National PBM Drug Monograph
Oseltamivir (Tamiflu®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

INTRODUCTION

In 1997, a highly pathogenic avian influenza A (H5N1) virus was transmitted to humans, killing 6 out of 18 people that were infected. During December 2003-February 2004, outbreaks of H5N1 in poultry were reported in Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand, and Vietnam.[1] During this recent outbreak, there have been 34 confirmed human cases of infection with the H5N1 strain in Vietnam and Thailand secondary to contact with infected poultry, with 24 resulting in death. Additionally, there is 1 unconfirmed case in a 12-year old boy from a southern province in Vietnam. The boy was hospitalized on March 13 and died 2 days later. A recently published study has found that the viruses isolated from human in 1997 were antigenically different from the ones isolated from humans in 2003.[2]

Table 1. Human cases of infection with H5N1 (2003-2004)

Country	Total cases	Deaths
Thailand	12	8
Viet Nam	22	15
Total	**34**	**23**

Laboratory confirmed cases as of March 24, 2004

Avian influenza A H5N1 appears to have re-emerged in poultry in several Asian countries in late June-early July of this year. On August 12, 2004, the Vietnamese Ministry of Health officially reported 3 human deaths from confirmed avian influenza H5N1 infection. It is unknown if this strain is the same as the one the one earlier this year. http://www.cdc.gov/flu/avian/outbreaks/asia.htm

In August 2004, avian influenza was isolated from pigs in China; however, this is awaiting confirmation. http://www.who.int/csr/don/2004_08_20/en/

Health officials are concerned about the strain mutating or reassorting with human influenza A, ultimately enabling the virus to be passed among humans. Late September 2004, officials in Thailand announced a probable case of human-human transmission in a family. Analysis of specimens is underway at a WHO collaborating laboratory to determine whether the virus has changed its genetic make-up. http://www.who.int/csr/don/2004_10_04/en/

A vaccine for the H5N1 strain is currently under development; however, it is not expected to be available until the 2005-2006 flu season at the earliest. Neither amantadine nor rimantadine are effective for treatment or prophylaxis of the H5N1 strain. Preliminary results show that viruses isolated from humans infected with H5N1 were resistant to amantadine and rimantadine. The WHO guidelines also state that amantadine and rimantadine should not be used because of "the risk of increasing the selective pressure for development of a resistant influenza virus with pandemic potential." Oseltamivir, a neuraminidase inhibitor, has activity against influenza A (H5N1).
http://www.who.int/csr/disease/avian_influenza/guidelines/en/Guidelines_Clinical%20Management_H5N1_rev.pdf

The VA is preparing to respond to this potential threat by purchasing a stockpile of oseltamivir. Oseltamivir has a 5-year shelf life. In the event an outbreak of influenza A (H5N1) in the U.S. does not occur, oseltamivir can be used for prophylaxis and treatment of uncomplicated human influenza A or B virus.

This review will present clinical data on use in general human influenza and the available data on its use in avian influenza A (H5N1).

MECHANISM OF ACTION

Oseltamivir is a neuraminidase inhibitor and is potentially active against influenza A and B. Neuraminidase is present on the surface of both influenza A and B. Neuraminidase catalyzes the cleavage of sialic acid residues on the surface of the influenza virus, which by doing so promotes release of the virus,

prevents viral inactivation by respiratory tract mucus, contributes to viral pathogenicity, and induces cellular apoptosis and release of pro-inflammatory cytokines.

The older antivirals, amantadine and rimantadine block the ion channel activity of the influenza M2 protein found in influenza A (not in influenza B).

PHARMACOKINETICS

Oseltamivir is a prodrug that is converted to the active metabolite oseltamivir carboxylate mainly via hepatic esterases. Approximately 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate.

Table 2. Pharmacokinetics

Parameter	Oseltamivir carboxylate
Peak plasma concentration (Cmax) when dosed at 75mg BID	348 ng/mL (concentration increases proportionally with dose)
Time to peak concentration (Tmax)	3-4 hours
Volume of distribution (Vd)	25.6L
Protein binding	3%
Interaction with CYP450 enzymes	Oseltamivir and oseltamivir carboxylate are not substrates for, or inhibitors of CYP450 enzymes
Elimination	Glomerular filtration and renal tubular secretion 63% of dose recovered in urine as oseltamivir carboxylate; < 20% recovered in feces as either unchanged drug or oseltamivir carboxylate
Half-life (t1/2)	6-10 hours

INFLUENZA SUSCEPTIBILITY TO OSELTAMIVIR

Influenza viruses were collected worldwide from the 2000-2001 and 2001-2002 flu seasons and susceptibility to oseltamivir determined using a chemiluminescent assay. There was a slight decrease in susceptibility for influenza B over the 2 years, while susceptibility to oseltamivir slightly increased for influenza A (Table 3). [3]

North American isolates from 1996-1999, before the introduction of oseltamivir to the market, were tested for susceptibility to oseltamivir. The mean IC_{50}, as determined by chemiluminescent assay, for H1N1, H1N2, and B were 0.66, 0.68, and 5.47nM respectively. Worldwide, the IC_{50} values were 0.62, 0.92, and 5.21nM respectively. While the susceptibility to oseltamivir has decreased since its introduction to the market, resistance remains uncommon. [4]

Table 3. Oseltamivir susceptibility

	2000-2001		2001-2002	
	# isolates	IC_{50}	# isolates	IC_{50}
H1N1	113	1.88 ± 0.58	120	0.8 ± 0.07
H1N2	-	-	29	1.14 ± 0.07
H3N2	137	0.67 ± 0.05	316	0.6 ± 0.04
B	122	11.85 ± 1.05	213	13.98 ± 0.61

Mean ± SE
Units are in nM

Data received from the WHO Global Influenza Surveillance Network indicate that recent influenza A (N5N1) viruses are susceptible to oseltamivir. All strains tested (4 human isolates and 33 bird isolates) demonstrated *in vitro* susceptibility to this drug. www.who.int/csr/don/2004_02_12a/en/

Another avian influenza A virus (H9N2) has also been shown to be susceptible to oseltamivir.[10]

RESISTANCE

The Neuraminidase Inhibitor Susceptibility Network has been established to monitor potential development of resistance to the neuraminidase inhibitors. [5]

Resistance to neuraminidase inhibitors can be the result of mutations that occur to the viral neuraminidase or viral hemagglutinin or both.

The development of viral resistance to oseltamivir has been studied by in vitro serial passage of influenza H3N2, H1N1, and B virus strains grown in MDCK cells in the presence of increasing concentrations of oseltamivir. After several passages, mutant viruses with single amino acid substitutions were selected with varying sensitivities to oseltamivir (Table 4). [6] Mice infected with these mutant viral strains showed reduced viral infectivity suggesting that reduced sensitivity in vitro may be of limited clinical significance.

Table 4. Virus neuraminidase mutations resulting from in vitro serial passage

Virus	Passage # at which mutation was detected	Neuraminidase mutation	Oseltamivir sensitivity (fold change)
A/Victoria/3/75 (H3N2)	12	Arg292Lys	30,000
A/Victoria/3/75 (H3N2)	12	Ile222Thr	4
	17	Arg292Lys	30,000
A/Port Chalmers/1/83 (H3N2)		Arg292Lys	Not determined
A/Texas/36/91 (H1N1)	7	Ile222Val	2
	12	Ile222Val, H274Y	1000
A/WS/33 (H1N1)	14	His274Tyr	200
A/WS/33 (H1N1)	11	His274Tyr	300
B/Lee/40		None	

Resistance to oseltamivir during challenge studies

Three influenza virus challenge studies were conducted in human volunteers. One study used strain A/Texas/36/91 (H1N1) (n=53) and the other 2 studies used strain B/yamagata/16/88 (n=49). Viruses from nasal washings obtained pre and post-treatment with oseltamivir were compared for potential emergence of resistance to oseltamivir. Three post-treatment influenza A isolates were found to be resistant to oseltamivir due to a mutation in viral neuraminidase at position His274Tyr. Mutations at the His274Tyr position have also emerged during in vitro serial passage studies using A/Texas/36/91 (H1N1) and have resulted in oseltamivir resistance. [6, 7]

Resistance to oseltamivir in naturally acquired influenza infection

Nasal viral swabs from patients (n=789) were obtained prior to and after treatment with oseltamivir for influenza. Fourteen post-treatment isolates (1.8%) had decreased sensitivity to oseltamivir and all were of the influenza A H3N2 subtype. The resistance that developed in these 14 isolates appeared to be due to a single substitution in viral neuraminidase (Arg292Lys n=10; Glu119Val n=3; His274Tyr n=1). The increase in IC_{50} values ranged from 50 to 86,850 fold. The clinical course of patients harboring the resistant viruses did not differ from those with the wild-type virus. The Arg292Lys and His274Tyr mutations occurring in vivo were also selected during in vitro serial passage studies of influenza A H3N2. [8]

Studies indicate that children may be at a higher risk of developing resistance to oseltamivir.[33, 34] During the 2002 and 2003 flu season in Japan, a total of 50 children received oseltamivir 4mg/kg/day (divided into 2 doses), within 48 hours of onset of symptoms.[33] Nasal swabs, nasal aspirate, or throat swabs were obtained during initial visit and at least once during treatment. Fourteen percent of children had received flu vaccine. Neuraminidase mutations were detected in 9/50 (18%) of samples (Arg292Lys n=6; Glu119Val n=2; Asn294Ser n=1). In 6 cases, the mutant virus co-existed with the wild-type virus and in 3 cases, the mutant fully replaced the wild-type virus. The reduction in sensitivity to oseltamivir compared to pre-treatment for Arg292Lys, Glu119Val, and Asn294Ser was 10^4-10^5-fold, 500-fold, and 300-fold respectively. The mutations occurred in 1/7 vaccinated and 8/43 unvaccinated children. The clinical course of children with resistant versus non-resistant virus was not described. It is also unknown if these mutant viruses with reduced susceptibility to oseltamivir are less virulent or transmissible than the wild-type virus.

USE IN INFLUENZA A (H5N1)

Animal studies

Study 1: The Hong Kong strain of H5N1 from 1997 (influenza A/HK/156/97) was tested in mice. [9] Oseltamivir was administered in doses of 0.1 (n=5), 1.0 (n=5), and 10mg/kg/day (n=5) and placebo (n=4) for 5 days. To study its use in prophylaxis, the first dose was administered 4 hours prior to inoculation of H5N1 (5MLD_{50}s). The mice were observed for 16 days. None of the mice in the placebo group survived (mean survival 7.5 days). All the mice given 1.0 and 10mg/kg/day survived, while only 4/5 survived in the 0.1mg/kg/day group. Virus titers in the lung and brain were determined in some of the mice from each group. Oseltamivir 1.0 and 10mg mg/kg/day significantly reduced virus titer in the lung. The H5N1 virus was undetectable in the brain of mice with a dose as low as 0.1mg/kg/day.

In order to test whether influenza A/HK/156/97 became resistant to oseltamivir during treatment, drug sensitivity of the inoculating virus was compared to virus obtained from the lungs of mice after treatment. Sensitivity of the virus to oseltamivir remained unchanged.

Change in animal weight was used as a tool to assess morbidity. Mice in the placebo group lost an average of 11% of their weight. Mice in the oseltamivir groups initially lost weight over the first week, and then regained weight thereafter.

To study oseltamivir as treatment for H5N1, oseltamivir 1mg/kg/day for 5 days was given 24, 36, 48, 60, and 72 hours after virus inoculation (10MLD_{50}s). Each group contained 10 mice except in the 36-hour group, which had 8 mice. None of the mice survived when treatment was delayed by 48, 60, and 72 hours (died between days 10-12). When oseltamivir was given 24 or 36 hours after inoculation, 75-80% of the mice survived.

Study 2: The same authors conducted a second study that was designed similarly to the one described above. [10] The Hong Kong strain of H5N1 from 1997 (influenza A/HK/156/97) was tested in mice. Oseltamivir was administered in doses of 0.01 (n=6), 0.1 (n=6), and 1.0mg/kg/day (n=5) and placebo (n=11) for 5 days with the first dose given 4 hours prior to inoculation of H5N1 (5MLD_{50}s). The mice were observed for 16 days. None of the mice in the placebo group survived (mean survival 6.3 days). All the mice given 0.1 and 1.0mg/kg/day survived, while only 2/6 survived in the 0.01mg/kg/day group. Virus titers in the lung and brain were determined in some of the mice from each group. Oseltamivir 1.0mg/kg/day significantly reduced virus titer in the lung and brain. Drug sensitivity of the inoculating virus compared to virus obtained from the lungs of mice after treatment remained unchanged.

Mice treated with 1.0mg/kg/day gained weight by day 16 whereas those treated with 0.1mg/kg/day initially lost approximately 12% of their weight by day 7, and then began regaining it over the remaining days. Mice treated with 0.01mg/kg/day lost approximately 25% of their weight.

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To study oseltamivir as treatment for H5N1, oseltamivir 10mg/kg/day for 5 days was given 24, 36, 48, or 60 hours after virus inoculation (10MLD_{50}s). When oseltamivir was given 24 hours after inoculation, 90% of the mice survived. When given 36, 48, or 60 hours after infection, 65-70% of the mice survived. All the control animals died between days 8-10.

Use in humans

There have been no clinical trials in H5N1 given the small number of humans infected. Patient outcomes are described in 10 Vietnamese patients infected with H5N1. Four were treated with oseltamivir 75mg BID and one 8-year old child with 35mg BID for up to 5 days. Oseltamivir was begun on day 5 of illness in 3 patients, day 6 in one patient and day 12 in one patient. Two out of 5 patients recovered (patients in whom treatment began on day 5 and day 12). Two other patients received ribavirin, starting on day 5 and 11 of illness for each patient respectively. Neither patient survived. There were no survivors among the 3 patients who did not receive any antiviral therapy.[11]

In another report, outcomes are described for 5 patients from Thailand infected with H5N1. Oseltamivir was started on day 18 in 2 patients and on day 5 for one patient. Two patients did not receive antiviral therapy. All 5 patients died.[12]

CLINICAL TRIALS FOR USE IN HUMAN INFLUENZA

Prophylaxis studies

Most studies present promising results of using oseltamivir for the prevention of influenza, although there are significant areas of unknown. Data is limited regarding the clinical effectiveness of oseltamivir for all preventative strategies and for certain population groups.

Meta-analysis

Cooper et al. (2003) [13] conducted a meta-analysis of clinical trials evaluating the prophylaxis use of oseltamivir. Seven prophylaxis trials were identified, 4 of which met the study eligibility criteria. The three different preventative strategies investigated in the 4 RCTs included in the meta-analysis were:

- **Seasonal prophylaxis of a healthy population (Hayden et al. 1999 Studies: WV15673, WV15697-data combined and published collectively)** [14]
- **Seasonal prophylaxis in residential care (Peters et al. 2001)** [15]
- **Post-exposure prophylaxis in households contacts (Welliver et al. 2001)** [16]

Pooling of the data across different preventative strategies is not appropriate except for the two Hayden studies specifically reporting the seasonal prophylaxis of oseltamivir in healthy adults. As a result, a brief description of each study results for each preventative strategy is included below.

1. Seasonal prophylaxis of a healthy population[14] (see Appendix A for study details)

Study Design: WV15673-DB, R, PC was conducted at 3 sites in Virginia, USA.WV15697-DB, R, PC was conducted at 2 sites in Texas, USA and 1 site in KC, USA. Both studies were done during the winter of 1997-98. An assumption was made that the incidence of laboratory-confirmed, symptomatic influenza virus infection in the treatment groups would be 10% and that the protective efficacy of oseltamivir would be at least 70%. Ironically, the overall incidence of laboratory-confirmed symptomatic influenza in both studies combined (n=1559) was only 2.4%. As a result, the investigators decided (prior to the unblinded analysis) to combine the data from both studies.

Protective Efficacy against laboratory-confirmed, symptomatic influenza-like illness (Table 5)

In the six-week trial, 38 subjects had episodes of laboratory-confirmed, influenza-like illness. Nineteen of the 38 subjects had positive cultures; all but two were positive due to influenza A virus. The % of events with laboratory-confirmed influenza-like illness was 1.2%, 1.3% and 4.8% in the combined oseltamivir 75mg qd, bid and placebo groups respectively. The protective efficacy from 75mg of oseltamivir QD and BID pooled studies using the individual data points provided a 74% protective efficacy overall (95% CI 53 to 88) p<.001, with an ARR of 3.5 and a corresponding NNT (CI) of 28 (17to 55). Results from the National Institute for Clinical Excellence (NICE) [15] (pooled meta-analysis derived from the Hayden et al. 1999 individual studies (versus individual data points) showed a relative reduction (oseltamivir vs. placebo) of 74% (95% CI 16-92), p =0.025.

Table 5: Laboratory-Confirmed Clinical Influenza*

Hayden et al. (1999)	**Placebo (% events)**	**O75mg/d (% events)**	**RRR (95% CI) p†**	**ARR**	**NNT (CI)**	**O75mg BID (%events)**	**RRR (95% CI) p†**	**ARR**	**NNT (CI)**
WV15673	7.1	1.1	84 (53 to 96) 0.004	6.0	17	1.5	79 (45 to 94) 0.006	5.6	18
WV15697	2.4	1.2	50 (-55 to 94) 0.49	1.2	83	1.2	50 (-54 to 94) 0.47	1.2	83
Combined Studies	4.8	1.2	76 (46 to 91) <0.001	3.6	27 (17 to 59)	1.3	72 (40 to 89) 0.001	3.5	29 (17 to 69)

†p values are for the comparison with the placebo group. O=Oseltamivir, CI= confidence interval, RRR=Relative Risk Reduction, ARR=Absolute Risk Reduction, NA=Not applicable, NNT= Numbers Needed to Treat,

*Laboratory –Confirmed defined as culture of influenza virus within 2 days after the onset of influenza symptoms, an antibody titer on hemagglutination-inhibition testing that was at least 4x as high as the baseline titer, or both. Clinical influenza defined as oral temperature of ≥ 37.2° C accompanied by at least one respiratory symptom (cough, sore throat, or nasal congestion) and one constitutional symptom (aches, fatigue, headache, or chills or sweat) occurring on the same day.

Incidence of Influenza and Influenza-Like Illness (Table 6)

Subjects with culture-positive influenza, in whom illness was a result of active replication of virus was 0.4% in the oseltamivir groups combined vs. 2.9% in the placebo group resulting in 87% relative reduction (95% CI 65 to 96; p=.001) (Table 6). In addition, the efficacy of oseltamivir as prophylaxis of laboratory-confirmed influenza with fever (≥ 37.8°C) was 82% (95% CI 60 to 93, <0.001). The efficacy of oseltamivir as prophylaxis against any laboratory confirmed, symptomatic or asymptomatic influenza virus infection was 50% overall and did not differ substantially between the once-daily and twice-daily oseltamivir groups.

Table 6: Incidence of Influenza and Influenza-Like Illness* in Combined Hayden et al. 1999 Studies

	% of events RRR (95% CI), p†					
	Placebo N=519	**O75mg BID n=520**	**O75mg/d N=520**	**Combined groups n=1040**	**ARR^**	**NNT^**
Culture-proved influenza-like influenza	2.9	1.5 79 (45 to 94), 0.006	0††	(0.4) 87 (65 to 96),<0.001	2.9	35
Laboratory-confirmed infection (symptomatic or asymptomatic)	10.6	5.4 49 (24 to 69), 0.002	5.2 51 (26 to 70), 0.001	5.3 50 (31 to 67), <0.001	5.4	19
Influenza-like illness without laboratory evidence of infection	1.3	1.0 29 (-83 to 87), 0.58	1.2 15 (-108 to 84), 0.79	1.1 22 (-67 to 83)**	0.1	1000

O=Oseltamivir, CI= confidence interval, RRR= Relative Risk Reduction, †p values are for the comparison with the placebo group, ARR=Absolute Risk Reduction, NNT= Numbers Needed to Treat, ^ARR and NNT are for O75mg/d versus placebo, †† 95% CI could not be estimated, **=p value not provided,

*defined clinically as oral temperature of ≥ 37.2° C accompanied by at least 1 respiratory symptom (cough, sore throat, or nasal congestion) and at least one constitutional symptom (aches, fatigue, headache, or chills or sweat) occurring the same day,

Adverse Events-Withdrawal

Ten subjects (1.9%) withdrew from the study due to adverse events or intercurrent illness in the placebo group, as compared with 8 (1.5%) and 7 (1.3%) in the oseltamivir 75mg qd and BID groups respectively.

Upper gastrointestinal disturbances (specifically nausea) occurred in 7.1%, 12.1% (95% CI, 1.4 - 8.6) and 14.6% (95% CI, 3.7 to 11.2) in the placebo, oseltamivir qd and BID groups respectively. Incidence of vomiting was 0.8%, 2.5% (95% CI, 2 to 3.3) and 2.7% (95% CI, 3 to 3.5) in the placebo, oseltamivir 75mg qd and BID groups respectively. NNH (CI) for nausea was 20 (12 to 70) and 13 (9 to 27) in the oseltamivir qd and BID groups respectively. NNH for vomiting was 58 (28 to 479) and 52 (26 to 267) for oseltamivir qd and BID groups respectively. [16] Discontinuation of treatment because of adverse gastrointestinal events was 0.6% in combined oseltamivir groups.

Compliance:

Fifty-three percent of the subjects took all the prescribed doses of the study drug, and 38% additional subjects had 90-99% level of compliance, based on the number of returned capsules.

2. Seasonal prophylaxis in residential care [17] (see Appendix A for study details)

Study Design:

Peters et al. (2001) conducted a randomized, double-blind, placebo-controlled multicenter, international trial comparing the efficacy of oseltamivir 75mg qd x 6 weeks prophylaxis in frail elderly subjects with a mean age 81 years, (range, 64-96) living in 31 residential homes across USA and Europe during the 1998-99 influenza season. Residents were randomized into placebo (n=272), and oseltamivir (n=276) groups. Although influenza vaccination was available and offered to all, it was not necessary for study participation. Eighty percent of the participants were vaccinated. Thirty-nine percent in each group had COPD.

Protective Efficacy against Laboratory-confirmed Clinical Influenza-(Table 7)

Incidence of influenza attack rates of laboratory-confirmed clinical influenza occurred in 1/276 (0.4%) in the oseltamivir group, and 12/272 (4.4%) in the placebo group resulting in a 92% (95% CI 39 to 99, p=.002) relative reduction. All but 2 cases in the placebo group were positive for Influenza A. Of note, 12/13 cases of laboratory-confirmed influenza occurred in vaccinated subjects. A similar protective effect

was seen when oseltamivir was administered in vaccinated residents, 11/218 (5%) and 1/222 (0.5%) in the placebo and oseltamivir groups respectively.

Oseltamivir use was associated with a 86% relative reduction (p=.037) in the incidence of secondary influenza complications (otitis media, sinusitis and chest infections such as bronchitis or pneumonia) in patients with laboratory confirmed influenza. Seven of 272 patients (2.6%) in the placebo group (6 of which were laboratory-confirmed clinical influenza) experienced bronchitis (1.5%), pneumonia (1.1), and sinusitis (0.4). One patient had both bronchitis and sinusitis. One patient (laboratory-confirmed clinical influenza) out of 276 in the oseltamivir group had a secondary complication (bronchitis)..

Table 7: Laboratory-Confirmed Clinical Influenza*

Peters et al (2001)	Placebo (% events)	O75mg/day (% events)	ARR	RRR (95% CI), p	NNT
All participants	4.4	0.4	4.0	92 (39 to 99), 0.002	25
Vaccinated participants	5	0.5	4.5	91 (33 to 99), 0.003	22

RRR=Relative Risk Reduction, O=Oseltamivir, CI= confidence interval, NNT= Numbers Needed to Treat, †p values are for the comparison with the placebo group.

*Clinical Influenza defined as oral temperature of ≥ 37.2° C accompanied by at least one respiratory symptom (cough, sore throat, or nasal congestion) and one constitutional symptom (aches and pains, fatigue, headache, or chills or sweat). Lab confirmation required ≥ 4 fold increase in influenza antibody titer (between baseline and wk 8) or detection of influenza virus replication from nasal wash or throat swab specimens

Adverse Events-Withdrawal

Approximately 60% reported at least one adverse event in the two treatment groups. Headache was reported with higher frequency in the oseltamivir group than in the placebo groups 8.35% vs. 5.5% respectively. The number of patients withdrawing due to adverse event or intercurrent illness was 18 (6.5%) in the oseltamivir and 11 (4%) in the placebo groups. Three subjects in each group withdrew due to upper GI events (nausea and vomiting).

3. Post-exposure prophylaxis in households [18] (see Appendix A for study details)

Study Design:

Cluster (household)-randomized, DB, PC, multicenter, international trial in 76 centers in North America and Europe during the winter of 1998-99. Primary end point was the proportion of contacts of an influenza-positive index case with laboratory-confirmed clinical influenza during dosing period.

Index cases (IC)

Index Cases **did not** receive any antiviral therapy and were considered to have clinical influenza (i.e. oral temperature of ≥ 37.2 °C and at least 1 respiratory symptom and at least 1 constitutional symptom within a single 24 hour period). Nose and throat swabs and a serum sample were collected within 48 hours from all IC to confirm presence of laboratory influenza. All ICs had clinical influenza but a subset had laboratory-confirmed infection.

Contacts:

All contacts had to have clinical symptoms and laboratory confirmation to be classified as contracting influenza. The number of eligible contacts was 955 in 371 households. Contacts had nose and throat swabs performed at day 8 and serum sample between study days 17 and 25.

Laboratory Confirmation of Influenza Infection:

The diagnosis of influenza infection in both ICs and contacts was made either by isolation of influenza virus from nose and throat swabs or detection of 4 fold or higher increase in influenza specific hemagglutinin inhibition assay (HAI) titer between baseline and convalescent serum samples.

Of the 377 ICs, 163 (43%) had laboratory confirmed influenza; 86/163 infected ICs had laboratory evidence of influenza A. The mean-age of influenza-infected IC was 27 years. (range, 1-76 years). There were 415 contacts (15% vaccinated) in 163 households in which the IC had laboratory-confirmed influenza. One percent of the contacts (12/955) was shedding influenza virus at baseline. Study analyses were done on two populations: Contacts of all ICs (Intention-to-Treat) and contacts of influenza-positive ICs. Contacts of all ICs were defined as those who were randomized, received at least one dose of study medication, and

reported efficacy data with or without a confirmed influenza-positive IC. Contacts of an influenza-positive IC were defined as those who were randomized, had efficacy data, received at least one dose of study medication, and with a confirmed influenza-positive IC.

Protective Efficacy against Laboratory-confirmed Clinical Influenza-Table 8

Oseltamivir provided greater than 83% protective efficacy in the Intention-to-Treat, influenza-positive and influenza - negative IC groups. Oseltamivir had an 89% (95% CI, 71-96, p<0.001) and an 86% (95% C,I 60-95, p>0.001) risk reduction in individual contacts and households exposed to all ICs respectively.

Oseltamivir provided similar protective efficacy in contacts of infected ICs. The percentage of contacts with laboratory-confirmed influenza-positive was 12.6% and 1.4% in the placebo and oseltamivir groups respectively. Oseltamivir demonstrated 89 and 84% protective efficacy in contacts and households of infected influenza-positive IC during the 7 day prophylaxis. Of note, 10 subjects among the contacts of an influenza-positive IC were confirmed to be shedding virus prior to the first dose of study medication. If the 10 subjects were excluded that were confirmed to be shedding virus, the protective efficacy of oseltamivir in this population was 92% (95% CI, 71-98, p <0.001) for the prevention of clinical influenza.

Of the 540 contacts of an influenza-negative IC, 3.1% of placebo contacts developed laboratory-confirmed clinical influenza compared with 0.4% of oseltamivir recipients. Protective efficacy for individuals exposed to influenza outside the household was also 89% (95% CI, 10-99, p=.009)

Table 8. Laboratory-confirmed clinical influenza*

Welliver et al. 2001	Placebo No. /Total (%)	Oseltamivir No. /Total (%)	RRR (95%CI)	p	ARR	NNT (CI)**
Intention-to-Treat						
Contacts of all index cases	34/462 (7.4)	4/493 (0.8)	8 9 (71 to 96)	<0.001	6.6	15
Affected Households	26/178 (14.6)	4/193 (2.1)	86 (60 to 95)	<0.001	12.5	8 (6 to 14)
Contacts of an influenza-positive IC						
Contacts of infected index cases	26/206 (12.6)	3/209 (1.4)	89 (67 to 97)	<0.001	11.2	9
Affected Households	18/79 (22.8)	3/84 (3.6)	84 (49 to 95)	<0.001	19.2	6 (4 to 11)
Contacts of an influenza-negative IC						
Contacts of infected index cases	8/256 (3.1)	1/284 (0.4)	89 (10 to 99)	0.009	2.7	37
Affected Households	8/99 (8.1)	1/109 (0.9)	89 (10 to 99)	0.01	7.2	14

RRR=Relative Risk Reduction, ARR= Absolute Risk Reduction, NNT=Numbers Needed to Treat, **CI for NNT was depicted in Evidence-Based Medicine- reference #19,
*defined as isolation of influenza virus from nose and throat swabs or detection of 4-fold or higher increase in influenza specific hemagglutinin inhibition assay (HIA) titer between baseline and convalescent serum samples.

Laboratory evidence of influenza infection (confirmed by viral shedding or seroconversion) in both symptomatic and asymptomatic contacts were reduced. Fifty percent of the subjects in the oseltamivir group who became infected with influenza remained asymptomatic compared with 16% of those taking placebo suggesting minimizing viral replication early following infection effectively prevents the development of clinical disease. A substantial level of protection was achieved without treating the IC. A protective efficacy of 63% (95% CI, 40-80, p=.003) was found for contacts of an influenza-positive IC and 49% (95% CI, 25-67, p=.007) for contacts of all ICs. (Table 9)

Table 9. Symptomatic and Asymptomatic Laboratory-confirmed clinical influenza[a]

	Placebo No. /Total (%)	Oseltamivir No. /Total (%)	RRR (95%CI)	p	ARR	NNT
Intention-to-Treat						
Contacts of all index cases	††60/462 (13)	** 33/493 (6.7)	49 (25- 67)	.007	6.3	16
Affected Households	45/178 (25.3)	29/193 (15)	41%	.02	10.3	10
Contacts of an influenza-positive IC						
Contacts of infected index cases	†43/206 (20.9)	*16/209 (7.7)	63 (40- 80)	.003	13.2	8
Affected Households	28/79 (35.4)	13/84 (15.5)	57	.004	19.9	5
Contacts of an influenza-negative IC						
Contacts of infected index cases	17/256 (6.6)	17/284 (5.9)	11	.76	0.7	142
Affected Households	17/99 (17)	16/109 (14.7)	14	.71	2.3	43

RRR=Relative Risk Reduction, AAA= Absolute Risk Reduction, NNT= Numbers Needed to Treat, % Asymptomatic: *50%, **55%; † 16%, ††23% [a] adapted from reference # 18

Tolerability
GI effects were reported with similar frequency in oseltamivir 9.3% (46/494) and placebo 7.2% (33/461) groups. Nausea occurred 5.5% (27/494) and 2.6% (12/461) in the oseltamivir and placebo group respectively.

Pooled results of the percentage of withdrawal in Hayden et al 1999 and Welliever et al (2001) Studies
The combined withdrawal rate in WV15673 and WV15697 and Welliver et al. (2001) was 3.2% (95% CI, 2.2% - 4.9%) and 2.5% (95% CI , 1.7 – 3.8%) in the placebo (n=980) and oseltamivir group (n=1014) respectively.[15]

Recently, Hayden et al. 2004[20] (not included in Cooper et al. [13] meta-analysis) published a study examining the incidence of influenza using post-exposure prophylaxis (PEP) in household and contact similar to Welliever et al. (2001)[16] study. The study differs in that the treatment of index case occurred with or without PEP in the household contacts AND prophylaxis treatment was also included in a subset of children.

Study Design: (See Appendix A for study details)
Cluster-randomized, prospective, open-label, parallel group, international study conducted during the 2000-2001 influenza season. Primary efficacy was the percentage of households with at least 1 secondary case of laboratory-confirmed influenza illness during the 10 day period after the start of treatment in the index case. Analysis was also performed for households without proven influenza in the index case and for households with introduction of influenza A or B virus. Similar analyses were completed for individual contacts and specifically for children aged 1-12 years.

Drug Administration:
All index cases received treatment with oseltamivir 75mg BID x 5 days, beginning within 48 hours of the reported onset of symptoms. Contacts were either randomized to the expectant treatment arm or PEP arm. Expectant treatment consisted of oseltamivir 75mg BID x 5 days if > 12 years of age. (see Appendix A for doses administered to children) The PEP group began oseltamivir (75mg qd x 10 days) within 48 hours of the first onset of influenza-like symptoms in the index cases.

Index cases (IC)
Index cases (n=298) from 277 households were included, with 139 households being randomized to the expectant treatment arm. Of those index cases with laboratory-confirmed influenza (n=184), 66% were infected with influenza type A (predominantly AH1N1) and 34% with influenza type B.

Contacts:
The total number of contacts included the study was 812 of which 402 were included in the expectant treatment and 410 in the PEP arms. Contacts of influenza-positive IC in the expectant and PEP arms were 64% and 60% respectively. In both groups, contacts were randomized within an average of 24 hours of the onset of symptoms in the index case.

A second course of treatment could have been provided when the subject developed an influenza-like illness. In fact, 20 individuals, 74% aged ≤ 18 years, received a second oseltamivir course; 4 index cases and 9 contacts switched to treatment during prophylaxis and 7 received a treatment course after completing the 10 day PEP period. Two of the 4 index case and 6/16 contacts had laboratory-confirmed influenza infection. The NNT of households given prophylaxis to prevent one household reporting a secondary case was 6. Among individual contacts, the NNT to prevent one secondary case was 11.

Protective Efficacy against Laboratory-confirmed Clinical Influenza-Appendix B

Individual Contacts:
The number of contact cases with febrile, laboratory, confirmed influenza in the intent-to-treat, the influenza positive and influenza negative groups decreased by 73.1%, 68.0%, 84.5%, respectively.

Overall, laboratory-confirmed influenza infection, regardless of associated symptoms, was confirmed in 75 (29%) of 258 contacts of influenza-infected IC in the expectant group compared with 46 (19%) of 244 in the PEP groups (protective efficacy 35.1% (95% CI, 8.5-54; p=.0137).

Household:
The PEP with oseltamivir was effective in preventing the secondary spread of influenza in households. In the expectant treatment households with an influenza-positive index case, the rate for laboratory-proven febrile influenza was 26%. The protective efficacy of PEP in such households with oseltamivir was 58.5% (95% CI, 15.6-79.6) increasing to 78.7% (95% CI, 40.6- 92.4) when influenza positive contacts at baseline were excluded. In all households (intent-to-treat population), the protective efficacy of PEP with oseltamivir was 62.7% (95% CI, 26.0-81.25).

Pediatric contacts:
The incidence of febrile, laboratory-confirmed influenza in children receiving PEP was 24% residing in households with influenza positive IC and 19% in the intent-to-treat group. The overall frequency of influenza virus infection, regardless of symptoms, was 41% (30/74) among contacts aged 1-12 years in the expectant treatment households. In pediatric contacts, PEP reduced the likelihood of febrile influenza by 55% in households with influenza-positive IC, by 80% when contacts were culture-positive at baseline were excluded, and by 64% in the intent-to-treat population.

Type-specific protection:
Prophylactic efficacy of oseltamivir was similar in households and contacts of both influenza A and B. There was a high concordance of virus serotype between primary and secondary cases (76% influenza A (H1N1) and 64% of influenza B) –approximately 1/3 of the cases appeared to have arisen through new introductions outside of household.

Alleviation of symptoms:
Median number of hours to alleviate symptoms among influenza-infected IC (n=94) was 56.7 hours (range, 0-709 hours) in the expectant therapy group and 75.1h (range, 0-701 hours) in the PEP groups (n=90, p=.1520).

The median duration of febrile, laboratory-confirmed influenza was generally shorter among contacts. Contacts in the PEP group (n=10) had a median duration of 5.5 hours (range 0-87 h) if they develop lab-confirmed influenza during prophylaxis, compared with those (n=33) in whom treatment began only after the onset of symptoms (39.8 hours; range, 0-627 hours; p=.103).

Burden of illness:
Eight percent (3/37) PEP households vs. 15/47 (32%) households in the expectant treatment group, (p=.0032) needed to stay in bed for at least 0.5 day during the 10 day treatment period. The number of contacts with laboratory-confirmed influenza who were bed-bound during the same time window was lower in the PEP group than in the expectant treatment; 7% (3/46) , 28% (21/75) respectively. Household or individual contacts in the PEP group were 5.9 and 6.3 times more likely, respectively to have a lower number of days in bed with influenza illness, compared with the expectant treatment group (both p=.003).

Safety and withdrawal:
Oseltamivir was generally well tolerated. Five oseltamivir subjects withdrew from the study because of adverse events. (1– PEP group with moderate allergic reaction, 4 - BID treatment group of which 1-epistaxis, 1-nausea, 2-vomiting.) No children withdrew because of tolerability problems.

Gastrointestinal problems were less in those subjects received oseltamivir QD for PEP than BID dosing (contacts and IC). Nausea occurred in 33/399 (8%) of PEP and 24/347 (7%) of BID group. The incidence of vomiting was more frequent in the BID group: 35/347 (10%) and 18/399 (4.5%) in the PEP group. Higher incidence of vomiting was also evident in the pediatric subgroup (aged 1-12 years), 31/158 (20%) in BID group, compared with 10/99 (10%) in the PEP group.

Of note, severe complications (bronchitis and pneumonia were only recorded in the treatment arm of the study.

Conclusion for all Prophylaxis Studies:

Prophylaxis with oseltamivir is an effective option for preventing the transmission of influenza within households. Hayden et al. (1999)[14] showed that oseltamivir administered either once or twice daily for 6 weeks was effective and safe for the prevention of influenza-associated illness. Hayden et al. (2004)[21] showed that post-exposure prophylaxis (PEP) therapy with oral oseltamivir 75mg QD for 10 days combined with the treatment of index cases, was more effective than treating the index case alone in preventing influenza illness in household contacts. Limited data is available to assess the benefit of oseltamivir prophylaxis in the elderly and children. However, one recent study[21] is now available using oseltamivir prophylaxis in children aged 1-12 years. In that study, PEP therapy reduced the incidence of febrile influenza illness by 55% and by 80% among those who were not already infected with influenza at baseline. Observed failure rate among contacts who received oseltamivir for PEP was higher in children than in adults or adolescents aged ≥13 years. It is unknown whether the earlier initiation of PEP or possibly higher doses might provide greater protection in children.

Treatment Studies

Time to symptom alleviation and return to normal activities:
The meta-analysis of randomized controlled trials conducted by Cooper et al. 2003[13] included three ranges of ages in certain populations i.e. children (<12 years), high risk adults (≥ 65 years), and otherwise healthy adults (12-65 years). Nine of 17 oseltamivir treatment trials were included. Five of the trials were conducted in high risk patients but the data supplied by the manufacturer including the treatment dose was provided as "commercial in confidence" and therefore not depicted in the published study but was included in the analysis. Of note, varying proportions of randomized individuals were vaccinated before entry into the trials.

The median days for the alleviation of symptoms and to return to normal activities in the Intention-to-Treat and Flu-positive Population (data converted to days from hours) is depicted in Table 10.

In the Intention-to-Treat group, the reduction in median time to alleviate symptoms when oseltamivir was used compared to placebo was 0.4. The mean number of days to alleviate symptoms in the high risk adults and for children was 0.9. In the flu-positive group, there was a difference of 3 days to return to normal activities in the high-risk adults compared to placebo.

Table 10. ***Median difference days for Alleviation of symptoms and to return to normal activities***[a]

	Otherwise healthy adults (3 trials)	High-Risk Adults (5 trials)	Children (age 1-12 years) (1 trial)
	Median No. days sooner (95% CI)		
Alleviation of symptoms:			
ITT	0.86 (0.31 to 1.42)	0.35 (-0.7 to 1.4)	0.88 (0.26 to 1.49)
Flu Positive	1.4 (0.8 to 2.0)	0.45 (0.96 to 1.87)	1.5 (0.76 to 2.2)
Return to normal activities:			
ITT	1.33 (0.71 to 1.96)	2.45 (0.05 to 4.86)	1.25 (0.70 to 1.80)
Flu Positive	1.64 (0.69 to 2.58)	3 (0.13 to 5.88)	1.86 (1.06 to 2.65)

[a] Adapted from References #13 and #20: http://www.nice.org.uk/pdf/58_Flu_fullguidance.pdf

Singh et al. [22] conducted a retrospective analysis of data from influenza-infected adolescent and adults participating in 10 R, PC studies and randomized within 36 hours of the onset of symptoms to either oseltamivir 75mg BID or placebo x 5 days. The investigators found there was a 1 day difference in the alleviation of symptoms and 2 days difference in the return to normal activity in the oseltamivir group. In a randomized controlled trials of 726 previously healthy non-immunized adults with febrile influenza-like

illness, Nicholson et al. [23] reported that the duration of illness (time from start of study-drug to relief of symptoms) was shortened by 29 hours (25% reduction, median duration 87.4 h (95% CI 73.3-104.7, p=.02) with oseltamivir 75mg BID x 5 days.

Complications requiring antibiotics

It is not clear how well complications requiring antibiotics correlate with the incidence of more serious complications of flu.

Kaiser et al. [24] (2003) analyzed prospectively data from 10 DB, PC, R, multicenter phase 3 trials during the influenza seasons from 1997-2000 for lower respiratory tract complications (LRTCs) leading to antibiotic treatment and hospitalizations following influenza illness. Data from oseltamivir 75mg bid or placebo x 5 days were included in the analysis. Patients presented within 36 hours of the onset of first symptoms. Of note, approximately 15% of the patients were taking antibiotics at the start of the study. In adults and adolescents with a proven influenza illness, oseltamivir reduced overall antibiotic use for any reason by 26.7% (14.0 vs 19.1% with placebo; p< 0.001) and the incidence of influenza-related LRTCs (primarily bronchitis) resulting in antibiotic therapy by 55% (4.6% vs. 10.3% with placebo; p< 0.001). In subjects considered at increased risk of complications, 74/401 (18.5%) developed a LRTC leading to antibiotic use in the placebo group compared with 45/368 (12.2%) in the oseltamivir groups (34% reduction; p=.02. .Magnitude of the reduction in LFTCs was similar in both influenza A and B infected subjects. The reduction in overall hospitalization in the oseltamivir-treated, influenza-infected at-risk patients was 50% compared with placebo recipients (1.6% vs 3.2%, p=.17)

USE IN IMMUNOCOMPROMISED PATIENTS

According to the manufacturer, efficacy of oseltamivir for treatment or prophylaxis has not been established in immunocompromised patients.

The Prevention of Opportunistic Infections Working Group of the US Public Health Service and the Infectious Disease Society of America have stated that antiviral prophylaxis can be considered in patients with HIV during outbreaks of influenza A or B.

There are 2 published uncontrolled observational studies evaluating oseltamivir in immunocompromised patients. One study[25] evaluated treatment of influenza A or B in 39 adult bone marrow recipients. The second study[26] evaluated influenza prophylaxis in 32 children > 5 years old with cancer who had received chemotherapy or bone marrow transplantation within 1 year. In both studies, oseltamivir was found to be useful and safe. Randomized controlled trials are needed to define the role of oseltamivir treatment and prophylaxis in this population.

Efficacy of oseltamivir has not been established in patients with underlying cardiac and/or respiratory disease.

USE IN PREGANANCY AND NURSING

Oseltamivir has been given the designation of Pregnancy Category C. Oseltamivir should be used in pregnancy only if the benefits outweigh the risk to the fetus. It is unknown if oseltamivir or oseltamivir carboxylate is excreted in human milk. Oseltamivir can be used only if benefits to the mother outweigh the risks to the infant.

SAFETY

Transient nausea and vomiting that was mild-moderate in nature was reported more frequently with oseltamivir than placebo. These events generally occurred within the first 2 days of treatment usually as a single event for over 90% of patients. It has been suggested that taking oseltamivir with a light snack significantly reduces the incidence of nausea. Gastrointestinal events were reported less frequently among the elderly than those < 65 years old. [27]

Table 11. Adverse events occurring in ≥ 1% of patients

	TREATMENT		PROPHYLAXIS	
Adverse event	**Placebo (n=716)**	**Oseltamivir 75mg BID (n=724)**	**Placebo (n=1434)**	**Oseltamivir 75mg qd (n=1480)**
Nausea	40 (5.6%)	72 (9.9%)	56 (3.9%)	104 (7.0%)
Vomiting	21 (2.9%)	68 (9.4%)	15 (1.0%)	31 (2.1%)
Diarrhea	70 (9.8%)	48 (6.6%)	38 (2.6%)	48 (3.2%)
Bronchitis	15 (2.1%)	17 (2.3%)	17 (1.2%)	11 (0.7%)
Abdominal pain	16 (2.2%)	16 (2.2%)	23 (1.6%)	30 (2.0%)
Dizziness	25 (3.5%)	15 (2.1%)	21 (1.5%)	24 (1.6%)
Headache	14 (2.0%)	13 (1.8%)	251 (17.5%)	298 (20.1%)
Cough	12 (1.7%)	9 (1.2%)	86 (6.0%)	83 (5.6%)
Insomnia	6 (0.8%)	8 (1.1%)	14 (1.0%)	18 (1.2%)
Vertigo	4 (0.6%)	7 (1.0%)	3 (0.2%)	4 (0.3%)
Pain	7 (1.0%)	7 (1.0%)	107 (7.5%)	117 (7.9%)

Information obtained from Tamiflu product package insert

In the overall population studied, there were no clinically noteworthy changes in laboratory parameters and vital signs.[27]

Adverse CNS effects in the elderly were reported less frequently with oseltamivir than with amantadine (comparisons made from non head-to-head trials).[27]

The effect of oseltamivir on the QTc-interval was evaluated in volunteers. Doses of 75, 225, or 450mg BID for 5 days did not have an effect on QTc-intervals. During the oseltamivir treatment studies, the overall incidence of patients experiencing adverse cardiac events during treatment with oseltamivir was lower than those receiving placebo (0.66% vs. 1.3%).[27]

Cardiac, neuropsychiatric, and respiratory safety was assessed in patients enrolled in the United Healthcare managed care organization. Between December 1, 1999 – March 31, 2000, enrollees with an ICD-9 code for influenza and who were dispensed oseltamivir (n=3304) were compared to those with an ICD-9 code for influenza but were not given oseltamivir (n=28,948). Patients were followed up using medical claims data, for a 30-day period following the diagnosis of influenza. The incidence of cardiac, neuropsychiatric, and respiratory adverse events was low in both groups.

The incidence rate ratio of events (oseltamivir + flu: flu no oseltamivir) for any cardiac outcome, major cardiac outcome, QT-specific cardiac outcome, major neuropsychiatric outcome and pulmonary outcomes (asthma, COPD, COPD exacerbation, bronchospasm, pneumonia, bronchitis, otitis media, and sinusitis) were less than or near 1.0. It should be noted that the 95% confidence interval for the incidence rate ratio for the upper limit exceeded zero in several cases (Qt specific outcome, asthma, COPD, exacerbation of COPD, bronchospasm, otitis media, and sinusitis). When adjusted for history of the outcome of interest, the incidence rate ratio remained less than 1.0 except for otitis media, which increased from 1.03 to 1.31. In the adjusted group, the upper limit of the 95% confidence interval exceeded zero for major cardiac, outcome, QT specific outcome, asthma, COPD, exacerbation of COPD, bronchitis, otitis media, and sinusitis.[28]

In a separate publication, the United Healthcare database was used to retrospectively evaluate the risk of skin reactions with oseltamivir. The study period included the flu months from December 1999-March 2002. Patients with a diagnosis of flu and who were dispensed oseltamivir on the same day (n=11,625) were compared to patients with a diagnosis of flu and had no oseltamivir dispensed (n=70,999). The follow up period was 30 days after the diagnosis of flu. The overall incidence of skin reactions in either group was approximately 3%. The incidence rate ratio (oseltamivir + flu: flu no oseltamivir) for atopic dermatitis, contact dermatitis and other eczema, erythematous conditions and urticaria was < 1.0. However, the 95% confidence intervals were wide and the upper limit exceeded 1.0. The incidence rate ratio was > 1.0 for general skin reaction, dermatitis due to substance taken internally, unspecified pruritic disorder, and adverse reaction to drug. As an exploratory analysis, the oseltamivir + flu group was also compared to patients who had oseltamivir dispensed but had no flu diagnosis (n=17, 610). There was no difference in risk between the 2 groups.[29]

The following post-marketing adverse events have been reported. Due to the nature of post-marketing reports, frequency or causality cannot be determined. (package insert)

- Rash, swelling of the face or tongue, toxic epidermal necrolysis
- Hepatitis, abnormal liver function tests
- Cardiac arrhythmia
- Seizure, confusion
- Aggravation of diabetes

DRUG INTERACTIONS

Clinically significant drug interactions are unlikely. The oral absorption of oseltamivir was unaffected by the co-administration of antacids containing aluminum, magnesium, or calcium.[30] Oseltamivir is not highly protein bound; therefore, drug displacement interactions should not occur. Hepatic esterases are needed to convert oseltamivir and ASA to oseltamivir carboxylate and salicylic acid respectively. There was no interaction regarding hepatic esterases when oseltamivir and ASA were co-administered.[31] Oseltamivir and the carboxylate are not substrates for or inhibitors of the CYP450 enzymes.

Probenecid competes with oseltamivir carboxylate for anionic renal tubular secretion. The renal clearance of oseltamivir was reduced by approximately 50% when co-administered with probenecid. This was not thought to be clinically significant; therefore, dosage adjustment of oseltamivir is not necessary. Oseltamivir had no effect on elimination of amoxicillin or salicyluric acid (metabolite of ASA), which is also eliminated by renal tubular secretion.[32, 31]

DOSAGE

Oseltamivir can be given without regards to meals.

Treatment

75mg BID for 5 days. Treatment should begin within 2 days of onset of symptoms

Prophylaxis

- H5N1: 75mg once daily for 28 days
- Influenza: 75mg once daily for at least 7 days. Therapy should begin within 2 days of exposure. The duration of protection lasts as long as the drug is continued. Safety and efficacy have been demonstrated for use up to 6 weeks.

For patients with CrCl 10-30mL/min, the recommended dose for treatment is 75mg once daily for 5 days and 75mg every other day for prophylaxis. Dosage recommendations are not available in patients with CrCl <10mL/min or in patients receiving hemodialysis or continuous peritoneal dialysis.

Dosage adjustment is not required in geriatric patients. Oseltamivir has not been evaluated in patients with hepatic impairment.

STORAGE

Store capsules at 25°C (77°F). Excursions between 15° and 30°C (59° - 86°F) are permitted.

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Appendix A: Description of Oseltamivir Prophylactic Studies included in Cooper et al. 2003 meta-analysis

	Study Design	Patient Characteristics	Treatment Arms # of pts in each arm-dose and duration
Hayden et al. 1999 WV15673 and WV15697	DB, R, PC at 3 sites in Virginia, USA B, R, PC conducted at 2 sites in Texas, USA site in KC, USA. Both studies conducted during the winter of 1997-98.	1562 nonimmunized healthy adults average age 34 years (range 18-65). 63% women	268-75mg qd x 6 wks 267-75mg bid x 6 wks 268- Placebo x 6 wks 252- 75mg qd x 6 wks 253- 75mg bid x 6 wks 251- Placebo x 6 wks
Peters et al 2001	R, DB, PC multicenter, international trial comparing the efficacy of oseltamivir prophylaxis in frail elderly subjects living in 31 residential homes across USA and Europe during 1998-99 influenza season	mean age of 81 (64-96). 80% vaccinated; ~70% were women, ~40% with COPD	276-75mg qd x 6 wks 272 -Placebo x 6 wks
Welliver et al 2001	Cluster-randomized, DB, PC, multicenter, international trial to investigate the efficacy of oseltamivir in preventing spread of influenza to household contacts cases in 76 centers in North American and Europe during winter of 1998-99.	Mean age 33 (12-85) years old, ~50% women;~ 13% of contacts in each group were vaccinated. Approx. 40% had pre-existing diseases—the most common were 3% asthma, 5.7% HTN, 3.9% hypersensitivity	493-contacts 75mg qd within 48 hours of first reported symptoms x 7 days + 193 household contacts 462 placebo contacts x 7 days +178 households contacts (were provided 500mg APAP if needed)

Additional prevention study not included in Cooper meta-analysis

Hayden et. al 2004 Treatment of index cases with or without post-exposure prophylaxis (PEP) in household contacts.	Cluster-randomized, prospective, open-label, parallel group, international during the 2000-2001 influenza season.	Mean age of expectant group 25 (1-83) and 23.5 (1-80) in the PEP group. Less than 10% were ≥65 years of age in expectant and PEP group. <1% were ≥65 years of age in Index Group. 7% in expectant and 8% PEP groups were immunized	298 Index cases 75mg Bid X 5 days within 48 hours of reported onset of symptoms 812 contacts randomized 1) expectant tx ● > 12 years old 75mg bid x 5 days ● Children (susp) - 1-2 years - 30mg BID suspension 3-5 years- 45mg BID 6-12 years- 60mg BID or 2) PEP -75mg qd x 10 days within 48 hrs of the first onset of symptoms of index case

Appendix B. Protective efficacy of oseltamivir against laboratory-documented febrile influenza illness*

Hayden et al. (2004)	No./Total (%)		RRR of PEP (95% CI), p	ARR	NNT
	Expectant treatment	PEP			
Intention-to-treat					
Contacts of all index cases	40/392 (10)	11/400 (3)	73.1 (47.1 to 86.3), 0.0001	7	14
Affected Households of all IC	27/136 (20)	10/135 (7)	62.7 (26.0 to 81.2), 0.0042	13	8
Children aged 1-12 years of all IC	21/111 (19)	7/104 (7)	64.4 (15.8 to 85.0), 0.0188	12	9
Contact of an influenza-positive IC					
Contacts of infected index cases	33/258 (13)	10/244 (4)	68 (34.9 to 84.2), 0.0017	9	11
Affected Households	23/89 (26)	9/84 (11)	58.5 (15.6 to 79.6), 0.0114	15	7
Children aged 1-12 years	17/74 (24)	6/55 (11)	55.3 (13.0 to 82.2), 0.0890	13	8
Contacts of an influenza-negative IC:					
Contacts of infected index cases	28/248 (12)	4/228 (2)	84.5 (59.1 to 94.1), 0.002	10	10
Affected Households	20/89 (22)	4/84 (5)	78.8 (40.6 to 92.4), 0.008	17	6
Children aged 1-12 years	15/70 (21)	2/47 (4)	80.1 (22.0 to 94.9), 0.0206	17	6

RRR=Relative Risk Reduction, ARR=Absolute Risk Reduction, NNT= Numbers Needed to Treat,
* defined as detection of viral shedding in nose/throat swabs or by a $\geq$ 4 fold increase in the hemagglutination-inhibition antibody titers