN-1203_{sens} (amantadine-sensitive) H5N1 influenza virus survival days were increased in mice treated with amantadine 15 mg/kg/day and oseltamivir 10 mg/kg/day combination therapy compared to placebo (12.6 ± 0.3 days vs. 8.7 ± 0.2 days; *P* < 0.01). A similar increase in survival days was observed in mice treated with amantadine 30 mg/kg/day and oseltamivir 10 mg/kg/day combination therapy (14.0 ± 0.0 days vs. 8.7 ± 0.2 days; *P* < 0.01). When inoculated with rgVN-1203_{resist} (amantadine-resistant) H5N1 influenza virus survival days were increased in mice treated with amantadine 15 mg/kg/day and oseltamivir 10 mg/kg/day combination therapy compared to placebo (11.5 ± 0.5 days vs. 8.6 ± 0.2 days; *P* < 0.01).

Virus titre levels in the lung of animals treated with oseltamivir and amantadine combination therapy

One study reported virus titre levels in the lung of animals treated with amantadine and oseltamivir oral gavage combination therapy. The results of this study is summarised in Table 10.2.7.4 (Appendix B).

Ilyushina *et al.* (2007)⁴⁶ found that in mice inoculated with rgVN-1203_{sens} (amantadine-sensitive) H5N1, virus titre levels in the lung were significantly lower in mice treated with amantadine 30 mg/kg/day and oseltamivir 10 mg/kg/day combination, and the amantadine 15 mg/kg/day and oseltamivir 10 mg/kg/day combination compared to placebo at 3, 6, and 9 days post inoculation (*P* < 0.05). In mice inoculated with rgVN-1203_{resist} (amantadine-resistant) H5N1, virus titre levels in the lung were significantly lower in mice treated with amantadine 15 mg/kg/day and oseltamivir 10 mg/kg/day combination compared to placebo at 3, 6, and 9 days post inoculation (*P* < 0.05).

Virus titre levels in the brain tissue of animals treated with oseltamivir and amantadine combination therapy

One study reported virus titre levels in the brain tissue of animals treated with amantadine and oseltamivir oral gavage combination therapy. The results of this study is summarised in Table 10.2.7.5 (Appendix B).

Ilyushina *et al.*(2007)⁴⁶ found that combination therapy with amantadine (15 or 30 mg/kg/day) plus oseltamivir (10 mg/kg/day) completely eliminated the CNS (central nervous system) penetration of rgVN-1203_{sens} (amantadine-sensitive) recombinant virus. Virus (rgVN-1203_{resist}) titre levels in the brain were significantly lower in those mice treated with combination therapy with amantadine 15 mg/kg/day plus oseltamivir 10 mg/kg/day compared to placebo and those receiving amantadine alone ($P < 0.05$).

Virus resistance in animals treated with amantadine and oseltamivir combination therapy

One study reported virus resistance in animals treated with amantadine and oseltamivir oral gavage combination therapy. The results of this study is summarised in Table 10.2.7.6 (Appendix B).

Ilyushina *et al.*(2007)⁴⁶ sequenced the HA, NA and M genes of viruses isolated from mouse brains and lungs on day 9 after inoculation. Ilyushina *et al.* report that no amino acid changes were identified in the surface glycoproteins or M proteins of any viruses (33 samples) isolated from mice inoculated with rgVN-1203_{sens} (amantadine-sensitive) or rgVN-1203_{resist} (amantadine-resistant) viruses and treated with any of the amantadine and/or oseltamivir regimens. During treatment Ilyushina *et al.* observed no amino acid substitutions in these proteins that might decrease virus sensitivity to antiviral drugs.

10.2.8 *In vitro* evidence of treatment for human and avian influenza (H5N1)

Of the studies identified in the literature search, five fulfilled the inclusion criteria and provided *in vitro* evidence of oseltamivir treatment for human and avian influenza (H5N1).^{39,43,47-49} The results of these studies are discussed below. A summary of the results from the included *in vitro* studies is presented in Appendix C.

The study conducted by Leneva *et al.*(2000)³⁹ established that GS4071 (the active metabolite of oseltamivir) inhibits the replication of the influenza viruses A/HK/156/97 (H5N1) and A/HK/1074/99 (H9N2) and the avian influenza virus A/Qa/HK/G1/97 (H9N2) in MDCK cells. In addition, Leneva *et al.* found that GS4071 inhibits the NA activity of these viruses. The mean EC₅₀ measured by ELISA and the mean IC₅₀ measured by NA inhibition tests were similar against A/HK/156/97 (H5N1), A/HK/1074/99 (H9N2), and A/Qa/HK/G1/97 (H9N2) influenza viruses, and the viruses did not differ in their sensitivities to the drug *in vitro*.³⁹

Rameix-Welti *et al.*(2006)⁴⁷ compared the sensitivities to oseltamivir of several highly pathogenic H5N1 viruses isolated in Asia from 1997 to 2005. The corresponding 50% inhibitory concentrations were determined using a standard *in vitro* neuraminidase (NA) inhibition assay. The K_m for the substrate and the affinity for the inhibitor (K_i) of NA were determined for a 1997 and a 2005 virus, using an NA inhibition assay on cells transiently expressing the viral enzyme. The results of the study conducted by Rameix-Welti *et al.* found that the sensitivities of the NAs of H5N1 viruses isolated in 2004 and 2005 to oseltamivir were about 10-fold higher than those of earlier H5N1 viruses or currently circulating H1N1 viruses. Rameix-Welti *et al.* stated that, although the clinical relevance of a 10-fold increase in the sensitivity of NA to oseltamivir requires further investigation, there remains the possibility that sensitivity to anti-NA drugs could increase (or possibly decrease) significantly, even in the absence of treatment. This underscores the need for continuous evaluation of the impact of genetic drift on this parameter, especially for influenza viruses with pandemic potential.⁴⁷

The study conducted by Selvam *et al.*(2006)⁴⁸ examined the antiviral activity of a number of compounds against influenza A (H1N1, H3N2, and H5N1) and B viruses in Madin Darby canine kidney (MDCK) cell culture. Fifty percent effective concentration (EC₅₀) values were determined in cytopathic effect (CPE) inhibition assays quantified by neutral red dye uptake. Selvam *et al.* found that oseltamivir carboxylate (used a positive control compound) inhibited viral replication in all viruses (influenza A H1N1, H3N2, H5N1, and influenza B) and exhibited greater antiviral potency than both ribavirin and the isatin compounds (0.01-0.032 µg/ml against influenza A viruses and 0.93 µg/ml against influenza B virus). Concentrations required to inhibit viral activity were lowest for H5N1 and highest for H3N2.

Sidwell *et al.*(2007)⁴³ conducted a study to ascertain the efficacy of T-705 (6-fluoro-3-hydroxy-2-pyrazinecarboxamide), oseltamivir carboxylate, zanamivir, and ribavirin against the avian influenza A (H5N1) virus both *in vitro* and in a mouse model. The following viruses were studied: influenza A/Duck/MN/1525/81 and A/Gull/PA/4175/83 (gull/PA) (H5N1), influenza A/Hong Kong/213/2003 × Ann Arbor/6/60 and A/Vietnam/1203/04 × Ann Arbor/6/60. Sidwell *et al.* found that oseltamivir carboxylate inhibited viral replication in all viruses but higher concentrations were required for A/Duck/MN/1525/81 and A/Gull/PA/4175/83 viruses. However, the experimental compound T-705 was less potent in reducing viral yield than both the neuraminidase inhibitors but more so than ribavirin.

Smee *et al.*(2001)⁴⁹ studied the influenza virus neuraminidase inhibitory effects of a novel series of cyclopentane derivatives designated RWJ-270201, BCX-1827, BCX-1898, and BCX-1923. These compounds were tested in parallel with zanamivir and oseltamivir carboxylate against a spectrum of influenza A (H1N1, H3N2, and H5N1) and influenza B viruses in MDCK cells. Inhibition of viral cytopathic effect ascertained visually and by neutral red dye uptake was used, with 50% effective (virus-inhibitory) concentrations (EC₅₀) determined. Overall, zanamivir and oseltamivir carboxylate were slightly less potent (usually threefold or less) than the cyclopentane derivatives against the H1N1 viruses. The activities of zanamivir and oseltamivir carboxylate were similar against 12 influenza A (H3N2) strains, with 50% inhibition at 0.65 µM or less. Against two strains of influenza A (H5N1) virus zanamivir and oseltamivir carboxylate were 10-fold less potent (0.2 to 0.26 µM) than the cyclopentane derivatives but were still highly active inhibitors of these viruses. Zanamivir and oseltamivir carboxylate were as potent as the cyclopentane derivatives against the influenza B virus strains.

10.2.8.1 Resistance evaluations by *in vitro* study and/or sequence data

The study conducted by de Jong *et al.*(2005)²² examined sequential pharyngeal swabs from eight Vietnamese patients with influenza A (H5N1) infection from whom at least one pharyngeal swab was obtained before treatment and during treatment with oseltamivir. Swabs were collected in viral-transport medium and stored at -80°C. Virus isolation was performed in Madin-Darby canine-kidney cells (MDCK). de Jong *et al.* reported that the isolation from two Vietnamese patients of influenza A (H5N1) viruses with a H274Y substitution in the neuraminidase gene, which confers high-level resistance to oseltamivir. de Jong *et al.* suggest that in some patients with influenza A (H5N1) virus infection, treatment with the recommended dose of oseltamivir incompletely suppresses viral replication, and besides allowing the infection to proceed, such incomplete suppression provides opportunities for drug resistance to develop.²²

McKimm-Breschkin *et al.*(2003)⁵⁰ established the baseline susceptibilities prior to and shortly after the introduction of the NA inhibitors (zanamivir, oseltamivir carboxylate,

oseltamivir phosphate) by testing 1,054 clinical influenza isolates (influenza A virus subtypes N1 and N2, and influenza B) recovered from 1996 to 1999. Susceptibilities were determined by enzyme inhibition assays with chemiluminescent or fluorescent substrates with known NA inhibitor-resistant viruses as controls. Viruses selected for screening were representative of the major strains circulating worldwide and were in proportion to the virus subtypes circulating in different regions of the world during that period: 139 influenza A virus subtype N1 isolates, 767 influenza A virus subtype N2 isolates, and 148 influenza B virus isolates. McKimm-Breschkin *et al.* found that the N2 viruses were generally more sensitive to oseltamivir in both assays, with mean IC_{50} s of 0.62 and 0.43 μ M by the chemiluminescent and fluorescent assays, respectively, whereas the mean IC_{50} s of zanamivir were 2.17 and 1.48 μ M, respectively. The N1 viruses were slightly more sensitive to zanamivir, with mean zanamivir IC_{50} s of 0.61 and 0.92 μ M by the chemiluminescent and fluorescent assays, respectively, whereas the mean oseltamivir IC_{50} s were 0.92 and 1.54 μ M, respectively. For influenza B viruses the mean IC_{50} s of zanamivir were approximately twofold lower than those of oseltamivir carboxylate by the chemiluminescent assay (2.57 and 5.21 μ M, respectively) and nearly sixfold lower than those of oseltamivir carboxylate by the fluorescent assay (2.02 and 12.46 μ M, respectively). Thus, the influenza B viruses had lower levels of sensitivity to oseltamivir by the fluorescent assay than by the chemiluminescent assay but by both assays had reduced susceptibilities to both drugs compared to the susceptibilities of the N1 and N2 viruses. Based on the results of their study McKimm-Breschkin *et al.* concluded that recently circulating human influenza A and B viruses, collected before introduction of the NA inhibitors into clinical use, were all susceptible to both zanamivir and oseltamivir carboxylate and that, in contrast to the M2 inhibitors (amantadine and rimantadine), there was no evidence for naturally occurring resistance.

Hurt *et al.*(2004)⁵¹ analysed human influenza viruses (influenza A strains H1N1, H1N2, H3N2 and influenza B strains) isolated from Australasia (Australia and New Zealand) and South East Asia to determine their sensitivity to the NA inhibitor drugs zanamivir and oseltamivir. A total of 532 strains isolated between 1998 and 2002 were tested using a fluorescence-based assay to measure the relative inhibition of NA activity over a range of drug concentrations. Hurt *et al.* found that based on median IC_{50} values, influenza A viruses (with neuraminidase subtypes N1 and N2) were more sensitive to both the NA inhibitors than were influenza B strains. Influenza A viruses with a N1 subtype and influenza B strains both demonstrated a greater sensitivity to zanamivir than to oseltamivir carboxylate, whereas influenza A strains with a N2 subtype were more susceptible to oseltamivir carboxylate. For each of the neuraminidase types, IC_{50} values for viruses from Australasia and South East Asia were found to be comparable. Hurt *et al.* concluded that the use of the NA inhibitors did not appear to have a significant impact on the susceptibility of the viruses tested to zanamivir or oseltamivir carboxylate.

10.2.8.2 *In vitro* evidence of treatment for human and avian influenza (H5N1) -combination therapy

Govorkova *et al.*(2004)⁵² tested combinations that paired a neuraminidase (NA) inhibitor (zanamivir, oseltamivir carboxylate, or peramivir) with rimantadine against infection of MDCK cells with H1N1 and H3N2 subtypes of influenza A virus and characterized their mode of interaction. Reduction of extracellular virus was analysed by individual regression models and three-dimensional representations of the data. Govorkova *et al.* found that the combination of rimantadine and zanamivir or rimantadine and oseltamivir resulted in complete reduction in H1N2 and H3N2 extracellular viral yield, with all three combinations showing additive and synergistic effects with no cytotoxicity.⁵²

10.2.8.3 Resistance evaluations by *in vitro* study and/or sequence data - combination therapy
 The study conducted by Ilyushina *et al.* (2006)⁵³ examined whether combination therapy with two classes of anti-influenza drugs can affect the emergence of resistant variants *in vitro*. Ilyushina *et al.* found that virus yields of human A/Nanchang/1/99 (H1N1), A/Panama/2007/99 (H3N2), and A/Hong Kong/156/97 (H5N1) viruses in MDCK cells were significantly reduced ($P < 0.005$) when the cells were treated with the combination of amantadine and low doses of oseltamivir carboxylate ($\leq \mu\text{M}$). The results of the study by Ilyushina *et al.* suggest that combination chemotherapy with M2 blocker and NA inhibitor reduced the emergence of drug-resistant influenza variants *in vitro*. *In vitro* passage of virus in the presence of amantadine alone results in the generation of amantadine-resistant variants. *In vitro* passage of virus in the presence of oseltamivir alone results in the generation of oseltamivir-resistant variants. No drug-resistant variants were detected when the drugs were used in combination at sufficient concentrations.⁵³

11 Summary of comparative evidence on safety

Adult – treatment studies

In adult phase III treatment studies of oseltamivir phosphate (75 mg twice daily), the most frequently reported adverse events during five days of treatment (incidence $\geq 1\%$) were nausea and vomiting.²⁶ These results are summarised in Table 11.1.1.

Table 11.1.1: Summary of adverse events in the treatment of influenza

Adverse event	Oseltamivir phosphate [†] N=496	Placebo N=475
Vomiting	59 (11.9%)	15 (3.2%)
Nausea (without vomiting)*	52 (10.5%)	25 (5.3%)
Insomnia	7 (1.4%)	3 (0.6%)
Headache	13 (2.6%)	11 (2.3%)
Abdominal pain	12 (2.4%)	11 (2.3%)

[†] Administered 75 mg twice daily (bd).

* Excludes reports of nausea associated with vomiting (i.e. nausea reported within 1 day of report of vomiting).

Source: Tamiflu® - Product Information²⁶

Adult – prevention studies

In phase III prevention studies involving adolescents, healthy adults and elderly subjects, adverse events experienced more frequently by subjects taking oseltamivir phosphate (at the recommended dose of 75 mg once daily for up to 6 weeks) than placebo included nausea (8.0% compared with 4.3%), vomiting (2.1% compared with 1.0%), diarrhoea (3.2% compared with 2.6%) and abdominal pain (2.0% compared with 1.6%). Headache was the most frequent adverse event with an incidence of 17.5% in the placebo group and 20.1% in the group receiving oseltamivir phosphate.²⁶ These results are summarised in Table 11.1.2.

Table 11.1.2: Summary of most frequent adverse events in all prophylaxis studies

Adverse event	Oseltamivir phosphate [†] N=1480	Placebo N=1434
Nausea	118 (8.0%)	62 (4.3%)
Headache	298 (20.1%)	251 (17.5%)
Vomiting	31 (2.1%)	15 (1.0%)
Diarrhoea	48 (3.2%)	38 (2.6%)
Pain	53 (3.6%)	43 (3.0%)
Fatigue	117 (7.9%)	107 (7.5%)
Rhinorrhoea	23 (1.6%)	16 (1.1%)

Abdominal pain	30 (2.0%)	23 (1.6%)
Insomnia	18 (1.2%)	14 (1.0%)
Dizziness (excluding vertigo)	24 (1.6%)	21 (1.5%)
Upper respiratory tract infection	120 (8.1%)	115 (8.0%)
Dyspepsia	25 (1.7%)	23 (1.6%)

† Administered 75 mg once daily for up to 6 weeks.

Source: Product Information - Tamiflu^{®26}

Children – treatment and prophylaxis studies

In phase III paediatric treatment studies (aged 1-12 years) the most frequently reported adverse event (occurring in >1% of patients) was vomiting. Other events reported more frequently by paediatric patients treated with oseltamivir phosphate included abdominal pain, epistaxis, ear disorder, and conjunctivitis. These events generally occurred once and resolved despite continued dosing. They did not cause discontinuation of drug in the majority of cases.²⁶ These results are summarised in Table 11.1.3.

Table 11.1.3: Summary of the most frequent adverse events (>1% of patients) occurring in children (aged 1-12 years) – oseltamivir treatment and prophylaxis

Adverse event	Treatment		Treatment	Prophylaxis
	Placebo N=517	Oseltamivir [†] N=515	Oseltamivir [‡] N=158	Oseltamivir [‡] N=99
Vomiting	48 (9.3%)	77 (15.0%)	31 (19.6%)	10 (10.1%)
Diarrhoea	55 (10.6%)	49 (9.5%)	5 (3.2%)	1 (1.0%)
Otitis media	58 (11.2%)	45 (8.7%)	2 (1.3%)	2 (2.0%)
Abdominal pain	20 (3.9%)	24 (4.7%)	3 (1.9%)	3 (3.0%)
Asthma	19 (3.7%)	18 (3.5%)	-	1 (1.0%)
Nausea	22 (4.3%)	17 (3.3%)	10 (6.3%)	4 (4.0%)
Epistaxis	13 (2.5%)	16 (3.1%)	2 (1.3%)	1 (1.0%)
Pneumonia	17 (3.3%)	10 (1.9%)	-	-
Ear disorder	6 (1.2%)	9 (1.7%)	-	-
Sinusitis	13 (2.5%)	9 (1.7%)	-	-
Bronchitis	11 (2.1%)	8 (1.6%)	3 (1.9%)	-
Conjunctivitis	2 (0.4%)	5 (1.0%)	-	-
Dermatitis	10 (1.9%)	5 (1.0%)	1 (0.6%)	-
Lymphadenopathy	8 (1.5%)	5 (1.0%)	1 (0.6%)	-
TMD	6 (1.2%)	5 (1.0%)	-	-

Abbreviations: TMD = tympanic membrane disorder.

* Includes aggravated asthma.

† Administered as a suspension 2 mg/kg twice daily.

‡ Unit dose – age-based dosing.

Source: Tamiflu[®] - Product Information²⁶

In post-marketing surveillance, rare cases of hypersensitivity reactions such as allergic skin reactions including dermatitis, rash, eczema and urticaria.²⁶ Very rare cases of erythema multiforme and Stevens-Johnson-Syndrome have been reported. There have also been rare reports of toxic epidermal necrolysis (TEN), allergy, anaphylactic/anaphylactoid reactions and facial oedema. In the case of the liver and biliary system, there have been rare reports of hepatitis and elevated liver enzymes. Rare cases of gastro-intestinal bleeding, in particular haemorrhagic colitis, have also been reported with the use of oseltamivir.²⁶

As a result of recommendations made by the FDA Pediatric Advisory Committee meeting held on 27 November 2007, Roche Laboratories Incorporated (Inc.) updated the package insert for oseltamivir phosphate (Tamiflu[®]). The following information and guidance are currently provided in the product information for oseltamivir phosphate (Tamiflu[®]):

- Convulsion and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, and nightmares) have been reported during oseltamivir phosphate (Tamiflu[®]) administration in patients with influenza, predominately in children and adolescents. These events often had an abrupt onset and rapid resolution. In rare cases, these events resulted in accidental injury, and some resulted in a fatal outcome. The contribution of oseltamivir phosphate (Tamiflu[®]) to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir phosphate (Tamiflu[®]). Patients with influenza should be closely monitored for signs of abnormal behaviour throughout the treatment period.²⁶

A recent systematic review conducted by Jones and Del Mar (2006)⁵⁴ examined the safety profile of oseltamivir and zanamivir used in the treatment and prevention of influenza in adults and children. Although data for this systematic review were obtained from two previously published systematic reviews,^{32,34} Jones and Del Mar⁵⁴ acknowledged that there was a paucity of good quality trials that report adverse event data, with the majority of safety outcomes based on the data from just one or two RCTs. The results of this systematic review and the results of the systematic reviews conducted by Jefferson *et al.*(2006)²⁹ and Matheson *et al.*(2007)³² generally concur with the safety data contained in the product information for oseltamivir phosphate (Tamiflu[®]) previously presented in this report. The results of these three systematic reviews is summarised in Tables 11.1.4-11.1.8.

Table 11.1.4: Summary of safety outcomes for oral oseltamivir for prophylaxis in adults

Dose and adverse outcome	Number of trials	Oseltamivir n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	P-value
75 mg/day					
Nausea	2	71/675 (10.5)	23/413 (5.6)	1.8 (1.1 – 2.9)	0.02
Vomiting	2	20/675 (3.0)	6/413 (1.5)	2.3 (0.9 – 6.0)	0.09
Diarrhoea	1	13/155 (8.4)	21/153 (13.7)	0.6 (0.3 – 1.2)	0.14
Abdominal pain	1	18/155 (11.6)	18/153 (11.8)	1.0 (0.5 – 2.0)	0.97
Other adverse events	1	46/155 (29.7)	47/153 (30.7)	1.0 (0.6 – 1.6)	0.84
150 mg/day					
Nausea	1	76/520 (14.6)	18/259 (6.9)	2.3 (1.3 – 3.9)	0.002
Vomiting	1	14/520 (2.7)	2/260 (0.8)	3.6 (0.8 – 15.8)	0.09

Source: Jones & Del Mar (2006)⁵⁴

Table 11.1.5: Cochrane review - safety outcomes for oral oseltamivir for prophylaxis in adults

Dose and adverse outcome	Number of trials	Oseltamivir n/N (%)	Placebo n/N (%)	Odds ratio (95% CI) [Random effects analysis]
75 mg/day				
Nausea	2	71/675 (10.5)	23/413 (5.6)	1.79 (1.10 – 2.93)
Vomiting	2	20/675 (3.0)	6/413 (1.5)	2.28 (0.87 – 5.95)
Diarrhoea	1	13/155 (8.4)	21/153 (13.7)	0.58 (0.28 – 1.20)
Abdominal pain	1	18/155 (11.6)	18/153 (11.8)	0.99 (0.49 – 1.97)
Other adverse events	1	46/155 (29.7)	47/153 (30.7)	0.95 (0.59 – 1.55)
150 mg/day				
Nausea	1	76/520 (14.6)	18/259 (6.9)	2.29 (1.34 – 3.92)
Vomiting	1	14/520 (2.7)	2/260 (0.8)	3.57 (0.81 – 15.82)

Source: Jefferson *et al.*(2006)²⁹

Table 11.1.6: Summary of safety outcomes for oral oseltamivir for treatment in adults

Dose and adverse outcome	Number of trials	Oseltamivir n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	P-value
150 mg/day					
Cough*	1	125/134 (93.3)	127/139 (91.4)	1.3 (0.5 – 3.2)	0.55
Headache*	1	119/134 (88.8)	124/139 (89.2)	1.0 (0.5 – 2.0)	0.92
Diarrhoea	1	14/154 (9.1)	24/159 (15.1)	0.6 (0.3 – 1.1)	0.11
Nasal symptoms*	1	93/134 (69.4)	101/139 (72.7)	0.9 (0.5 – 1.4)	0.55
Nausea	2	91/565 (16.1)	31/363 (8.5)	1.8 (0.7 – 4.4)	0.20
All adverse events	1	71/154 (46.1)	89/159 (56.0)	0.7 (0.4 – 1.1)	0.08

Based on symptom severity score of ≥ 1 , where 0 = no symptom, 1 = minor, 2 = moderate, 3 = severe.
Source: Jones & Del Mar (2006)⁵⁴

Table 11.1.7: Summary of safety outcomes for oral oseltamivir for treatment in children

Dose and adverse outcome	Number of trials	Oseltamivir n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	P-value
Any adverse event	2	251/514 (48.8)	269/515 (52.2)	0.9 (0.7 – 1.1)	0.3
Serious adverse events	2	8/514 (1.6)	4/515 (0.8)	2.0 (0.6 – 6.7)	0.3
Adverse events leading to study withdrawal	2	8/514 (1.6)	8/515 (1.6)	1.0 (0.4 – 2.7)	1.0
Nausea	2	17/514 (3.3)	22/515 (4.3)	0.8 (0.4 – 1.5)	0.4
Vomiting	2	76/514 (14.8)	48/515 (9.3)	1.2 (1.1 – 2.5)	0.008
Diarrhoea	2	40/514 (7.8)	49/514 (9.5)	0.8 (0.5 – 1.3)	0.3

Source: Jones & Del Mar (2006)⁵⁴

Table 11.1.8: Cochrane review - safety outcomes for oral oseltamivir for treatment in children

Dose and adverse outcome	Number of trials	Oseltamivir n/N (%)	Placebo n/N (%)	Odds ratio (95% CI) [Fixed effect analysis]
Any adverse event	2	251/514 (48.8)	269/515 (52.2)	0.87 (0.68 – 1.12)
Serious adverse events	2	8/514 (1.6)	4/515 (0.8)	2.00 (0.60 – 6.69)
Adverse events leading to study withdrawal	2	8/514 (1.6)	8/515 (1.6)	1.00 (0.47 – 2.68)
Nausea	2	17/514 (3.3)	22/515 (4.3)	0.77 (0.40 – 1.46)
Vomiting	2	76/514 (14.8)	48/515 (9.3)	1.68 (1.15 – 2.47)
Diarrhoea	2	40/514 (7.8)	49/514 (9.5)	0.81 (0.52 – 1.25)

Source: Matheson *et al.* (2007)³²

In summary, the most frequent side effects associated with the administration of oseltamivir for either treatment or prophylaxis of influenza are transient nausea, vomiting, and abdominal pain, which occur in approximately 5 to 10 percent of patients. Generally, adverse events occur only once, close to the initiation of therapy, and resolve spontaneously within one to two days.⁵⁵

12 Summary of available data on comparative cost and cost effectiveness within the pharmacological class or therapeutic group

12.1 Global comparative pricing of oseltamivir

British National Formulary (2008)

Oseltamivir phosphate (Tamiflu® - Roche)

Capsules: 30 mg (10 pack) = £8.18

Capsules: 45 mg (10 pack) = £16.36
Capsules: 75 mg (10 pack) = £16.36
Liquid suspension: 60 mg / 5 ml (75 ml) = £16.36

MIMS Australia – oseltamivir phosphate (Tamiflu®) pricing details (<http://mims.com.au>) – (Australian dollars)

Oseltamivir phosphate (Tamiflu® - Roche)
Capsules: 75 mg (10 pack) = \$49.20
Liquid suspension: 75 mg (100 ml) = \$49.20

12.2 Comparative cost-effectiveness

Literature searches of MEDLINE, EMBASE, and the Cochrane Library identified 21 economic evaluations of oseltamivir in the treatment and/or prophylaxis of influenza. These studies are summarised in Tables 12.2.1 and 12.2.2.

The National Institute for Health and Clinical Excellence (NICE) reviewed the evidence of clinical effectiveness and conducted a cost-effectiveness analysis of oseltamivir, zanamivir, and amantadine in the treatment of influenza. The findings of this study were published in the NICE Technology Appraisal Guidance – No.58 (February 2003).⁵⁶ The results of the cost-effectiveness analysis are summarised as follows:

- The 'base case' in the economic model assumed that the availability of an antiviral drug does not increase the number of GP consultations for influenza and that the probability that the ILI is influenza (A or B for zanamivir and oseltamivir; A only for amantadine) is 46%. The 'alternative case' assumed that the availability of an antiviral drug increases the percentage of people consulting their GP by eight percentage points (from 28% to 36% for healthy adults) and that the probability that ILI is influenza is 31%. Where it was assumed that the antiviral drug in question reduces the mortality rate from complications of influenza, it was further assumed that anyone who dies of complications of influenza would otherwise have had an average life expectancy for a person of that age group. In each case the comparator was best supportive care.
- In the model, for otherwise healthy adults, for the base case, the estimated cost per quality adjusted life year (QALY) gained for amantadine is about £13,000. In the alternative case, the estimated cost per QALY gained is £129,000 (Because of the lack of evidence, it is assumed that amantadine does not reduce the rate of hospitalisation or death due to complications of influenza).
- For zanamivir, the estimated base-case cost per QALY gained for healthy adults is £30,000 if the reduction in hospital admissions and deaths due to the use of zanamivir are not included, but falls to £8000 if they are. In the 'alternative case', the estimated cost per QALY gained rises to £100,000 if reductions in hospital admissions and death are not taken into account and £27,000 if they are.
- For oseltamivir, the estimated base-case cost per QALY gained for healthy adults is £18,000 if the reduction in hospital admissions and deaths due to the use of oseltamivir are not included, but falls to £4300 if they are. In the 'alternative case', the estimated cost per QALY gained rises to £75,000 if reductions in hospital admissions and death are not taken into account and £19,000 if they are.
- For 'at-risk' adults, the cost per QALY gained for amantadine was estimated to be around £4300 (the 'base case'). For the 'alternative case', the estimated cost per QALY gained increased to £130,000. For zanamivir, the estimated base-case cost per QALY gained for 'at-risk' adults was £19,000 when the reduction in hospital admissions and deaths due to the use of zanamivir were not included and £3700 if they were. In the 'alternative case', the estimated cost per QALY gained increased to £82,000 if reductions in hospital admissions and deaths were not taken into account and £17,000 if they were. For oseltamivir, the estimated base-case cost per QALY gained for 'at-

risk' adults was £26,000 when the reduction in hospital admissions and deaths due to the use of oseltamivir were not included and £3900 if they were. In the 'alternative case', the estimated cost per QALY gained increased to £134,000 if reductions in hospital admissions and deaths were not taken into account and £25,000 if they were.

- In the case of children, for oseltamivir, the estimated base-case cost per QALY gained was £19,000 if the reduction in hospital admissions and deaths due to the use of oseltamivir were not included, and £11,000 if they were. In the 'alternative case', the estimated cost per QALY gained increased to £45,000 if reductions in hospital admissions and deaths were not taken into account and £25,000 if they were.

NICE have also provided guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza. The findings of this study were published in the NICE Technology Appraisal Guidance – No.67 (September 2003).⁴ The results of the cost-effectiveness analysis are summarised as follows:

- In the case of post-exposure prophylaxis, for healthy adults and adolescents (where the comparator was unvaccinated people), the cost per QALY gained for amantadine against no treatment was estimated to be £31,000 (for the case of a high probability of influenza A), while for oseltamivir against no treatment, the cost per QALY gained was estimated to be £28,000.
- In the case of post-exposure prophylaxis, for both 'at-risk' people and people in residential care establishments, the more appropriate comparator is vaccinated people. For vaccinated people, the estimated cost per QALY gained for oseltamivir against no treatment was £29,000 for the 'at-risk' group and £3000 for the at-risk residential care group. For unvaccinated groups, the estimated cost per QALY gained for oseltamivir against no treatment for the 'at-risk' group was £7000 while for the 'at-risk' residential care group oseltamivir was cost saving.
- In the case of seasonal prophylaxis, for healthy adults and adolescents (where the appropriate comparator is unvaccinated people), and for both groups the cost per QALY gained for amantadine or oseltamivir was estimated to be more than £100,000. For both the 'at-risk' and elderly residential care groups, the estimated cost per QALY gained for vaccinated people was more than £60,000 for oseltamivir. The estimated cost per QALY gained for the unvaccinated 'at-risk' group was £80,000 for oseltamivir. The cost per QALY gained for unvaccinated elderly people in residential care was estimated to be £12,000 for oseltamivir.

Table 12.2.1: Summary of economic evaluations of oseltamivir

Study	Year	Country	Specific subgroups analysed	Intervention	Comparator	Model time-horizon	Perspective	Type of economic analysis
Armstrong <i>et al.</i> ⁵⁷	2000	USA	Otherwise healthy patients; High-risk patients	Oseltamivir	Standard care; Zanamivir	One year	Health care provider	CEA
Husereau <i>et al.</i> ³¹	2001	Canada	Otherwise healthy patients; At-risk patients	Oseltamivir	No active medical intervention	NR	Government payer	CEA
Jarvinen <i>et al.</i> ⁵⁸	2007	Finland	Otherwise healthy patients; Children; At-risk patients	Oseltamivir	Usual care	Life-time	Health care payer; Societal	CEA
Lee <i>et al.</i> ⁵⁹	2002	USA	Healthy employed patients	Oseltamivir	Standard care; Vaccination; Zanamivir; Rimantidine	A complete influenza season	Societal	CBA
Muennig & Khan ⁶⁰	2001	USA	Healthy adults	Oseltamivir	Standard care; Vaccination	One year	Societal	CEA
O'Brien <i>et al.</i> ⁶¹	2003	Canada	Healthy adults	Oseltamivir	Standard care	7 days	Health care payer	CEA
Postma <i>et al.</i> ⁶²	2005	Netherlands	Healthy working adults	Oseltamivir	Standard care; Vaccination	Period of illness	Societal	CBA
Postma <i>et al.</i> ⁶³	2007	Netherlands	Elderly patients without chronic illness; Elderly patients with chronic disease; Chronically ill non-elderly patients	Oseltamivir	Standard care	Life-time	Societal	CEA
Reisinger <i>et al.</i> ⁶⁴	2004	UK	Children	Oseltamivir	Usual care	Life-time	Health care payer	CEA

Abbreviations: CBA = cost-benefit analysis; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; RCT = randomised controlled trial; ICI = ion channel inhibitors; ILI = influenza-like illness; NICE = National Institute for Health and Clinical Excellence; NR = not reported; NI = neuraminidase inhibitor; NHS = National Health Service; Tx = treatment

Table 12.2.1 (continued): Summary of economic evaluations of oseltamivir

Study	Year	Country	Specific subgroups analysed	Intervention	Comparator	Model time-horizon	Perspective	Type of economic analysis
Rothberg <i>et al.</i> ⁶⁵	2005	USA	Healthy children	Oseltamivir; Oseltamivir + rapid testing	No antiviral therapy; Amantadine; Amantadine + rapid testing	Period of influenza outbreak	Societal	CEA
Rothberg <i>et al.</i> ⁶⁶	2005	USA	Working adults	Oseltamivir with rapid testing	No intervention; Vaccination; Amantadine	10 years	Societal	CEA
Rothberg <i>et al.</i> ⁶⁷	2003	USA	Otherwise healthy adults	Oseltamivir with or without rapid testing	Standard care; Amantadine; Rimantadine; Zanamivir with or without rapid testing	NR	Societal	CEA
Rothberg <i>et al.</i> ⁶⁸	2003	USA	Elderly	Oseltamivir with or without rapid testing	Standard care; Amantadine; Rimantadine; Zanamivir with or without rapid testing	Life-time	Societal	CEA
Sander <i>et al.</i> ⁶⁹	2004	UK	Elderly and high-risk	Oseltamivir	Standard care	Life-time	Health-care payer	CEA
Sander <i>et al.</i> ⁷⁰	2005	UK	Otherwise healthy adults	Oseltamivir	Standard care; zanamivir	Life-time	Health-care payer; Societal	CEA
Scuffham & West ⁷¹	2002	England; Wales; France; Germany	Elderly populations	Treatment with NIs; Prophylaxis with NIs	Opportunistic vaccination; Comprehensive vaccination; ICI chemoprophylaxis; Tx with ICIs	NR	Health care system	CEA

Abbreviations: CBA = cost-benefit analysis; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; RCT = randomised controlled trial; ICI = ion channel inhibitors; ILI = influenza-like illness; NICE = National Institute for Health and Clinical Excellence; NR = not reported; NI = neuraminidase inhibitor; NHS = National Health Service; Tx = treatment.

Table 12.2.1 (continued): Summary of economic evaluations of oseltamivir

Study	Year	Country	Specific subgroups analysed	Intervention	Comparator	Model time-horizon	Perspective	Type of economic analysis
Turner <i>et al.</i> ³⁰	2003	UK	Healthy adults; High-risk adults; Children; Residential care elderly	Oseltamivir - treatment & prophylaxis	Standard treatment; Amantadine; Zanamivir - treatment & prophylaxis	21 days; Life-time	Primarily NHS; Reduced time away from work investigated in sensitivity analyses	CEA
Vindt Holm <i>et al.</i> ⁷²	2004	Denmark	Otherwise healthy adults and adolescents	Oseltamivir	Usual care	Life-time	Societal; Health care payer	CEA
Risebrough <i>et al.</i> ⁷³	2005	Canada	Residential care elderly – influenza vaccinated	Oseltamivir - PEP	Standard treatment; Amantadine; PEP	30 days	Government payer	CEA
Sander <i>et al.</i> ⁷⁴	2006	UK	Families - adults and adolescents ≥13 years	Oseltamivir - treatment & no PEP; Oseltamivir - PEP & no treatment;	No prophylaxis & no treatment	1 year – including one influenza season	Health care payer (UK NHS); Societal perspective tested in sensitivity analysis	CEA/CUA
Doyle <i>et al.</i> ⁷⁵	2006	France	Age groups - 0-19, 20-64, ≥65 years; High-risk; Average risk of complications	Oseltamivir - treatment & prophylaxis	Influenza vaccination	Influenza pandemic scenario	Government payer	CEA

Abbreviations: CBA = cost-benefit analysis; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; RCT = randomised controlled trial; ICI = ion channel inhibitors; ILI = influenza-like illness; NICE = National Institute for Health and Clinical Excellence; NR = not reported; NI = neuraminidase inhibitor; NHS = National Health Service; Tx = treatment; PEP = post-exposure prophylaxis

Table 12.2.2: Summary of the results of the economic evaluations of oseltamivir

Study	Year	Utility weights	Economic outcome measure	ICER
Armstrong <i>et al.</i> ⁵⁷	2000	N/A	Cost per successfully treated patient; Cost per complication averted; Cost per symptom free day; Cost per member per month	<u>Otherwise healthy adults</u> \$US 38.51 per symptom free day gained
Husereau <i>et al.</i> ³¹	2001	Derived from a small sample of healthy patients	Cost per symptom day avoided; Cost per QALY	<u>Healthy adults</u> <\$CAD 50,000/QALY under favourable assumptions; >\$CAD 100,000/QALY under unfavourable assumptions <u>At-risk population</u> <\$CAD 50,000/QALY under favourable assumptions; >\$CAD 100,000/QALY under unfavourable assumptions
Jarvinen <i>et al.</i> ⁵⁸	2007	Disability weights used as a proxy for utility - modified by trial based symptom improvement	Cost per day of normal activity gained; Cost per QALY	<u>Otherwise healthy adults:</u> €13,405/QALY <u>Children:</u> €15,404/QALY <u>At-risk patients:</u> €754/QALY
Lee <i>et al.</i> ⁵⁹	2002	N/A	Cost; Net benefit	N/A
Muennig & Khan ⁶⁰	2001	QWB-scale = 0.61	Cost per QALY	<u>Otherwise healthy adults</u> \$US 27,619/QALY
O'Brien <i>et al.</i> ⁶¹	2003	7-day benefit converted from within trial data VAS scores	Cost per influenza days averted; Cost per QALY	<u>Otherwise healthy adults</u> \$CAD 57,863/QALY
Postma <i>et al.</i> ⁶²	2005	N/A	Cost; Net benefit	N/A
Postma <i>et al.</i> ⁶³	2007	N/A	Cost per LYG	<u>Chronically ill non-elderly patients:</u> Oseltamivir dominates <u>Elderly patients with chronic disease:</u> Oseltamivir dominates <u>Elderly patients without chronic disease:</u> €1,759/LYG

Abbreviations: TTO = time-trade off; LYG = life year gained; MDA = morbidity day avoided; NICE = National Institute for Health and Clinical Excellence; N/A = not applicable; NR = not reported; QALY = Quality-adjusted life-year; QALY = Quality-adjusted life-year; QWB = quality of wellbeing RCT = randomised controlled trial; VAS = visual analogue scale

Table 12.2.2 (continued): Summary of the results of the economic evaluations of oseltamivir

Study	Year	Utility weights	Economic outcome measure	ICER
Reisinger <i>et al.</i> ⁶⁴	2004	Same quality of life as adults; disability weights used as a proxy for utility; modified by trial based symptom improvement	Cost per QALY	<u>Children</u> £11,173/QALY (assuming 60% diagnostic accuracy, full compliance and 100% receive treatment within 48 hours) Sensitivity analysis: £22,859/QALY (no complications, mortality, hospitalizations, 47.5% diagnostic certainty)
Rothberg <i>et al.</i> ⁶⁵	2005	Unpublished data from zanamivir trials using EQ-5D; values were similar to those seen in healthy adults	Cost per QALY	Not reported for oseltamivir treatment versus usual care
Rothberg <i>et al.</i> ⁶⁶	2005	QWB-scale = 0.61	Cost per QALY	Not reported for oseltamivir treatment alone
Rothberg <i>et al.</i> ⁶⁷	2003	Base-case utility: calculated from a survey of 15 patients with a history of influenza	Cost per QALY	Not reported for oseltamivir versus usual care
Rothberg <i>et al.</i> ⁶⁸	2003	EQ-5D	Cost per QALY saved	<u>Elderly patients:</u> \$US 5,025 – 70,300/QALY saved
Sander <i>et al.</i> ⁶⁹	2004	Disability weights used as a proxy for utility - modified by trial based symptom improvement.	Cost per day gained to return to normal activity; Cost per QALY gained	<u>Elderly and high-risk patients</u> £3.16 per day gained to return to normal activity £225/QALY gained Sensitivity analysis: £17,873/QALY gained
Sander <i>et al.</i> ⁷⁰	2005	Nine day utility benefit; disability weights used as a proxy for utility of complications - modified by trial based symptom improvement	Cost per day of normal activity gained; Cost per QALY gained	<u>Otherwise healthy adults</u> £14.36 per day of normal activity gained £5,600/QALY gained Sensitivity analysis – Healthcare payer perspective: £20,717/QALY gained (diagnostic certainty = 34% & hospitalizations, complications & mortality excluded)
Scuffham & West ⁷¹	2002	N/A	Cost per responder; Cost per morbidity days averted	<u>Elderly population</u> England and Wales: €568.3 per morbidity days averted; France: €41 per morbidity days averted; Germany: €371.1 per morbidity days averted

Abbreviations: TTO = time-trade off; LYG = life year gained; MDA = morbidity day avoided; NICE = National Institute for Health and Clinical Excellence; N/A = not applicable; NR = not reported; QALY = Quality-adjusted life-year; QALY = Quality-adjusted life-year; QWB = quality of wellbeing RCT = randomised controlled trial; VAS = visual analogue scale

Table 12.2.2 (continued): Summary of the results of the economic evaluations of oseltamivir

Study	Year	Utility weights	Economic outcome measure	ICER
Turner <i>et al.</i> ³⁰	2003	21-day benefit converted from within trial data - VAS transformed to TTO scores	Cost per influenza day avoided; Cost per QALY	<u>Healthy adults:</u> £18,690/QALY <u>High-risk:</u> £21,441/QALY <u>Children:</u> £19,739/QALY
Vindt Holm <i>et al.</i> ⁷²	2004	Disability weights used as a proxy for utility - modified by trial based symptom improvement.	Cost per day to return to normal activity; Cost per QALY	<u>Otherwise healthy adults & adolescents</u> €12.3 per gain in day to return to normal activity €5,063/QALY; €26,174/QALY excluding hospitalisation, complications, & mortality (sensitivity analysis)
Risebrough <i>et al.</i> ⁷³	2005	N/A	Cost per influenza-like illness case avoided	<u>Elderly in long-term care facilities</u> Oseltamivir dominant compared to amantadine Cost saving: CDN\$1,249 per 100 patients Oseltamivir dominant compared to no prophylaxis Cost saving: CDN\$3,357 per 100 patients Both PEP strategies were more cost-effective than no PEP
Sander <i>et al.</i> ⁷⁴	2006	21-day benefit converted from within trial data - VAS transformed to TTO scores; loss of life included in QALY – based on expected life expectancy	Cost per influenza-like illness case avoided; Cost per QALY gained	<u>Contact attack rate = 8%</u> <u>Scenario One</u> £467 per case avoided; £29,938 per QALY gained <u>Scenario Two</u> £52,202 per QALY gained <u>Contact attack rate = 12%</u> £293 per case avoided; £18,697 per QALY gained <u>Contact attack rate = 30%</u> £84 per case avoided; £5,403 per QALY gained
Doyle <i>et al.</i> ⁷⁵	2006	N/A	Cost per health event avoided - case of influenza; hospitalization; death	<u>Priority population: Oseltamivir – seasonal prophylaxis</u> €96,000 per death avoided €21,500 per hospitalisation avoided <u>Priority population: Oseltamivir – treatment</u> €3,900 per death avoided €900 per hospitalisation avoided <u>Influenza vaccination:</u> €9,300 per death avoided; €2,200 per hospitalisation avoided

Abbreviations: CDN = Canadian; TTO = time-trade off; LYG = life year gained; MDA = morbidity day avoided; NICE = National Institute for Health and Clinical Excellence; N/A = not applicable; NR = not reported; QALY = Quality-adjusted life-year; QALY = Quality-adjusted life-year; QWB = quality of wellbeing RCT = randomised controlled trial; VAS = visual analogue scale; $TTO = -0.445 + (2.112 \times VAS) + (-0.580 \times VAS^2)$

13 Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Oseltamivir phosphate has gained regulatory approval for the treatment and prevention of influenza A and B in both adults and children from the age of one and over (United States FDA approved,²⁵ Australia TGA approved²⁷). However, oseltamivir phosphate has not gained regulatory approval for the treatment or prevention of avian influenza (H5N1).

14 Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

British Pharmacopoeia: Yes (2008, British National Formulary, 55 ed.)

International Pharmacopoeia: Yes (2008, Martindale: The Complete Drug Reference)

United States Pharmacopoeia: Yes

15 Proposed (new/adapted) text for the WHO Model Formulary

The following information was sourced from the PI for oseltamivir phosphate (Tamiflu[®])²⁶ and relate specifically to the use of oseltamivir phosphate in seasonal influenza.

Indications

Oseltamivir phosphate is indicated for the treatment of infections due to influenza A and B viruses in adults and children aged 1 year and older. Treatment should commence as soon as possible, but no later than 48 hours after the onset of the initial symptoms of infection.

Oseltamivir phosphate is indicated for the prevention of influenza in adults and children aged 1 year and older. Vaccination is the preferred method of routine prophylaxis against infection with influenza virus.

Contraindications

Oseltamivir phosphate is contraindicated in patients with known hypersensitivity to any of the components of the product.

Precautions

Oseltamivir phosphate is a specific treatment for infections due to Influenza A or B viruses. Use should be limited to patients who have characteristic symptoms of influenza when Influenza A or B virus infections have been documented locally. Data on the treatment of influenza B are limited. There is no current evidence for the safety or efficacy of oseltamivir in persons with complications of an acute influenza episode such as viral or bacterial pneumonia. Such patients may require extensive supportive and adjunctive care. Antiviral therapy has not been shown to reduce the need for such care and monitoring.

Efficacy of oseltamivir in the treatment of subjects with chronic cardiac diseases/or respiratory diseases has not been established.

Safety and efficacy of repeated treatment or prophylaxis courses have not been studied.

Oseltamivir phosphate powder for oral suspension contains sorbitol. One dose of 45 mg oseltamivir phosphate oral suspension administered twice daily delivers 2.6 g of sorbitol. For subjects with hereditary fructose intolerance, this is above the recommended daily maximum limit of sorbitol.

Use in Paediatric Patients

The safety and efficacy of oseltamivir phosphate in paediatric patients have not been established in children aged less than 1 year of age. Oseltamivir phosphate should not be used in children under 1 year of age.

Use in Geriatric Patients

Limited numbers of subjects aged 65 and over have been included in the clinical trials. However, on the basis of drug exposure and tolerability, dose adjustments are not required for elderly patients unless there is co-existent renal impairment.

Use in Renal Impairment

Dose adjustment is recommended for patients with creatinine clearance of 10 - 30 mL/min for the treatment and prevention of influenza. Oseltamivir phosphate should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance < 10 mL/min. Therefore, caution should be taken when administering oseltamivir phosphate to those patients.

Dosage and Administration

Oseltamivir phosphate may be taken with or without food. However, taking with food may enhance tolerability in some patients.

Treatment of influenza

Treatment should begin within the first or second day of onset of symptoms of influenza.

Adults and adolescents

The recommended oral dose of oseltamivir phosphate capsules in adults and adolescents 13 years of age and older is 75 mg twice daily, for 5 days. Adults and adolescents 13 years of age and older who are unable to swallow capsules may receive a dose of 75 mg oseltamivir phosphate suspension twice daily for five days.

Paediatric patients

The recommended oral dose of oseltamivir phosphate oral suspension for paediatric patients 1 year and older or adult patients who cannot swallow a capsule is:

Recommended paediatric dosages – influenza treatment

Body weight in kg	Recommended dose for 5 days
≤15 kg	30 mg twice daily
>15 to 23 kg	45 mg twice daily
>23 to 40 kg	60 mg twice daily
>40 kg	75 mg twice daily

Source: Product Information (Roche, 20 February, 2008)²⁶

An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser. Paediatric patients weighing > 40 kg who are able to swallow capsules, may also receive treatment with a 75mg capsule twice daily as an alternative to the recommended dose of oseltamivir phosphate suspension.

Prophylaxis of influenza*Adults and adolescents*

The recommended oral dose of oseltamivir phosphate for prevention of influenza following close contact with an infected individual is 75 mg once daily for 10 days. Therapy should begin within two days of exposure. The recommended dose for prevention during a community outbreak of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to six weeks. The duration of protection lasts for as long as dosing is continued.

Paediatric patients

Children weighing > 40 kg, who are able to swallow capsules, may also receive prophylaxis with a 75 mg capsule once daily for 10 days as an alternative to the recommended dose of oseltamivir phosphate suspension. The recommended prophylactic oral dose of oseltamivir phosphate suspension for children ≥ 1 year of age is:

Recommended paediatric dosages – influenza prophylaxis

Body weight in kg	Recommended dose for 10 days
≤ 15 kg	30 mg once daily
>15 to 23 kg	45 mg once daily
>23 to 40 kg	60 mg once daily
>40 kg	75 mg once daily

Source: Product Information (Roche, 20 February, 2008)²⁶

A dosing syringe marked with 30 mg, 45 mg and 60 mg dosing levels is provided. It is recommended that oseltamivir phosphate powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient.

Supplied

Oseltamivir phosphate 75 mg capsules are available in blister packages of 10 capsules. Oseltamivir phosphate capsules are supplied as hard gelatin capsules with a light yellow/opaque cap and grey/opaque body.

Oseltamivir phosphate 12 mg/mL powder for oral suspension is available in a 100 mL bottle with 30 g of white to light yellow powder for reconstitution. Oseltamivir phosphate suspension is supplied with a plastic adapter, a plastic oral dispenser and a measuring plastic cup. After reconstitution with 52 mL of water, the usable volume of oral suspension allows the retrieval of 10 doses of 75 mg oseltamivir.

Appendix A

DRUGDEX® Tradename List	
Tradename list for: OSELTAMIVIR PHOSPHATE	
Name	Contact
Agucort	LKM, Argentina. Laboratorio LKM SA
Rimivat	Andromaco, Chile Laboratorios Andromaco SA
Tamiflu	Chugai, Japan Chugai Pharmaceutical Co. Ltd
Tamiflu	Roche, Argentina. Productos Roche S.A.Q. e I.
Tamiflu	Roche, Australia. Roche Products P/L
Tamiflu	Roche, Austria Roche Austria GmbH
Tamiflu	Roche, Belgium. Roche SA/NV
Tamiflu	Roche, Brazil. Produtos Roche Quimicos e Farmaceuticos S.A.
Tamiflu	Roche, Canada. Hoffmann-La Roche Ltd
Tamiflu	Roche, Chile Productos Roche Ltda
Tamiflu	Roche, Denmark. Roche A/S
Tamiflu	Roche, Finland. Roche Oy
Tamiflu	Roche, France. Produits Roche
Tamiflu	Roche, Germany. Hoffmann-La Roche AG
Tamiflu	Roche, Gr. Roche (Hellas) S.A.
Tamiflu	Roche, Hong Kong Roche Hong Kong Ltd
Tamiflu	Roche, Hung. Roche (Magyarország) Kft
Tamiflu	Roche, Irl. Roche Pharmaceuticals (Ireland) Ltd
Tamiflu	Roche, Israel Roche Pharmaceuticals (Israel) Ltd
Tamiflu	Roche, Ital. Roche S.p.A.
Tamiflu	Roche, NZ Roche Products (New Zealand) Ltd
Tamiflu	Roche, Norw. Roche Norge AS
Tamiflu	Roche, Philipp. Roche (Phils) Inc.
Tamiflu	Roche, Pol. Roche Polska Sp. zo.o.
Tamiflu	Roche, Port. Roche Farmaceutica Quimica, Lda
Tamiflu	Roche, S.Afr. Roche Products (Pty) Ltd
Tamiflu	Roche, Singapore Roche Singapore Pte Ltd
Tamiflu	Roche, Swed. Roche AB
Tamiflu	Roche, Switz. Roche Pharma (Schweiz) AG
Tamiflu	Roche, Thai. Roche Thailand Ltd
Tamiflu	Roche, Turk. Roche Mustahzarlari San. A.S.
Tamiflu	Roche, UK Roche Products Ltd
Tamiflu	Roche, USA Roche Pharmaceuticals
Virobin	Pharmabiotics, Chile

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Martindale Products	
Tradename list for: OSELTAMIVIR PHOSPHATE	
Agucort	LKM, Arg. Laboratorio LKM SA Monroe 1378, 1428 Buenos Aires, Argentina
Rimivat	Andromaco, Chile Laboratorios Andromaco SA Av. Quilin 5273, Penalolen, Santiago, Chile
Tamiflu	Chugai, Jpn Chugai Pharmaceutical Co. Ltd 2-1-9 Kyobashi, Chuo-ku, Tokyo 104-8301, Japan
Tamiflu	Roche, Arg. Productos Roche S.A.Q. e I. Ruta 9 Km 34, 1610 Ricardo Rojas Tigre, Buenos Aires, Argentina
Tamiflu	Roche, Austral. Roche Products P/L P.O. Box 255, Dee Why, NSW 2099, Australia
Tamiflu	Roche, Austria Roche Austria GmbH Engelhorngasse 3, A-1211 Vienna, Austria
Tamiflu	Roche, Belg. Roche SA/NV Rue Dante 75, 1070 Brussels, Belgium
Tamiflu	Roche, Braz. Produtos Roche Quimicos e Farmaceuticos S.A. Avenida Engenheiro Billings 1729, 05321-900 Sao Paulo, Brazil
Tamiflu	Roche, Canad. Hoffmann-La Roche Ltd 2455 Meadowpine Blvd, Mississauga, L5N 6L7, Canada
Tamiflu	Roche, Chile Productos Roche Ltda Av. Quilin 3750, Macul, Santiago, Chile
Tamiflu	Roche, Denm. Roche A/S Industriholmen 59, 2650 Hvidovre, Denmark
Tamiflu	Roche, Fin. Roche Oy Sinimaentie 10 B, PL 12, 02631 Espoo, Finland
Tamiflu	Roche, Fr. Produits Roche 52 bd du Parc,

WHO EML - Oseltamivir phosphate

Martindale Products	
Tradename list for: OSELTAMIVIR PHOSPHATE	
	92521 Neuilly-sur-Seine cdx, France
Tamiflu	Roche, Ger. Hoffmann-La Roche AG Emil-Barell-Str. 1, 79639 Grenzach-Wyhlen, Germany
Tamiflu	Roche, Gr. Roche (Hellas) S.A. 4 Alamanas & Delfon St., 151 25 Marousi, Greece
Tamiflu	Roche, Hong Kong Roche Hong Kong Ltd 802 The Lee Gardens, 33 Hysan Ave, Causeway Bay, Hong Kong
Tamiflu	Roche, Hung. Roche (Magyarország) Kft Edison u 1, 2040 Budaors, Hungary
Tamiflu	Roche, Irl. Roche Pharmaceuticals (Ireland) Ltd 3004 Lake Drive, City West, Naas Rd, Dublin 24, Ireland
Tamiflu	Roche, Israel Roche Pharmaceuticals (Israel) Ltd P.O. Box 7543, Petach Tikva, Israel
Tamiflu	Roche, Ital. Roche S.p.A. Viale G.B. Stucchi 10, 20052 Monza (MI), Italy
Tamiflu	Roche, NZ Roche Products (New Zealand) Ltd P.O. Box 12-492, Penrose, Auckland, New Zealand
Tamiflu	Roche, Neth. Roche Nederland BV P.O. Box 42, 3640 AA Mijdrecht, Netherlands
Tamiflu	Roche, Norw. Roche Norge AS Kristoffer Robinsv. 13, Postboks 41 Haugenstua, 0915 Oslo, Norway
Tamiflu	Roche, Philipp. Roche (Phils) Inc. 2252 Don Chino Roces Ave, Makati City, Philippines
Tamiflu	Roche, Port. Roche Farmaceutica Quimica, Lda Estrada Nacional 249, 2720-413 Amadora, Portugal
Tamiflu	Roche, Pol. Roche Polska Sp. zo.o. ul. Domaniewska 39 B,

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Martindale Products	
Tradename list for: OSELTAMIVIR PHOSPHATE	
	02-672 Warsaw, Poland
Tamiflu	Roche, S.Afr. Roche Products (Pty) Ltd P.O. Box 129, Gauteng, Isando 1600, South Africa
Tamiflu	Roche, Singapore Roche Singapore Pte Ltd 1 Kim Seng Promenade, 15-07/12 Great World City, S 237994, Singapore
Tamiflu	Roche, Swed. Roche AB Box 47327, 100 74 Stockholm, Sweden
Tamiflu	Roche, Switz. Roche Pharma (Schweiz) AG Schonmattstrasse 2, 4153 Reinach, Switzerland
Tamiflu	Roche, Thai. Roche Thailand Ltd 19 Fl, Rasa Tower, 555 Phaholyothin Rd, Chatuchak, Bangkok 10900, Thailand
Tamiflu	Roche, Turk. Roche Mustahzarlari San. A.S. Mecidiyekoy Yolu No: 102, Mecidiyekoy Sisli, Istanbul, 34387, Turkey
Tamiflu	Roche, UK Roche Products Ltd Hexagon Place, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, UK
Tamiflu	Roche, USA Roche Pharmaceuticals 340 Kingsland St, Nutley, NJ 07110-1199, USA

Appendix B

Table 10.2.6.1: Summary of results – survival after oral gavage with oseltamivir

Study	Virus	Model	Treatment	Regimen	Results	Conclusion
Leneva 2000 ³⁹	A/HK/156/97	Mouse	0.1 mg/kg/day	4 h pre infection, twice daily for 5 days	T=4/5* C=0/4	Partly protected
Leneva 2000 ³⁹	A/HK/156/97	Mouse	1 and 10 mg/kg/day	4 h pre infection, twice daily for 5 days	T=5/5 for each treatment dose* C=0/4	Completely protected
Leneva 2000 ³⁹	A/HK/156/97	Mouse	1 mg/kg/day	Delayed until 36 h after infection, continued twice daily for 5 days	T=100% at day 10† C=0%	Completely protected at day 10
Leneva 2000 ³⁹	A/HK/156/97	Mouse	1 mg/kg/day	Delayed until 48 h after infection, continued twice daily for 5 days	T=80% at day 10† C=0%	Partly protected at day 10
Leneva 2000 ³⁹	A/HK/156/97	Mouse	1 mg/kg/day	Delayed until 72 h after infection, continued twice daily for 5 days	T=0% at day 10† C=0%	No protection at day 10
Govorkova 2001 ⁴⁰	A/HK/156/97	Mouse	0.1- 1.0 mg/kg/day	4 h pre infection, twice daily for 5 days	T=6/6* C=0/11	Completely protected
Govorkova 2001 ⁴⁰	A/HK/156/97	Mouse	0.01 mg/kg/day	4 h pre infection, twice daily for 5 days	T=2/6* C=0/11	Partly protected
Govorkova 2001 ⁴⁰	A/HK/156/97	Mouse	10 mg/kg/day	Delayed until 36 h after infection, twice daily for 5 days	T=70%† C=0%	Increased survival
Govorkova 2001 ⁴⁰	A/HK/156/97	Mouse	10 mg/kg/day	Delayed until 48 h after infection, twice daily for 5 days	T=70%† C=0%	Increased survival

Abbreviations: T = treated; C = control

* Viral dose 5 MLD₅₀S

† Viral dose 10 MLD₅₀S

‡ Viral dose 5 MLD₅₀S but virus is significantly more virulent than HK/156/97 (results in Yen 2005)

§ Viral dose 10 EID₅₀

¶ Viral dose 10² EID₅₀

Viral dose 10⁶ EID₅₀

** Viral dose 10^{5.5} CCID₅₀

NB: At dose of 100 MLD₅₀S the combination of treatment did not completely protect mice from death.

Table 10.2.6.1 (continued): Summary of results – survival after oral gavage with oseltamivir

Govorkova 2001 ⁴⁰	A/HK/156/97	Mouse	10 mg/kg/day	Delayed until 60 h after infection, twice daily for 5 days	T=70%† C=0%	Increased survival
Yen 2005 ⁴¹	A/Vietnam/1203/04	Mouse	10 mg/kg/day	4 h pre infection, twice daily for 5 days	T=50%‡ C=0%	Increased survival
Yen 2005 ⁴¹	A/Vietnam/1203/04	Mouse	10 mg/kg/day	4 h pre infection, twice daily for 8 days	T=80%‡ C=0%	Increased survival
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	4 h post infection, twice daily for 5 days	T=3/3§ C=1/3	Completely protected
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	4 h post infection, twice daily for 5 days	T=3/3¶ C=0/3	Completely protected
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	10 mg/kg/day	Delayed until 24 h after infection, twice daily for 5 days	T=0/3¶ C=0/3	No protection
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	25 mg/kg/day	Delayed until 24 h after infection, twice daily for 5 days	T=3/3¶ C=0/3	Completely protected
Govorkova 2007 ⁴²	A/Turkey/15/06	Ferret	10 mg/kg/day	Delayed until 24 h after infection, twice daily for 5 days	T=3/3# C=3/3	No difference in survival
Sidwell 2007 ⁴³	A/Duck/MN/1525/81	Mice	20 mg/kg/day	First dose administered simultaneous to infection, thereafter twice daily for 5 days in two parallel experiments	T=2/10** C=0/20 T=1/10** C=0/20	Weakly effective though significant positive effect on mean days to death compared to control

Abbreviations: T = treated; C = control

* Viral dose 5 MLD₅₀s† Viral dose 10 MLD₅₀s‡ Viral dose 5 MLD₅₀s but virus is significantly more virulent than HK/156/97 (results in Yen 2005).§ Viral dose 10 EID₅₀¶ Viral dose 10² EID₅₀# Viral dose 10⁶ EID₅₀** Viral dose 10^{5.5} CCID₅₀

NB: At dose of 100 MLD 50s the combination of treatment did not completely protect mice from death.

Table 10.2.6.2: Summary of results - virus titer in lung measured in five studies

Study	Virus	Model	Treatment	Regimen	Results	Conclusion
Leneva 2000 ³⁹	A/HK/156/97	Mouse	1 and 10 mg/kg/day	4 h pre infection, twice daily for 5 days	T=reduced	Decreased viral titre
Govorkova 2001 ⁴⁰	A/HK/156/97	Mouse	1 and 10 mg/kg/day	4 h pre infection, twice daily for 5 days	T=reduced	Decreased viral titre
Yen 2005 ⁴¹	A/Vietnam/1203/04	Mouse	1 and 10 mg/kg/day	4 h pre infection twice daily for 5 days	T=reduced*	Decreased viral titre
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	First dose administered simultaneous to infection, thereafter twice daily for 5 days	T=not detected †,¶ C=4.0 (SD 0.8)	Completely inhibited viral replication (p<0.05)
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	4 h post infection twice daily for 5 days	T=not detected‡,¶ C=5.8 (SD 0.5)	Completely inhibited viral replication (p<0.05)
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	10 mg/kg/day	24 h post infection, twice daily for 5 days	T=3.6 (SD 0.4) ‡,¶ C=5.0 (SD 0.6)	Significantly inhibited viral replication (p<0.05)
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	25 mg/kg/day	24 h post infection, twice daily for 5 days	T=not detected‡,¶ C=5.0 (SD 0.6)	Completely inhibited viral replication (p<0.05)
Govorkova 2007 ⁴²	A/Turkey/15/06	Ferret	10 mg/kg/day	24 h post infection, twice daily for 5 days	T=not detected§,¶ C=2.9 (SD 0.7)	Completely inhibited viral replication (p<0.05)
Sidwell 2007 ⁴³	A/Duck/MN/1525/81	Mice	20 mg/kg/day	1h post infection, twice daily for 5 days in two parallel experiments	T=6.1+0.5# C=6.3+0.4 T=6.3+0.1# C=6.4+0.4	No significant difference in viral titre levels between oseltamivir and control groups**

Abbreviations: T = treated; C = control

* Reduced at day 3 and 6 post infection but not day 9

† Viral dose 10 EID₅₀

‡ Viral dose 10² EID₅₀

§ Viral dose 10⁶ EID₅₀

¶ Virus titre log₁₀ EID₅₀/g on day 6 (mean and standard deviation (SD) based on 2 animals; data read from graphs); limit of detection 0.75 log₁₀ EID₅₀/g

Day 1 mean virus titre

** This lesser activity of oseltamivir against H5N1 infection in mice has been reported by Yen *et al.* (2005), they suggested lengthening the treatment course had a more protective effect. The authors note that treatment with oseltamivir began 1h after virus exposure, which may also affect the drugs ability to inhibit infection.

Table 10.2.6.3: Summary of results - virus titre in brain measured in four studies

Study	Virus	Model	Treatment	Regimen	Results	Conclusion
Leneva 2000 ³⁹	A/HK/156/97	Mouse	0.1 mg/kg/day	4 h pre infection, twice daily for 5 days	T=not detected	Prevented spread to brain
Govorkova 2001 ⁴⁰	A/HK/156/97	Mouse	0.1 mg/kg/day	4 h pre infection, twice daily for 5 days	T=not detected	Prevented spread to brain
Yen 2005 ⁴¹	A/Vietnam/1203/04	Mouse	10 mg/kg/day	4 h pre infection twice daily for 5 or 8 days	T=not detected*	Prevented spread to brain
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	4 h post infection, twice daily for 5 days	T=3.2#, †, ¶ C=4.4 (SD 1.2)	Virus detected in 1/2 animals
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	4 h post infection, twice daily for 5 days	T=4.6#, †, ¶ C=5.4 (SD 0.8)	Virus detected in 1/2 animals
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	10 mg/kg/day	24 h post infection, twice daily for 5 days	T=4.0 (SD 1.2) ‡, ¶ C=5.4 (SD 0.6)	Not significantly different
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	25 mg/kg/day	24 h post infection, twice daily for 5 days	T=3.8#, †, ¶ C=5.4 (SD 0.6)	Virus detected in 1/2 animals
Govorkova 2007 ⁴²	A/Turkey/15/06	Ferret	10/mg/kg/day	24 h post infection, twice daily for 5 days	T=not detected §, ¶ C=not detected	Virus not detected

Abbreviations: T = treated; C = control

* Virus was detected in brain at lower concentrations of treatment (0.1 mg/kg/day and 1 mg/kg/day).

† Viral dose 10 EID₅₀

‡ Viral dose 10² EID₅₀

§ Viral dose 10⁶ EID₅₀

¶ Virus titre log₁₀ EID₅₀/g on day 6

Virus detected in 1/2 animals otherwise mean and standard deviation (SD) based on 2 animals; data read from graphs; limit of detection 0.75 log₁₀ EID₅₀/g.

Table 10.2.6.4: Summary of results - virus titre in spleen measured in one study

Study	Virus	Model	Treatment	Regimen	Results	Conclusion
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	4 h post infection, twice daily for 5 days	T=not detected *, ‡ C=3.0 (SD 0.8)	Completely inhibited viral replication (p<0.05)
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	4 h post infection, twice daily for 5 days	T=3.1#, †, ‡ C=3.8 (SD 0.4)	Virus detected in 1/2 animals
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	10 mg/kg/day	24 h post infection, twice daily for 5 days	T=2.8 (SD 0.4) †, ‡ C=3.8 (SD 0.4)	Significantly inhibited viral replication (p<0.05)
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	25 mg/kg/day	24 h post infection, twice daily for 5 days	T=not detected †, ‡ C=3.8 (SD 0.4)	Completely inhibited viral replication (p<0.05)

Abbreviations: T= treated; C = control

* Viral dose 10 EID₅₀

† Viral dose 10² EID₅₀

‡ Virus titre log₁₀ EID₅₀/g on day 6

Virus detected in 1/2 animals otherwise mean and standard deviation (SD) based on two animals; data read from a graph; limit of detection 0.75 log₁₀ EID₅₀/g

Table 10.2.6.5: Summary of results - virus titre in liver measured in one study

Study	Virus	Model	Treatment	Regimen	Results	Conclusion
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	4 h post infection, twice daily for 5 days	T=not detected *, ‡ C=3.7 (SD 0.2)	Completely inhibited viral replication (p<0.05)
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	4 h post infection, twice daily for 5 days	T=3.0#, †, ‡ C=4.0 (SD 0.8)	Virus detected in 1/2 animals
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	10 mg/kg/day	24 h post infection, twice daily for 5 days	T=3.0 (SD 0.5) †, ‡ C=4.2 (SD 0.2)	Significantly inhibited viral replication (p<0.05)
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	25 mg/kg/day	24 h post infection, twice daily for 5 days	T=not detected †, ‡ C=4.2 (SD 0.2)	Completely inhibited viral replication (p<0.05)

Abbreviations: T = treated; C = control

* Viral dose 10 EID₅₀

† Viral dose 10² EID₅₀

‡ Virus titre log 10 EID₅₀/g on day 6

Virus detected in 1/2 animals otherwise mean and standard deviation (SD) based on two animals; data read from a graph; limit of detection 0.75 log₁₀ EID₅₀/g

Table 10.2.6.6: Summary of results - virus titre in small intestine measured in one study

Study	Virus	Model	Treatment	Regimen	Results	Conclusion
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	4 h post infection, twice daily for 5 days	T=not detected*,‡ C=1.4#	Completely inhibited viral replication (p<0.05)
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg/day	4 h post infection, twice daily for 5 days	T=not detected†,‡ C=2.7#	Completely inhibited viral replication (p<0.05)

Abbreviations: T = treated; C = control

* Viral dose 10 EID₅₀

† Viral dose 10² EID₅₀

‡ Virus titre log₁₀ EID₅₀/g on day 6

Virus detected in 1/2 animals otherwise mean and standard deviation (SD) based on 2 animals; data read from a graph; limit of detection 0.75 log₁₀ EID₅₀/g

Table 10.2.6.7: Summary of results - viral titer (nasal wash samples) measured in two studies

Study	Virus	Model	Treatment	Regimen	Results	Conclusion
Le 2005 ⁴⁴	A/Hanoi/30408 (oseltamivir resistant strain)	Ferret	25 mg/kg orally	2 h post infection, twice daily for 5 days	<u>Treated</u> Viral titers higher after treatment than animals infected with oseltamivir-sensitive virus*	Possible resistance*
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg orally	4 h post infection, twice daily for 5 days	<u>Treated</u> not detected on day 3, 5 and 7†, <u>Control</u> 2.8 on day 3 4.1 on day 5 4.5 on day 7‡	Significantly inhibited viral replication (p<0.05)
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 mg/kg orally	4 h post infection, twice daily for 5 days	<u>Treated</u> not detected on day 3, 5 and 7 ¶, <u>Control</u> 4.4 on day 3 5.5 on day 5 6.5 on day 7§	Significantly inhibited viral replication (p<0.05)
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	10 mg/kg orally	24 h post infection, twice daily for 5 days	<u>Treated</u> 3.6 on day 3 5.4 on day 5 5.4 on day 7 ¶, <u>Control</u> 4.0 on day 3 4.9 on day 5 6.1 on day 7	No significant difference
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	25 mg/kg orally	24 h post infection, twice daily for 5 days	<u>Treated</u> 3.0 on day 3 3.2 on day 5 3.6 on day 7 ¶, <u>Control</u> 4.0 on day 3 4.9 on day 5 6.1 on day 7	Mean titer on day 7 significantly lower (p<0.05)

* Quality of effect measurement: Data is from a brief communication in Nature, some details not clear. Results not significant (p=0.23, Student's T-test). Results are based on isolation of oseltamivir-resistant (either high resistance or low resistance) and oseltamivir-sensitive strains of virus from a single patient.

† Viral dose 10 EID₅₀

¶ Viral dose 10² EID₅₀

Viral dose 10⁶ EID₅₀

|| Virus titer mean log₁₀ EID₅₀/mL, limit of detection 0.75 log₁₀ EID₅₀/mL; 3 animals per group (†day 7 data based on 1/3 animal in which virus was detected; §day 7 data based on 1/3 surviving animal); data read from graphs.

Table 10.2.6.7 (continued): Summary of results - viral titer (nasal wash samples) measured in two studies

Study	Virus	Model	Treatment	Regimen	Results	Conclusion
Govorkova 2007 ⁴²	A/Turkey/15/06	Ferret	10 mg/kg/day	Delayed until 24 h after infection, twice daily for 5 days	<u>Treated</u> 5.2 on day 3 4.4 on day 5 not detected on day 7 #, <u>Control</u> 5.0 on day 3 3.8 on day 5 3.2 on day 7 †	No significant difference

* Quality of effect measurement: Data is from a brief communication in Nature, some details not clear. Results not significant ($p=0.23$, Student's T-test). Results are based on isolation of oseltamivir-resistant (either high resistance or low resistance) and oseltamivir-sensitive strains of virus from a single patient.

† Viral dose 10 EID_{50}

¶ Viral dose 10^2 EID_{50}

Viral dose 10^6 EID_{50}

|| Virus titer mean $\log_{10} \text{ EID}_{50}/\text{mL}$, limit of detection $0.75 \log_{10} \text{ EID}_{50}/\text{mL}$; 3 animals per group ([‡]day 7 data based on 1/3 animal in which virus was detected; [§]day 7 data based on 1/3 surviving animal); data read from graphs.

Table 10.2.6.8: Summary of results – resistance in animals treated with oseltamivir

Study	Virus	Model	Treatment	Regimen	Virus resistant after trial
Govorkova 2001 ⁴⁰	A/HK/156/97	Mouse	1 - 10 mg/kg/day	4 h pre infection, twice daily for 5 days	Not resistant
Yen 2005 ⁴¹	A/Vietnam/1203/04	Mouse	1 – 10 mg/kg/day	4 h pre infection twice daily for 5 or 8 days	Not resistant
Govorkova 2007 ⁴²	A/Vietnam/1203/04	Ferret	5 – 25 mg/kg/day	4 h or 24 h post infection twice daily for 5 days	Sequence analysis showed no substitutions known to cause drug resistance†
Govorkova 2007 ⁴²	A/Turkey/15/06	Ferret	10 mg/kg/day	24 h post infection twice daily for 5 days	Sequence analysis showed no substitutions known to cause drug resistance

† No change in oseltamivir sensitivity was found in one clone in which a H274Y mutation was found

Table 10.2.7.1: Summary of results - survival measured in two studies

Study	Virus	Model	Treatment	Regimen	Results	Conclusion
Leneva 2000 ³⁹	A/Quail/ HK/G1/97 (H9N2)	Mouse	Rimantadine 1 mg/kg/day + Oseltamivir 0.1 mg/kg/day	4 h pre infection, twice daily for 5 days	T=10/10* C=0/10	Completely protected**
Galabov 2006 ⁴⁵	A/Aichi/2/ 68 (H3N2)	Mouse	Rimantadine 5 mg/kg/day + Oseltamivir 0.05 mg/kg/day*	4 h pre infection, three times daily for 5 days	T=6/11† T=8/11‡ C=4/19‡	Increased survival§

Abbreviations: T = treated; C = control

* Combinations of varying concentrations of oseltamivir (0.05, 0.1 and 0.2 mg/kg/day) and rimantadine (2.5, 5.0 and 7.5 mg/kg/day) were tested to establish the optimal combination dose. The control group received a placebo (PBS).

† 10 MLD₅₀s

‡ 20 MLD₅₀s. When rimantadine alone given at 5 mg/kg/day 2/24 mice survived and when oseltamivir alone given at 0.05 mg/kg/day 4/24 mice survived.

§ There was a statistically significant increase in mean survival time for mice receiving combination treatment.

NB: At dose of 100 MLD₅₀s the combination of treatment did not completely protect mice from death.

Table 10.2.7.2: Summary of results - virus titre in the lung measured in one study

Study	Virus	Model	Treatment	Regimen	Results	Conclusion
Galabov 2006 ⁴⁵	A/Aichi/2/ 68 (H3N2)	Mouse	Rimantadine 5 mg/kg/day and Oseltamivir 0.05 mg/kg/day	4 h pre infection, three times daily for 5 days	<u>Treated</u> 2.8 log decrease compared with control*	Decreased viral titre†

* Log₁₀ TCID₅₀/mL on day 5. Oseltamivir alone produced 0.1-1.0 log decrease and rimantadine alone produced 1.1-1.4 log decrease in virus titres in lung.

† The lung virus content curve reached a peak at 84 hours, a 24 hour delay compared to the control group.

Table 10.2.7.3: Summary of results - survival measured in one study (dose and regimen vary)

Study ID	Virus	Model	Treatment	Regimen	Results	Conclusion
Ilyushina 2007 ⁴⁶	A/Vietnam/ 1203/04 (H5N1) sensitive	Mouse	Amantadine 15 mg/kg/day + Oseltamivir 10 mg/kg/day Amantadine 30 mg/kg/day + Oseltamivir 10 mg/kg/day	24h pre- infection, thereafter twice daily for 5 days	T= 6/10* C=0/10§ T= 9/10*	Increased survival†
	A/Vietnam/ 1203/04 (H5N1) resistant	Mouse	Amantadine 15 mg/kg/day + Oseltamivir 10 mg/kg/day	24h pre- infection, thereafter twice daily for 5 days	T=3/10* C=0/10§	Increased survival‡

Abbreviations: T = treated; C = control

* Viral dose 10 MLD₅₀s.

† There was a statistically significant increase in the survival rate for mice receiving combination treatment. Among those receiving amantadine 15mg/kg/day alone and 30 mg/kg/day alone 4/10 and 6/10 survived respectively and for those receiving oseltamivir 10mg/kg/day alone 3/10 survived.

‡ There was a statistically significant increase in the survival rate for mice receiving combination treatment compared to no-treatment controls and amantadine alone. For the resistant strain, survival

in the combination group was not greater than that observed with oseltamivir 10 mg/kg/day alone (3/10).

§ Controls received placebo.

Table 10.2.7.4: Summary of results - virus titre in lung measured in one study

Study	Virus	Model	Treatment	Regimen	Results	Conclusion
Ilyushina 2007 ⁴⁶	A/Vietnam/1203/04 (H5N1) sensitive	Mouse	Amantadine 15 mg/kg/day + Oseltamivir 10 mg/kg/day Amantadine 30 mg/kg/day + Oseltamivir 10 mg/kg/day	24h pre-infection, thereafter twice daily for 5 days	Reduced Reduced	Decreased viral titre*
Ilyushina 2007 ⁴⁶	A/Vietnam/1203/04 (H5N1) resistant	Mouse	Amantadine 15mg/kg/day + Oseltamivir 10 mg/kg/day	24h pre-infection, thereafter twice daily for 5 days	T=6.2 ± 0.2† C=7.5 ± 0.3	Decreased viral titre‡

Abbreviations: T = treated; C = control

* Viral titre levels significantly lower than the combination group with lower dose amantadine at days 3, 6 and 9 post infection. Data was presented graphically. Viral titre levels significantly lower compared to no-treatment controls and those receiving amantadine or oseltamivir alone.

† At day 6 (± SE)

‡ Viral titre levels significantly lower compared to no-treatment controls and those receiving amantadine alone. Viral titres among those receiving amantadine 15 mg/kg/day alone was 7.8 ± 0.1 and among those receiving oseltamivir 10mg/kg/day alone was 6.2 ± 0.1.

Table 10.2.7.5: Summary of results – virus titre in brain measured in one study

Study ID	Virus	Model	Treatment	Regimen	Results	Conclusion
Ilyushina 2007 ⁴⁶	A/Vietnam/1203/04 H5N1 sensitive	Mouse	Amantadine 15 mg/kg/day + Oseltamivir 10 mg/kg/day Amantadine 30 mg/kg/day + Oseltamivir 10 mg/kg/day	24h pre-infection, thereafter twice daily for 5 days	Not detected Not detected	Prevented spread to the brain*
Ilyushina 2007 ⁴⁶	A/Vietnam/1203/04 H5N1 resistant	Mouse	Amantadine 15mg/kg/day + Oseltamivir 10mg/kg/day	24h pre-infection, thereafter twice daily for 5 days	T=1.3 ± 0.6† C=5.0 ± 0.6†	Efficacy of drug combination against resistant virus was the comparable to that of oseltamivir alone‡

Abbreviations: T = treated; C = control.

* Data was presented graphically. Viral titre levels significantly lower compared to no-treatment controls and those receiving amantadine or oseltamivir alone (although at the higher concentration amantadine did prevent spread to the brain).

† At day 6, ± SE.

‡ Viral titre levels significantly lower compared to no-treatment controls and those receiving amantadine alone. Viral titres among those receiving amantadine 15 mg/kg/day alone was 5.2 ± 0.4 and among those receiving oseltamivir 10mg/kg/day alone was 1.8 ± 0.7.

Table 10.2.7.6: Summary of results – virus resistance measured in one study

Study ID	Virus	Model	Treatment	Regimen	Virus resistant after trial
Ilyushina 2007 ⁴⁶	A/Vietnam/1203/04 H5N1 sensitive and resistant strains	Mouse	Amantadine 15 mg/kg/day + Oseltamivir 10 mg/kg/day Amantadine 30 mg/kg/day + Oseltamivir 10 mg/kg/day	24h pre-infection, thereafter twice daily for 5 days	No evidence of amino acid mutations in HA, NA or M2 genes after the drugs used in combination

Appendix C

Summary of results – *in vitro* evidence of oseltamivir treatment for human and avian influenza (H5N1)

Study	Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Conclusions
Leneva 2000 ³⁹	1. A/HK/156/97 (H5N1)	1. ELISA 2. NA inhibition	1. H5N1 vs. H9N2 (A/HK/1974/99)	Inhibited viral replication of both viruses. Concentrations required in each virus were similar.	NA was inhibited for both viruses. Sensitivity of viruses were similar	Oseltamivir inhibits replication and NA activity of both viruses. Viruses did not differ in sensitivity to drug.
Rameix-Welti 2006 ⁴⁷	Pre 2004 Hong Kong (H5N1): 1. A/HK/156/97 2. A/HK/213/03 Post 2004 Vietnam (H5N1): 3. A/VN/JP14/05 4. A/VN/JP20-2/05 5. A/VN/JP4207/05 6. A/VN/JPHN/30321/05 7. A/VN/1203/04 Cambodia (H5N1): 8. A/Ck/CB/07/05 9. A/Goose/CB/26/04 10. A/Ck/CB/013LC1b/05 11. A/Ck/CB/013LC2b/05 12. A/CB/408008/05	1. NA in vitro inhibition 2. MDCK cell-based virus inhibition 3. NA enzymatic activity and inhibition using whole cells expressing the viral enzyme	1. H5N1 vs. A/Paris/0650/04 (H1N1)	Inhibited viral replication in all viruses. Concentrations required were similar for both pre 2004 H5N1 and H1N1. Concentrations required to inhibit viral replication of post-2004 H5N1 viruses were reduced compared to pre-2004.	NA was inhibited for both viruses. Post-2004 H5N1 viruses were 10x more sensitive compared to H1N1 virus and pre-2004 H5N1.	Oseltamivir inhibits viral replication and NA activity much more effectively for post-2004 H5N1 viruses than pre-2004 H5N1. The implication of this finding is uncertain.
Selvam 2006 ⁴⁸	1. A/Duck/MN/1525/81 (H5N1) 2. A/New Caledonia/20/99 (H1N1) 3. A/Panama/2007/99 (H3N2)	1. Inhibition of cytopathic effect (CPE) assay. 2. Virus yield reduction assay.	1. Viruses 2. Six experimental substances (isatin compounds), oseltamivir and ribavirin	Oseltamivir inhibited viral replication in all viruses and exhibited greater antiviral potency than both ribavirin and the isatin compounds. Concentrations required to inhibit viral activity were lowest for H5N1 and highest for H3N2.	Not studied	Oseltamivir inhibited virus replication of all viruses studied.

Summary of results – *in vitro* evidence of oseltamivir treatment for human and avian influenza (H5N1)

Study	Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Conclusions
Sidwell 2007 ⁴³	1. A/Hong Kong/213/03 x Ann Arbor/6/60 2. A/Vietnam/1203/04 x Ann Arbor/6/60 3. A/Duck/MN/1525/81 4. A/Gull/PA/4175/83 (All H5N1)	1. CPE assay 2. Virus yield reduction assay	1. Viruses 2. Experimental substance T-705 vs zanamivir and oseltamivir and ribavirin	Oseltamivir inhibited viral replication in all viruses. Required concentrations of zanamivir and oseltamivir were similar. The experimental substance T-705 was less potent in reducing viral yield than the neuraminidase inhibitors but more so than ribavirin.	Not studied	Zanamivir and oseltamivir inhibited virus replication of all viruses, but higher concentrations were required for the duck/MN and gull/PA viruses. T-705 required higher concentrations than zanamivir and oseltamivir.
Smee 2001 ⁴⁹	1. A/Duck/MN/1525/81 (H5N1) 2. A/Gull/PA/4175/83 (H5N1) 3. H1N1 (5 strains) 4. H3N2 (12 strains)	1. Inhibition of cytopathic effect 2. Virus yield reduction 3. Time-of-addition studies	1. Viruses 2. Zanamivir vs. oseltamivir	Inhibited viral replication in all viruses. Required concentrations of zanamivir and oseltamivir were similar.	Not studied	Zanamivir and oseltamivir inhibited virus replication of all viruses.

Summary of results - resistance evaluations by *in vitro* study and/or sequence data

Study	Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Outcome: Change in sensitivity	Conclusions
de Jong 2005 ²²	1. H5N1 variant in Vietnam patients (H274Y substitution in neuraminidase gene)	1. isolation by RT-PCR, then sequence	N/A	N/A	N/A	Virus with mutations that confirm high-resistance to oseltamivir were isolated from two patients after treatment with oseltamivir.	In some patients treatment with oseltamivir incompletely suppresses viral replication. Higher doses, longer duration or other antiviral agents may be necessary.
McKimm-Breschkin 2003 ⁵⁰	1. A/N1 (human, 139 strains) 2. A/N2 (human, 767 strains)	1. NA inhibition by fluorescence 2. NA inhibition by chemiluminiscent	1. Viruses 2. Zanamivir vs. oseltamivir	N/A	N2 viruses were generally more sensitive to oseltamivir than zanamivir. Slight differences seen between assay types. N1 viruses were slightly more sensitive to zanamivir than oseltamivir.	No altered sensitivity in viruses that had variations in sequence residues.	H1N1 and H3N2 viruses circulating 1996-1999 were susceptible to zanamivir & oseltamivir. This is before the drugs were introduced for use in the area. Some variants were seen but no evidence of naturally occurring resistance to these two drugs.
Hurt 2004 ⁵¹	1. A/H1N1 (human, 235 strains) 2. A/H3N2 (human, 160 strains) 3. A/H1N2 (human, 9 strains)	1. NA inhibition by fluorescence	1. N1 vs. N2 2. Year of isolation 3. Australasia vs. South East Asia	N/A	N1 viruses were more sensitive to zanamivir than oseltamivir. N2 strains were more sensitive to oseltamivir. Similar susceptibility of Australasia & South East Asia strains.	No significant decline in sensitivity in Australasia strains by year of isolation.	After NA inhibitors were in use in the region, no significant impact on susceptibility of viruses to zanamivir or oseltamivir.

Summary of *in vitro* evidence of combination treatment for human and avian influenza (H5N1)**Summary of results - combinations of NA inhibitor plus rimantadine (data from H1N1 and H3N2)**

Study	Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Conclusions
Govorkova 2004 ⁵²	1. A/New Caledonia/20/99 (H1N1) 2. A/Panama/2007/99 (H3N2)	1. Extra-cellular virus yield reduction assay 2. ELISA to determine the cell-associated virus reduction	1. zanamivir + rimantadine vs. single drug 2. oseltamivir + rimantadine vs. single drug	Combination of rimantadine and zanamivir or rimantadine and oseltamivir resulted in complete reduction in H1N2 and H3N2 extracellular viral yield. Interactions were mainly synergistic or additive.	Not studied	Combination treatment with zanamivir or oseltamivir with rimantadine markedly reduces the extracellular H1N1 and H3N2 virus yield. Synergism or additive effects seen at a range of concentrations.

Summary of results - resistance evaluations by *in vitro* study and/or sequence data

Study	Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Development of drug resistance after several viral passages	Outcome: Development of drug resistance mutations detected by RT-PCR after several viral passages	Conclusions
Ilyushina 2006 ⁵³	1. A/Hong Kong/156/97 (H5N1) 2. A/Nanchang/1/99 (H1N1) 3. A/Panama/2007/99 (H3N2)	1. Plaque reduction assay 2. NA enzyme inhibition 3. RT-PCR and sequencing for mutations	1. Amantadine alone 2. Oseltamivir alone 3. Amantadine and Oseltamivir in combination 4. No anti-viral drugs (control)	Increasing amantadine concentrations reduced virus yields by 90-100%. Increasing oseltamivir concentrations reduced virus yields by 0-90%. Amantadine and oseltamivir in combination caused complete viral inhibition. Interactions between the drugs were both synergistic and additive.	Viruses passaged in the presence of amantadine alone had 100-200 fold lower susceptibility to amantadine in the plaque reduction assay than viruses passaged in the absence of anti-viral drugs. Viruses passaged in the presence of oseltamivir alone had 10-1000 fold lower susceptibility to oseltamivir in the NA enzyme inhibition assay without anti-viral drugs. When amantadine and oseltamivir were used in combination at sufficient concentration, drug resistant variants did not develop	No mutations were detected when the viruses were passaged in the absence of anti-viral drugs M2 gene mutations were detected after viruses were passaged in the presence of amantadine alone. HA gene mutations were detected after viruses were passaged in the presence of oseltamivir alone. No significant mutations were detected in the HA, NA and M2 genes when the viruses were passaged in the presence of both amantadine and oseltamivir at sufficient concentrations.	In vitro passage of virus in the presence of amantadine alone results in the generation of amantadine-resistant variants. In vitro passage of virus in the presence of oseltamivir alone results in the generation of oseltamivir-resistant variants. No drug-resistant variants were detected when the drugs were used in combination at sufficient concentrations.

Summary of *in vitro* evidence for H5N1

Inhibition of viral replication – determined by 50% inhibition of viral replication in MDCK cells*			
		Oseltamivir phosphate/ carboxylate	NA inhibitor + M2 ion channel blocker
STUDY	HUMAN H5N1		
Leneva 2000 ³⁹	A/HK/156/97	Y	
Rameix-Welti 2006 ⁴⁷	A/HK/156/97	Y	
Rameix-Welti 2006 ⁴⁷	A/HK/213/03	Y	
Rameix-Welti 2006 ⁴⁷	A/VN/JP14/05	Y	
Rameix-Welti 2006 ⁴⁷	A/VN/JP20-2/05	Y	
Rameix-Welti 2006 ⁴⁷	A/VN/JP4207/05	Y	
Rameix-Welti 2006 ⁴⁷	A/VN/JPHN/30321/05	Y	
Rameix-Welti 2006 ⁴⁷	A/VN/1203/04	Y	
Rameix-Welti 2006 ⁴⁷	A/CB/408008/05	Y	
	AVIAN H5N1		
Smee 2001 ⁴⁹	A/Duck/MN/1525/81	Y [†]	
Smee 2001 ⁴⁹	A/Gull/PA/4157/83	Y [†]	
Selvam 2006 ⁴⁸	A/Duck/MN/1525/81	Y	
Rameix-Welti 2006 ⁴⁷	A/Goose/CB/26/04	Y	
Rameix-Welti 2006 ⁴⁷	A/Ck/CB/07/05	Y	
Rameix-Welti 2006 ⁴⁷	A/Ck/CB/013LC1b/05	Y	
Rameix-Welti 2006 ⁴⁷	A/Ck/CB/013LC2b/05	Y	
Sidwell 2007 ⁴³	A/Hong Kong/213/03 x Ann Arbor/6/60	Y	
Sidwell 2007 ⁴³	A/Vietnam/1203/04 x Ann Arbor/6/60	Y	
Sidwell 2007 ⁴³	A/Duck/MN/1525/81	Y	
Sidwell 2007 ⁴³	A/Gull/PA/4175/83	Y	
Ilyushina 2006 ⁵³	A/Hong Kong/156/97		Y [‡]
	HUMAN FLU A		
Smee 2001 ⁴⁹	Multiple strains (H1N1)	Y	
Smee 2001 ⁴⁹	Multiple strains (H3N2)	Y	
Govorkova 2004 ⁵²	A/New Caledonia/20/99 (H1N1)		Y [§]
Govorkova 2004 ⁵²	A/Panama/2007/99 (H3N2)		Y [¶]
Ilyushina 2006 ⁵³	A/Nanchang/1/99 (H1N1)		Y [‡]
Ilyushina 2006 ⁵³	A/Panama/2007/99 (H3N2)		Y [‡]
Selvam 2006 ⁴⁸	A/New Caledonia/20/99 (H1N1)	Y	
Selvam 2006 ⁴⁸	A/Panama/2007/99 (H3N2)	Y	

Y = Yes (an effect was demonstrated); N = No (no effect demonstrated).

† Activities of zanamivir and oseltamivir were similar.

‡ The combination of a amantadine and oseltamivir was both synergistic and additive.

§ The combination of a NA-inhibitor (either zanamivir or oseltamivir) and rimantadine is synergistic or additive.

¶ The combination of a NA-inhibitor (either zanamivir or oseltamivir) and rimantadine is mainly synergistic.

Summary of *in vitro* evidence for H5N1

Inhibition of oseltamivir phosphate (OP) – determined by 50% inhibition of OP in MDCK cells		
		Oseltamivir phosphate
STUDY ID	HUMAN H5N1	
Leneva 2000 ³⁹	A/HK/156/97	Y
Rameix-Welti 2006 ⁴⁷	A/HK/156/97	Y
Rameix-Welti 2006 ⁴⁷	A/HK/213/03	Y
Rameix-Welti 2006 ⁴⁷	A/VN/JP14/05	YY
Rameix-Welti 2006 ⁴⁷	A/VN/JP20-2/05	YY
Rameix-Welti 2006 ⁴⁷	A/VN/JP4207/05	YY
Rameix-Welti 2006 ⁴⁷	A/VN/JPHN/30321/05	YY
Rameix-Welti 2006 ⁴⁷	A/VN/1203/04	YY
Rameix-Welti 2006 ⁴⁷	A/CB/408008/05	YY
	HUMAN FLU A	
McKimm-Breschkin 2003 ⁵⁰	Multiple strains/N1	Y
Hurt 2004 ⁵¹	Multiple strains H1N1	Y
McKimm-Breschkin 2003 ⁵⁰	Multiple strains/N2	YY*
Hurt 2004 ⁵¹	Multiple strains A/H3N2	YY*
Hurt 2004 ⁵¹	Multiple strains A/H1N2	YY*
Rameix-Welti 2006 ⁴⁷	A/Paris/0650/04	Y

Y = Yes (an effect was demonstrated); N = No (no effect demonstrated).

YY = indicates a slight increase in susceptibility compared to the other compound.

* Sensitivity to each compound was compared among N1 and N2 viruses in the same study.

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