

Tamiflu
(Oseltamivir)
vs.
Relenza
(Zanamivir)

Neuraminidase
Inhibitors

Anti-Influenza Drug Class Review
Gary M. Oderda Pharm D, M.P.H

Contents

Introduction	3
Anti-Influenza Agents	3
Methodology	3
Clinical Guidelines	4
Table 1	5
Clinical Efficacy	6
Efficacy comparison	6
Adverse Drug Reactions	6
Safety comparison	7
Table 2	7
Utah Medicaid Utilization Data	7
Conclusions	9
Appendix 1 – Evidence Table	10
Appendix 2 – Detailed Utilization Data	12
References	13

Introduction

During seasonal influenza epidemics in the United States, it is estimated up to 431,000 patients are hospitalized and nearly 51,000 deaths can be attributed to influenza per annual epidemic.^{1,2} Influenza-related complications requiring hospitalization can result from direct effects of the disease or from complications associated with age, pregnancy, or underlying chronic conditions. An influenza infection can cause severe disease in patients of all ages but rates of infection tend to be highest among children and persons aged ≥ 65 years. Estimated rates of pulmonary or cardiac deaths related to an influenza infection per 100,000 persons are 0.4 to 0.6 in patients aged ≤ 49 years, 7.5 in patients aged 50-64 years, and 98.3 in patients aged ≥ 65 years.^{1,2}

The influenza virus belongs to the family of RNA viruses known as the orthomyxoviridae family.³ The influenza virus is divided into three serologic types (A, B, or C) and classified based on the type of surface glycoprotein present (hemagglutinin or sialidase). Only influenza viruses A and B appear to cause significant disease in humans and influenza A viruses have been associated with higher mortality. Both hemagglutinin and sialidase surface glycoproteins are essential for the influenza virus to attach to its host, trigger the internalization process, and become pathogenic.³

The adamantane-based M2 ion channel protein inhibitors, rimantadine and amantadine, were the first drugs available for the treatment of influenza.³ Rimantadine and amantadine are only effective in the treatment of influenza A infection, as only the A strains contain the M2 ion channel proteins. The adamantane inhibitors are effective against the influenza A virus but are associated with CNS side effects and resistance. Because of the growing problem of resistance, efforts were made to develop new therapies for the treatment and prevention of influenza infection. The neuraminidase inhibitors, oseltamivir (Tamiflu) and zanamivir (Relenza), were developed in 1990s in an attempt to combat both influenza A and B infections, particularly in influenza epidemics.³

Anti-Influenza Agents

Adamantanes

The adamantane-based M2 ion channel protein inhibitors block the uncoating of influenza A virus and prevent penetration of the virus into its host. Rimantadine is up to eight times more active than amantadine against influenza A viruses, but neither has any activity against influenza B viruses. Amantadine is also thought to exhibit antiparkinsonian activity by either blocking the reuptake of dopamine or by increasing dopamine release in presynaptic neurons/fibers.

Neuraminidase Inhibitors

The neuraminidase inhibitors prevent the influenza virus enzyme known to cleave the budding viral progeny from its cellular envelope attachment point just prior to release. This is thought to alter virus particle aggregation and replication. Oseltamivir is a prodrug that is hydrolyzed to the active form, oseltamivir carboxylate.

Methodology

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2010), the Cochrane Library, and reference lists of review articles. For the clinical efficacy

section, only clinical trials published in English and indexed on MEDLINE after January 2001, evaluating efficacy of the anti-influenza agents in either treatment or prophylaxis of influenza. Trials evaluating the anti-influenza agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than one reason):

- Individual clinical trials which evaluated endpoints other than reduction of symptoms, such as assay studies,⁴⁻⁸ modeling study,⁹⁻¹¹ epidemiology studies,^{1, 12} bioequivalence studies,¹³ pharmacodynamics,¹⁴ or pharmacokinetics¹⁵⁻¹⁹ .
- Individual trials comparing anti-influenza agents in dose-finding studies, animals²⁰⁻²², or in healthy volunteers.^{13, 23}
- Individual clinical trials evaluating anti-influenza agents or formulations not currently available in the US^{24, 25} or clinical trials without access to the full article.

Clinical Guidelines

According to the Centers for Disease Control and Prevention (CDC), the Advisory Committee on Immunization Practices (ACIP) guidelines published in 2011 are pending review for the 2013-2014 influenza season, but those guidelines should be considered current regarding the use of influenza antiviral medication. Based on this information, the 2011 ACIP guidelines are the basis of the guideline information contained herein.²⁶

According to the 2011 ACIP, vaccination is the most effective method for preventing an influenza infection.² The guidelines recommend the annual influenza vaccine for all patients 6 months or older. Early treatment with antiviral medications to prevent or treat influenza may reduce the severity and duration of the infection. Growing resistance to the antiviral agents during the previous 5 years has complicated antiviral use recommendations. According to the 2011 ACIP guidelines, oseltamivir and zanamivir are recommended for the treatment of confirmed or suspected influenza cases based on surveillance and resistance data demonstrating virus strain sensitivity to these medications. The adamantanes are active against influenza A viruses, but not influenza B viruses. In recent years, adamantanes have become less useful because widespread use and circulating H1N1 virus strains has led to widespread adamantane resistance. As a result, amantadine and rimantadine are not recommended for treatment of influenza. Ongoing testing of circulating influenza virus strains shows continued inhibition by oseltamivir and zanamivir.²⁷

Antiviral treatment is recommended in patients with confirmed or suspected influenza infection who have severe illness, require hospitalization, or who are at higher risk for influenza complications based on age or chronic medical conditions. Oseltamivir is indicated for treatment of influenza in patients as young as two weeks old or chemoprophylaxis of influenza among patients aged 1 year and older.²⁸ Zanamivir is indicated for treatment of influenza in patients aged 7 years and older and chemoprophylaxis of influenza among patients aged 5 years and older.²⁹ In general, the decision to use antiviral therapy should be based on the most up-to-date guideline recommendations, current surveillance data, individual characteristics of the patient, and, if available, results from influenza diagnostic testing.

Table 1. Comparison of the Neuraminidase Inhibitors ^{2, 30, 31}

Product	Available Doses	Labeled Uses	Dose Range (mg), Adult	Dose Range (mg), Pediatric	Generic Available
Neuraminidase Inhibitors					
Oseltamivir (Tamiflu®)	Capsule: 30 mg, 45 mg, 75 mg Powder for suspension: 6 mg/mL (60 mL)	Treatment of uncomplicated influenza (A or B) infection in children ≥1 year of age and adults who have been symptomatic for no more than 2 days. Prophylaxis of influenza (A or B) infection in children ≥1 year of age and adults.	Influenza prophylaxis: Oral: 75 mg once daily for 10 days; initiate within 48 hours of contact Influenza treatment: Oral: 75 mg twice daily for 5 days; initiate within 48 hours of onset of symptoms **Adjust dose based on renal function	Influenza prophylaxis <u>Children 1-12 years:</u> ≤15 kg: 30 mg once daily >15 kg to ≤23 kg: 45 mg once daily >23 kg to ≤40 kg: 60 mg once daily >40 kg: 75 mg once daily <u>Adolescents ≥13 years:</u> Refer to adult dosing. Influenza treatment <u>Children; 1-12 years:</u> ≤15 kg: 30 mg twice daily >15 kg to ≤23 kg: 45 mg twice daily >23 kg to ≤40 kg: 60 mg twice daily >40 kg: 75 mg twice daily <u>Adolescents ≥13 years:</u> Refer to adult dosing.	No; 6/2017
Zanamivir (Relenza®)	Powder, for oral inhalation: 5 mg/blister (20)	Treatment of uncomplicated influenza (A or B) infection in patients who have been symptomatic for no more than 2 days. Prophylaxis of influenza (A or B) infection.	Prophylaxis, household setting: Two inhalations (10 mg) once daily for 10 days. Begin within 36 hours. Prophylaxis, community outbreak: Two inhalations (10 mg) once daily for 28 days. Begin within 5 days. Treatment: Two inhalations (10 mg total) twice daily for 5 days. Begin within 2 days.	Prophylaxis <u>Household setting:</u> Children ≥5 years: Refer to adult dosing. <u>Community outbreak:</u> Adolescents: Refer to adult dosing. Treatment Children ≥7 years: Refer to adult dosing.	No; 12/2014

Clinical Efficacy

The oral/inhaled anti-influenza agents were compared in two large meta-analyses^{32, 33} and two comparative clinical trials^{34, 35} published within the preceding 10 years. See Appendix 1 at the end of this document for more detailed information on each of the trials.

Efficacy comparison

The clinical effectiveness of all four anti-influenza agents was evaluated in one meta-analysis. Jefferson et al³³ evaluated 52 randomized controlled trials comparing the four anti-influenza agents. According to the meta-analysis, amantadine is as effective as the neuraminidase inhibitors for influenza A but is associated with higher rates of central nervous system (CNS) adverse events. More recent research suggests resistance is high with amantadine. Current guidelines recommend against the use of amantadine or rimantadine for the treatment of influenza A due to high incidence of resistance as well as high rates of CNS adverse events (insomnia, agitation, dizziness, fatigue, or headache). A second meta-analysis evaluated 26 clinical trials comparing only the neuraminidase inhibitors in the treatment of seasonal influenza.³² According to the evidence, the neuraminidase inhibitors are more effective than placebo in reducing symptoms associated with influenza. No differences in efficacy were reported between the agents.

Two clinical trials comparing the effectiveness of the neuraminidase inhibitors are available. The first trial³⁵ compared the neuraminidase inhibitors in the treatment of influenza A and B in 349 children aged 4-15 years. Patients diagnosed with influenza infection were randomized to either oseltamivir or zanamivir twice daily for five days. No differences in duration of fever were reported between the agents. The second trial³⁴ compared the neuraminidase inhibitors in the treatment of influenza in 1113 Japanese patients during the 2006-2007 influenza season. Duration of fever was shorter with oseltamivir treatment compared to treatment with zanamivir ($p < 0.05$) for both influenza A and B. The evidence suggests oseltamivir is more effective against Influenza A than Influenza B. Of note, the statistically significant differences in duration of fever between treatment groups were clinically very similar (see Appendix 1).

Clinical evidence evaluating the risk of influenza-related complications and hospitalization suggests improved outcomes with oseltamivir therapy compared to no antiviral therapy.³⁶ A second trial found reduced risk of influenza-related complications and healthcare costs when oseltamivir was prescribed immediately upon presentation of influenza.³⁷ In addition, when oseltamivir was used as post-exposure prophylaxis, improvements were seen in rates of morbidity and mortality associated with influenza infection.³⁸ Overall, current evidence suggests oseltamivir and zanamivir are effective options for treatment of influenza A or B. Treatment with the adamantane antiviral agents should be avoided due to increased risk of resistance and adverse events. The decision to use antiviral therapy should be based on the most up-to-date guideline recommendations and surveillance data.

Adverse Drug Reactions

The oral/inhaled anti-influenza agents were compared in two large meta-analyses^{32, 33} and two comparative clinical trials^{34, 35} published within the preceding 10 years. See Appendix 1 at the end of this document for more detailed information on each of the trials.

Safety comparison

The neuraminidase inhibitors are well tolerated by patients with influenza infection.^{29-31, 39-42} The most common drug-related adverse reactions to neuraminidase inhibitors include gastrointestinal adverse events (vomiting, nausea, abdominal pain, and diarrhea). Higher rates of respiratory adverse events, including wheezing, shortness of breath and bronchospasm have been reported with the inhaled anti-influenza medication, zanamivir. The adamantanes are less well tolerated. Amantadine and rimantadine are associated with high rates of CNS side effects including insomnia, agitation, dizziness, fatigue, and headache. Gastrointestinal adverse events are also reported with the adamantanes. These agents should be used cautiously in geriatric patients and other patients with increased risk of neurologic reactions^{30, 31}. A comparison of common adverse events reported with the oral and inhaled antiviral agents, based upon the labeling for each product, is presented in Table 2.

Table 2. Adverse Reactions (%) to Anti-Influenza Agents Based on Package Inserts³⁰

	CNS adverse reactions	Gastrointestinal adverse reactions	Orthostatic hypotension	Peripheral edema	Respiratory adverse reactions	Weakness
Adamantanes						
Amantadine	1-10	1-10	1-10	1-10	1-10	<1
Rimantadine	Insomnia (2-3), Concentration impaired (≤2), Dizziness (1-2), Nervousness (1-2), Fatigue (1), Headache (1)	1-3	NR	<1	<1	1
Neuraminidase Inhibitors						
Oseltamivir	NR	Vomiting (2-15), Nausea (4-10), Abdominal pain (2-5), Diarrhea (1-3)	NR	NR	1-10	NR
Zanamivir	>10	>0	NR	NR	>10	1-10

Utah Medicaid Utilization Data

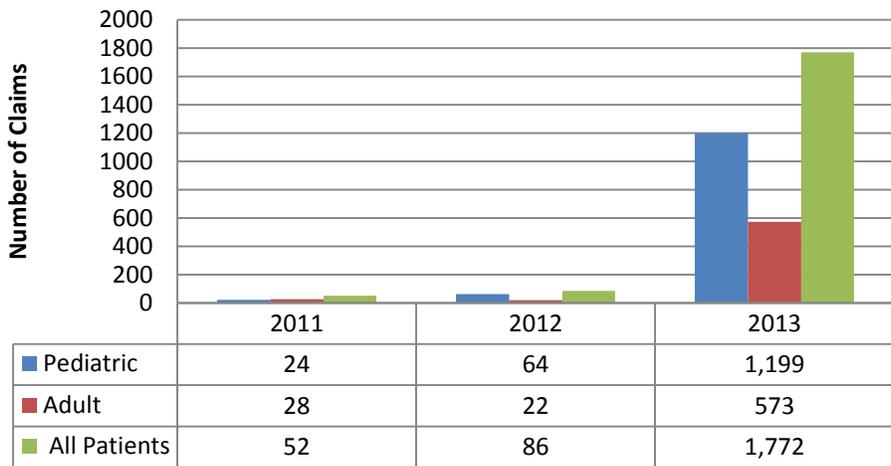
More detailed utilization data is included in Appendix 2.

Relenza

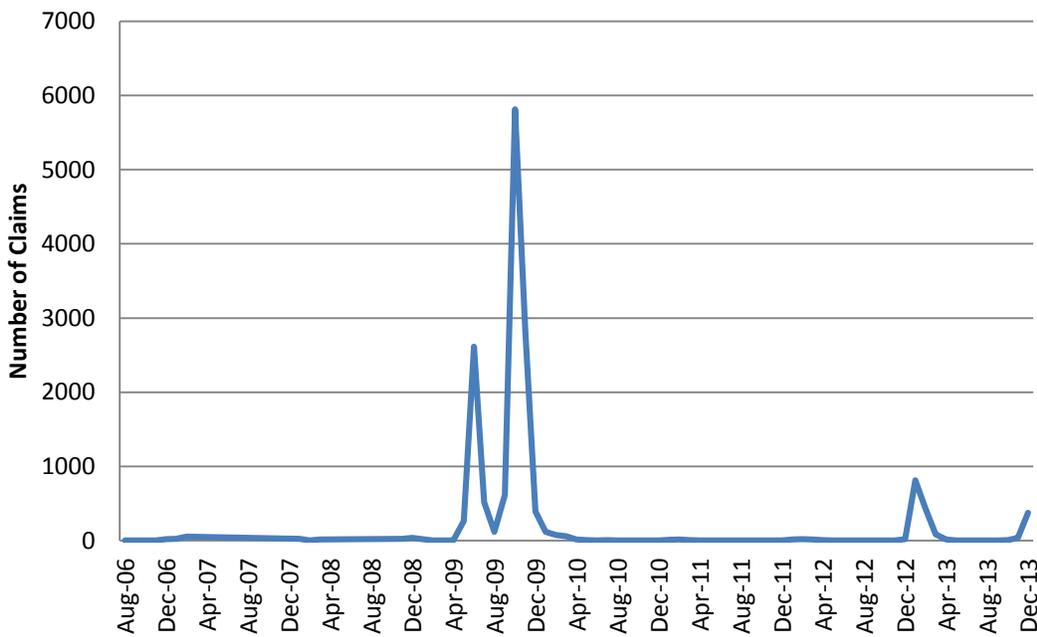
While Relenza has been on the market for several years, there was no utilization from 2011 through 2013.

Tamiflu

Claims for Tamiflu (oseltamivir)



Tamiflu total claims by month



Conclusions

Two classes of anti-influenza medications are available for use in the United States: adamantanes and neuraminidase inhibitors. According to guidelines for the use of antiviral agents in the treatment and prophylaxis of influenza, vaccination is the most effective method for preventing infection. Early treatment with antiviral medications may reduce the severity and duration of infection. Currently, oseltamivir or zanamivir are recommended for the treatment of confirmed or suspected cases of influenza. Treatment with amantadine or rimantadine in treatment of influenza is not currently recommended due to high levels of resistance. The efficacy of the oral/inhaled anti-influenza agents was compared in two large meta-analyses and two comparative clinical trials. According to the most recent evidence, oseltamivir and zanamivir are effective options for treatment of influenza A or B. Some evidence suggests oseltamivir is less effective against Influenza B. With regard to safety, the neuraminidase inhibitors are generally well tolerated and the most common drug-related adverse reactions reported are gastrointestinal adverse events. The adamantane-based antiviral agents are less well tolerated and are associated with high rates of CNS side effects. Overall, the decision to use antiviral therapy should be based on the most up-to-date guideline recommendations, current surveillance data, individual characteristics of the patient, and, if available, results from influenza diagnostic testing.

Appendix 1 – Evidence Table

Evidence Table. Clinical Trials Evaluating the Efficacy of the Antiviral agents in the Treatment of Influenza

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects
				Results	Change from baseline	
Burch et al, 2009 ³² Meta-analysis of 26 clinical trials	NR	Clinical studies of the use of neuraminidase inhibitors for the treatment of seasonal influenza.	Zanamivir Oseltamivir Placebo	Zanamivir = Oseltamivir > Placebo	Median time to reduction in symptom alleviation (days) <ul style="list-style-type: none"> • zanamivir: 0.57 • oseltamivir: 0.55 Median time to reduction in symptom alleviation in those at risk (days) <ul style="list-style-type: none"> • zanamivir: 0.98 • oseltamivir: 0.74 	Insufficient information
Jefferson et al, 2006 ³³ Meta-analysis 52 randomized controlled trials	NR	Randomized controlled trials comparing prophylactic or treatment efficacy against influenza.	Amantadine Rimantadine Zanamivir Oseltamivir Placebo	Zanamivir = Oseltamivir ≥ Amantadine = Rimantadine > Placebo	Prevention of Influenza A cases <ul style="list-style-type: none"> • amantadine: 61-79% • rimantadine: 84% • zanamivir: 62% • oseltamivir: 61-73% 	Nausea (odds ratio) <ul style="list-style-type: none"> • amantadine: 2.56 • rimantadine: 4.39 • zanamivir: 0.63 • oseltamivir: 1.79-2.29 Insomnia/hallucinations <ul style="list-style-type: none"> • amantadine: 2.54 • rimantadine: 1.58 • zanamivir: NR • oseltamivir: NR Withdrawal Rate <ul style="list-style-type: none"> • amantadine: 2.54 • rimantadine: 1.10 • zanamivir: NR • oseltamivir: 3.51-3.52

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects
				Results	Change from baseline	
Kawai et al, 2007 ³⁴ Multi-center clinical trial.	1113	Japanese patients with influenza A or B during 2006-7 influenza season.	Zanamivir 10 mg inhaled twice per day for five days Oseltamivir 75 mg or 2 mg/kg patients <37.5 kg orally twice per day for five days	Zanamivir > Oseltamivir	Duration of fever with Influenza A (hours post first dose) <ul style="list-style-type: none"> • zanamivir: 31.8 ± 18.4 h • oseltamivir: 35.5 ± 23.9 h, p < 0.05 Duration of fever with Influenza B (hours post first dose) <ul style="list-style-type: none"> • zanamivir: 35.8 ± 22.4 h • oseltamivir: 52.7 ± 31.3 h, p < 0.001 	Not reported
Sugaya et al, 2008 ³⁵ Experimental, multi-center, double-blind, parallel, randomized	349	Children aged 4-15 with influenza A (H3N2 & H1N1) and B viruses.	Zanamivir 10 mg inhaled twice per day for five days Oseltamivir weight-based dosing in divided doses twice per day for 5 days (15 kg = 60 mg per day; 15–23 kg = 90 mg per day; 23–40 kg = 120 mg per day; 140 kg = 150 mg per day)	Zanamivir = Oseltamivir	Mean duration of fever post first dose <ul style="list-style-type: none"> • zanamivir = oseltamivir 	Not reported

NR = not reported

Appendix 2 – Detailed Utilization Data

GENERIC	DESCRIPTION	2011				2012				2013			
		Claims	Pediatric	Adult	All Patients	Claims	Pediatric	Adult	All Patients	Claims	Pediatric	Adult	All Patients
Oseltamivir Phosphate	Tamiflu 30 mg Caps	1	1	0	1	0	0	0	0	60	0	55	55
Oseltamivir Phosphate	Tamiflu 45 mg Caps	0	0	0	0	0	0	0	0	62	0	59	59
Oseltamivir Phosphate	Tamiflu 75 mg Caps	31	4	26	30	22	2	19	21	788	223	549	772
Oseltamivir Phosphate	Tamiflu 6 mg/ml Susp	13	12	1	13	64	62	2	64	857	805	12	817
Oseltamivir Phosphate	Tamiflu 12 mg/ml Susp	7	7	0	7	0	0	0	0	5	4	1	5
		52	24	27	51	86	64	21	85	1,772	1,146	562	1708

References

1. To KK, Wong SS, Li IW, et al. Concurrent comparison of epidemiology, clinical presentation and outcome between adult patients suffering from the pandemic influenza A (H1N1) 2009 virus and the seasonal influenza A virus infection. *Postgrad Med J.* Sep;86(1019):515-521.
2. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM. Antiviral agents for the treatment and chemoprophylaxis of influenza --- recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* Jan 21;60(1):1-24.
3. von Itzstein M. The war against influenza: discovery and development of sialidase inhibitors. *Nat Rev Drug Discov.* Dec 2007;6(12):967-974.
4. Deng YM, Caldwell N, Hurt A, et al. A comparison of pyrosequencing and neuraminidase inhibition assays for the detection of oseltamivir-resistant pandemic influenza A(H1N1) 2009 viruses. *Antiviral Res.* Apr;90(1):87-91.
5. Wan Y, Zhou Z, Yang Y, Wang J, Hung T. Application of an In-Cell Western assay for measurement of influenza A virus replication. *J Virol Methods.* Nov;169(2):359-364.
6. Bolotin S, Robertson AV, Eshaghi A, et al. Development of a novel real-time reverse-transcriptase PCR method for the detection of H275Y positive influenza A H1N1 isolates. *J Virol Methods.* Jun 2009;158(1-2):190-194.
7. Jing X, Ma C, Ohigashi Y, et al. Functional studies indicate amantadine binds to the pore of the influenza A virus M2 proton-selective ion channel. *Proc Natl Acad Sci U S A.* Aug 5 2008;105(31):10967-10972.
8. Ferraris O, Kessler N, Lina B. Sensitivity of influenza viruses to zanamivir and oseltamivir: a study performed on viruses circulating in France prior to the introduction of neuraminidase inhibitors in clinical practice. *Antiviral Res.* Oct 2005;68(1):43-48.
9. Dobrovolny HM, Gieschke R, Davies BE, Jumbe NL, Beauchemin CA. Neuraminidase inhibitors for treatment of human and avian strain influenza: A comparative modeling study. *J Theor Biol.* Jan 21;269(1):234-244.
10. Yang Y, Halloran ME, Longini IM, Jr. A Bayesian model for evaluating influenza antiviral efficacy in household studies with asymptomatic infections. *Biostatistics.* Apr 2009;10(2):390-403.
11. Welton NJ, Cooper NJ, Ades AE, Lu G, Sutton AJ. Mixed treatment comparison with multiple outcomes reported inconsistently across trials: evaluation of antivirals for treatment of influenza A and B. *Stat Med.* Nov 29 2008;27(27):5620-5639.
12. Harvala H, Gunson R, Simmonds P, et al. The emergence of oseltamivir-resistant pandemic influenza A (H1N1) 2009 virus amongst hospitalised immunocompromised patients in Scotland, November-December, 2009. *Euro Surveill.* 15(14).
13. Kongpatanakul S, Chatsiricharoenkul S, Panich U, Sathirakul K, Pongnarin P, Sangvanich P. A randomized, open-label, 2-period, crossover bioequivalence study of two oral formulations of 75 mg oseltamivir in healthy Thai volunteers. *Int J Clin Pharmacol Ther.* Dec 2008;46(12):654-662.
14. Yang J, Shi D, Yang D, Song X, Yan B. Interleukin-6 alters the cellular responsiveness to clopidogrel, irinotecan, and oseltamivir by suppressing the expression of carboxylesterases HCE1 and HCE2. *Mol Pharmacol.* Sep 2007;72(3):686-694.
15. Schentag JJ, Hill G, Chu T, Rayner CR. Similarity in pharmacokinetics of oseltamivir and oseltamivir carboxylate in Japanese and Caucasian subjects. *J Clin Pharmacol.* Jun 2007;47(6):689-696.
16. Abe M, Smith J, Urae A, Barrett J, Kinoshita H, Rayner CR. Pharmacokinetics of oseltamivir in young and very elderly subjects. *Ann Pharmacother.* Oct 2006;40(10):1724-1730.
17. Robson R, Buttimore A, Lynn K, Brewster M, Ward P. The pharmacokinetics and tolerability of oseltamivir suspension in patients on haemodialysis and continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant.* Sep 2006;21(9):2556-2562.

18. Snell P, Dave N, Wilson K, et al. Lack of effect of moderate hepatic impairment on the pharmacokinetics of oral oseltamivir and its metabolite oseltamivir carboxylate. *Br J Clin Pharmacol*. May 2005;59(5):598-601.
19. Macdonald SJ, Cameron R, Demaine DA, et al. Dimeric zanamivir conjugates with various linking groups are potent, long-lasting inhibitors of influenza neuraminidase including H5N1 avian influenza. *J Med Chem*. Apr 21 2005;48(8):2964-2971.
20. Wong ZX, Jones JE, Anderson GP, Gualano RC. Oseltamivir treatment of mice before or after mild influenza infection reduced cellular and cytokine inflammation in the lung. *Influenza Other Respi Viruses*. Sep;5(5):343-350.
21. Langlois RA, Meyerholz DK, Coleman RA, Cook RT, Waldschmidt TJ, Legge KL. Oseltamivir treatment prevents the increased influenza virus disease severity and lethality occurring in chronic ethanol consuming mice. *Alcohol Clin Exp Res*. Aug;34(8):1425-1431.
22. Hernandez E, Ramisse F, Lhonneux A, Noury J, Bazin H, Cavallo JD. Compared protective effect of nasal immunoprophylaxis using a new human monoclonal IgM antibody, human polyclonal antibodies, F(ab')₂, amantadine, and zanamivir for prophylaxis of influenza A virus pneumonia in mice. *Mil Med*. Mar 2003;168(3):246-251.
23. Jhee SS, Yen M, Ereshefsky L, et al. Low penetration of oseltamivir and its carboxylate into cerebrospinal fluid in healthy Japanese and Caucasian volunteers. *Antimicrob Agents Chemother*. Oct 2008;52(10):3687-3693.
24. Sugaya N, Ohashi Y. Long-acting neuraminidase inhibitor laninamivir octanoate (CS-8958) versus oseltamivir as treatment for children with influenza virus infection. *Antimicrob Agents Chemother*. Jun;54(6):2575-2582.
25. Stittelaar KJ, Tisdale M, van Amerongen G, et al. Evaluation of intravenous zanamivir against experimental influenza A (H5N1) virus infection in cynomolgus macaques. *Antiviral Res*. Nov 2008;80(2):225-228.
26. CDC. Antiviral Agents for Influenza. 2014; <http://www.cdc.gov/flu/professionals/antivirals/antiviral-agents-flu.htm>. Accessed 29 Jan 2014, 2014.
27. Sleeman K, Mishin VP, Guo Z, et al. Antiviral susceptibility of variant influenza A(H3N2)v viruses isolated in the United States during 2011 - 2013. *Antimicrob Agents Chemother*. Jan 21 2014.
28. Genentech I. Tamiflu (oseltamivir) Capsules and suspension, for oral use [package insert]San Francisco, CA: Genentech, Inc. A Member of the Roche Group; 2013.
29. GlaxoSmithKline. Relenza (zanamivir) Inhalation Powder, for oral inhalation [package insert]Research Triangle Park, NC: GlaxoSmithKline; 2013.
30. Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. *Drug Information Handbook*. 12th ed. Hudson, OH: Lexi-Comp; 2011.
31. McEvoy GK, Snow EK, Kester L, Litvak K, Miller J, Welsh OH, eds. *AHFS 2011 Drug Information*. Bethesda, MD: American Society of Health-System Pharmacists; 2011.
32. Burch J, Corbett M, Stock C, et al. Prescription of anti-influenza drugs for healthy adults: a systematic review and meta-analysis. *Lancet Infect Dis*. Sep 2009;9(9):537-545.
33. Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. *Lancet*. Jan 28 2006;367(9507):303-313.
34. Kawai N, Ikematsu H, Iwaki N, et al. A comparison of the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and B. *J Infect*. Jan 2008;56(1):51-57.
35. Sugaya N, Tamura D, Yamazaki M, et al. Comparison of the clinical effectiveness of oseltamivir and zanamivir against influenza virus infection in children. *Clin Infect Dis*. Aug 1 2008;47(3):339-345.
36. Peters PH, Moscona A, Schulman KL, Barr CE. Study of the impact of oseltamivir on the risk for pneumonia and other outcomes of influenza, 2000-2005. *Medscape J Med*. 2008;10(6):131.
37. Gums JG, Pelletier EM, Blumentals WA. Oseltamivir and influenza-related complications, hospitalization and healthcare expenditure in healthy adults and children. *Expert Opin Pharmacother*. Feb 2008;9(2):151-161.

38. Sander B, Hayden FG, Gyldmark M, Garrison LP, Jr. Post-exposure influenza prophylaxis with oseltamivir: cost effectiveness and cost utility in families in the UK. *Pharmacoeconomics*. 2006;24(4):373-386.
39. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. *Lancet*. Dec 12 1998;352(9144):1877-1881.
40. Hayden FG. Clinical applications of antiviral agents for chemoprophylaxis and therapy of respiratory viral infections. *Antiviral Res*. 1985;Suppl 1:229-239.
41. Monto AS, Fleming DM, Henry D, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. *J Infect Dis*. Aug 1999;180(2):254-261.
42. Gravenstein S, Johnston SL, Loeschel E, Webster A. Zanamivir: a review of clinical safety in individuals at high risk of developing influenza-related complications. *Drug Saf*. 2001;24(15):1113-1125.