

# Antivirals, Influenza Review

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## Antivirals, Influenza Review

### FDA-Approved Indications

Drug	Manufacturer	FDA-Approved Indications
amantadine (Symmetrel®) <sup>1</sup>	generic	<ul style="list-style-type: none"> <li>◆ Prophylaxis and treatment of illness caused by influenza A virus in adults</li> <li>◆ Prophylaxis of influenza A in patients older than one year of age</li> <li>◆ Treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication</li> <li>◆ Treatment of drug-induced extrapyramidal reactions</li> </ul>
oseltamivir (Tamiflu®) <sup>2</sup>	Roche	<ul style="list-style-type: none"> <li>◆ Uncomplicated acute illness due to influenza infection in patients older than one year of age who have been symptomatic for no more than two days</li> <li>◆ Prophylaxis of influenza in patients older than one year of age                             <ul style="list-style-type: none"> <li>◆ There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza virus A and B.</li> </ul> </li> </ul>
rimantadine (Flumadine®) <sup>3</sup>	generic	<ul style="list-style-type: none"> <li>◆ Prophylaxis and treatment of illness caused by influenza A virus in adults (≥ 17 years older)</li> <li>◆ Prophylaxis of influenza A in patients older than one year of age (ages one to 16 years)</li> </ul>
zanamivir (Relenza®) <sup>4</sup>	GlaxoSmithKline	<ul style="list-style-type: none"> <li>◆ Treatment of uncomplicated acute illness due to influenza A or B virus in adults and pediatric patients seven years and older who have been symptomatic for no more than two days</li> <li>◆ Prophylaxis of influenza in patients older than five years of age                             <ul style="list-style-type: none"> <li>◆ Not recommended for treatment or prophylaxis for influenza for patients with underlying airways diseases due to risk of bronchospasm</li> <li>◆ Not proven effective for treatment in patients with underlying airways diseases</li> <li>◆ Not proven effective for prophylaxis of influenza in nursing home residents</li> </ul> </li> </ul>

All antivirals for the treatment of influenza should be started as soon as possible and within 48 hours after illness onset to maximize the potential benefit of reducing duration of illness by one to two days.

Emergency Use Authorizations ((EUAs) remain in effect until June 23, 2010 unless declaration of emergency is terminated or the Emergency Use Authorizations are revoked sooner or the declaration of emergency is extended.<sup>5</sup>

Zanamivir (Relenza) is authorized for use at a later time point such as for patients who are symptomatic for more than two days and/or in patients who require hospitalization.

Oseltamivir (Tamiflu) is authorized for use at a later time point such as for patients who are symptomatic for more than two days and/or in patients who require hospitalization. Oseltamivir is also authorized for use in patients less than one year of age.

## **Overview**

Influenza is a common illness affecting most people at least once in their lifetime. Influenza is most often self-limiting; however, very young, old, or immunocompromised patients are predisposed to secondary complications with potential fatalities. Symptoms include abrupt onset of fever, myalgia, headache, malaise, and respiratory signs and symptoms including nonproductive cough, sore throat, and rhinitis.<sup>6</sup> Children may also experience otitis media, nausea, and vomiting. Uncomplicated influenza illness typically resolves after three to seven days for most patients; however, cough and malaise can persist for more than two weeks.

In 2009 to 2010, a novel influenza A (H1N1) virus (swine flu) garnered much attention worldwide.<sup>7</sup> World Health Organization (WHO) elevated the pandemic to Phase 6, indicating the virus achieved widespread human infection.<sup>8</sup> In contrast to seasonal influenza, the novel influenza A (H1N1) virus does not pose increased risk of adverse outcomes to persons over age 64. Groups who are at higher risk for more severe or complicated illness related to influenza H1N1 include pregnant women (including two weeks postpartum), infants, and young children particularly under age two years; people of any age with certain chronic health conditions (including asthma or lung disease, heart disease, diabetes, kidney disease or some neurological conditions); and people with severely compromised immune systems. Currently, people age 65 or older are the least likely to be infected with the pandemic influenza, but those who do get sick are also at high risk of developing serious complications, just as they are from seasonal flu.<sup>9</sup>

## Vaccination

Influenza vaccination is the primary method for preventing influenza and the severe complications.<sup>10</sup> The Advisory Committee on Immunization Practices (ACIP) provisional recommendations for the upcoming 2010-2011 influenza season recommend an annual influenza vaccination for all persons age six months and older.<sup>11</sup>

## Treatment<sup>12</sup>

The Centers for Disease Control and Prevention (CDC) issued updated interim recommendations for the use of antivirals in the treatment and prevention of Influenza H1N1 for the 2009-2010 Season in December 2009. The latest recommendations focus on the treatment and prevention of 2009 H1N1 Influenza A (swine flu) as approximately 99 percent of circulating influenza viruses in the United States were reported as 2009 H1N1 influenza.

Empiric treatment with oseltamivir (Tamiflu) or zanamivir (Relenza) is recommended for all persons with suspected or confirmed influenza requiring hospitalization; progressive, severe or complicated illness, regardless of previous health status; and/or patients at risk for severe disease. High risk groups include children younger than two years, adults 65 years or older, and pregnant women and those up to two weeks after delivery or miscarriage. In addition, persons at high-risk include those with immunosuppression; disorders compromising respiratory tract function or handling of respiratory secretions or increasing risk for aspiration; or chronic pulmonary (including asthma, chronic obstructive pulmonary disease and cystic fibrosis), cardiovascular (including congenital heart disease, congestive heart failure and coronary artery disease but excludes hypertension), renal, hepatic, hematologic (including sickle cell disease), neurologic or neuro-developmental disorders, persons younger than 19 years of age who are receiving long-term aspirin therapy, or metabolic diseases (including diabetes mellitus and inherited metabolic disorders and mitochondrial disorders). Children two to four years old are more likely to require hospitalization or urgent medical evaluation for influenza compared with older children and adults, although the risk is much lower than for children younger than two

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years old. Children aged two years to four years without high risk conditions and with mild illness do not necessarily require antiviral treatment.

Persons who are not at higher risk for complications or do not have severe influenza requiring hospitalization generally do not require antiviral medications for treatment or prophylaxis. However, any suspected influenza patient presenting with warning symptoms (e.g., dyspnea) or signs (e.g., tachypnea, unexplained oxygen desaturation) for lower respiratory tract illness should promptly receive empiric antiviral therapy. Clinical judgment is an important factor in antiviral treatment decisions for all patients presenting for medical care who have illnesses consistent with influenza. Treatment should be initiated as early as possible because studies show that treatment initiated early (e.g., within 48 hours of illness onset) is more likely to provide benefit. Treatment should not wait for laboratory confirmation of influenza because laboratory testing can delay treatment and because a negative rapid test for influenza does not rule out influenza. The sensitivity of rapid tests can range from 10 to 70 percent.

### Prophylaxis

According to the CDC, antiviral chemoprophylaxis generally should be reserved for persons at higher risk for influenza-related complications who have had contact with someone likely to have been infected with influenza.<sup>13</sup> Infectious period for 2009 H1N1 influenza A virus is similar to other seasonal influenza strains. The infectious period for influenza is defined as one day before until 24 hours after fever ends. Children can shed influenza viruses for longer periods.

Postexposure antiviral chemoprophylaxis of 2009 H1N1 influenza A virus infection with either oseltamivir or zanamivir can be considered for the following: persons who are at higher risk for complications of influenza and are in close contact with a confirmed, probable, or suspected influenza case; health care workers and emergency medical personnel, and pregnant women. As an alternative to post exposure chemoprophylaxis, early recognition and prompt initiation of treatment is emphasized for patients with risk factors for influenza complications.

Antiviral chemoprophylaxis is not appropriate for healthy children or adults based on potential exposure in the community. Antivirals are not generally recommended if more than 48 hours have elapsed since the last contact with an infectious person.

**Pharmacology**

<b>Drug</b>	<b>Mechanism of Action</b>
amantadine (Symmetrel) <sup>14</sup>	<ul style="list-style-type: none"> <li>◆ Amantadine is thought to prevent the release of infectious viral nucleic acid into the host cell and may also interfere with the viral penetration into cells. Amantadine is also known to prevent virus assembly during virus replication.</li> <li>◆ It is active against the influenza A virus, but not influenza B.</li> </ul>
oseltamivir (Tamiflu) <sup>15</sup>	<ul style="list-style-type: none"> <li>◆ Oseltamivir is a prodrug that is converted to the active form, oseltamivir carboxylate. It inhibits influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release. Oseltamivir is active against influenza A and B viruses.</li> </ul>
rimantadine (Flumadine) <sup>16</sup>	<ul style="list-style-type: none"> <li>◆ Rimantadine appears to exert its inhibitory effect early in the viral replication cycle, possibly inhibiting the uncoating of the virus.</li> <li>◆ It is active against the influenza A virus, but not influenza B.</li> </ul>
zanamivir (Relenza) <sup>17</sup>	<ul style="list-style-type: none"> <li>◆ Zanamivir inhibits influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release. Zanamivir is active against influenza A and B viruses.</li> </ul>

**Viral Resistance**

Influenza viral resistance has been documented following treatment with zanamivir and oseltamivir.<sup>18,19</sup> *In vitro* viral cross-resistance between oseltamivir (Tamiflu) and zanamivir (Relenza) has been identified; however, the incidence and extent of clinical cross-resistance is difficult to determine.

High levels of resistance (93 percent) of influenza A virus to amantadine and rimantadine have been observed in the US in 2005-2006.<sup>20</sup> The CDC monitors viral resistance and responds to changes in resistance by publishing recommendations based on the incidence of viral resistance.<sup>21</sup> In past years such as the influenza season of 2007-2008, 98.9 percent of influenza A (H3N2) viruses and 4.7 percent of influenza A (H1N1) viruses were resistant to the adamantanes. Over the last few years, emerging influenza A strains were showing increasing resistance to oseltamivir. However, 2009 H1N1 influenza remains susceptible to oseltamivir (98.8 percent) and zanamivir (100 percent).<sup>22</sup>

Oseltamivir-resistant strains of 2009 H1N1 influenza have been identified in the United States in 2009.<sup>23</sup> The mutation of these viruses shows the H275Y mutation that confers resistance to the antiviral oseltamivir, but not to the antiviral zanamivir. According to WHO, the risk of viral resistance is considered higher in patients with severely compromised or suppressed immune systems who have prolonged illness, have received oseltamivir treatment (especially for an extended duration), but still have evidence of persistent viral replication.<sup>24</sup> The risk of resistance is also considered higher in people who receive oseltamivir for post-exposure prophylaxis and who then develop illness despite taking oseltamivir. No evidence exists that oseltamivir-resistant viruses are causing different or more severe form of illness.

Susceptibilities as of January 2010 according to WHO<sup>25</sup>

Influenza type	oseltamivir	zanamivir	amantadine and rimantadine
Pandemic (H1N1) 2009	Susceptible	Susceptible	Resistant
Seasonal A (H1N1)	Mostly resistant	Susceptible	Mostly susceptible
Seasonal A (H3N2)	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	Resistant

### Pharmacokinetics

Drug	Bioavailability (%)	Half-Life (hr)	Metabolism	Excretion
amantadine (Symmetrel) <sup>26,27</sup>	86-94	9-31	Eight metabolites	Predominantly renal
oseltamivir (Tamiflu) <sup>28</sup>	75	1-3 (parent); 6-10 (metabolite)	One active -- oseltamivir carboxylate	Predominantly renal
rimantadine (Flumadine) <sup>29</sup>	--	13-65	At least four metabolites	Hepatically metabolized, metabolites renally excreted
zanamivir (Relenza) <sup>30</sup>	4-17	2.5-5.1	No metabolites	Renally excreted

### Contraindications/Warnings

Cross-hypersensitivity between rimantadine and amantadine is possible and is a contraindication for use.<sup>31</sup>

Amantadine overdoses in suicide attempts have been associated with death with 1 gm as the lowest lethal dose reported.<sup>32</sup> Amantadine may exacerbate mental problems in patients with a history of psychiatric disorders or substance abuse. Patients who attempt suicide may exhibit abnormal mental states which include disorientation, confusion, depression, personality changes, agitation, aggressive behavior, hallucinations, paranoia, other psychotic reactions, and somnolence or insomnia. Patients with a history of epilepsy or other seizures should be observed closely for possible increased seizure activity while on amantadine. Patients with a history of congestive heart failure or peripheral edema should be followed closely as there is a risk for the development of congestive heart failure while receiving amantadine. Amantadine has anticholinergic effects and may cause mydriasis; therefore, patients with untreated angle closure glaucoma should not receive amantadine.

Rimantadine has been associated with an increase in seizure activity for patients who have a history of seizure activity.<sup>33</sup> Patients with renal or hepatic insufficiency should be closely observed for signs of adverse effects when taking rimantadine due to an accumulation of the parent drug and its metabolites. Transmission of rimantadine resistant virus should be considered when treating patients whose contacts are at high risk for influenza A illness.

Influenza A virus strains resistant to rimantadine can emerge during treatment, and such resistant strains have been shown to be transmissible and to cause typical influenza illness.

Zanamivir (Relenza) should not be used in patients with a history of allergic reaction to any component of zanamivir including lactose (contains milk proteins).<sup>34</sup> Zanamivir is not recommended for treatment or prophylaxis of influenza in individuals with underlying airway diseases such as asthma or chronic obstructive pulmonary disease due to risk of serious bronchospasm. Zanamivir should be discontinued in any patient who develops bronchospasm or respiratory difficulty. Effectiveness of prophylaxis of influenza in the nursing home setting has not been established. Allergic-like reactions, including oropharyngeal edema, serious skin rashes, and anaphylaxis have been reported in postmarketing experience with zanamivir. There is no evidence for efficacy of zanamivir in an illness caused by infectious agents other than influenza A or B. Patients should be advised that the use of zanamivir for the treatment of influenza has not been shown to reduce the risk of transmission of influenza to others nor has zanamivir been proven to prevent serious complications including serious bacterial infections.

Oseltamivir (Tamiflu) is contraindicated in patients with known serious hypersensitivity to oseltamivir or any component of the product. Severe allergic reactions have included anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme. Efficacy of oseltamivir in the treatment of influenza has not been established in patients with chronic cardiac disease and/or respiratory disease.<sup>35</sup> No difference in the incidence of complications was observed between the treatment and placebo groups in this population. No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalization. Efficacy of oseltamivir for treatment or prophylaxis of influenza has not been established in immunocompromised patients. Serious bacterial infections may begin with influenza-like symptoms or may co-exist or occur as complications during the course of influenza. Oseltamivir has not been shown to prevent these complications.

### Neuropsychiatric Reactions<sup>36,37</sup>

Hallucinations, delirium and abnormal behavior have been reported with influenza infection. Neuropsychiatric reactions have been noted in post-marketing surveillance of oseltamivir and zanamivir. Reports including those with fatal outcomes have described self-injury and delirium in mostly pediatric patients on oseltamivir or zanamivir with influenza. Event reports in pediatric patients have noted abrupt onset and rapid resolution of neuropsychiatric events. Unusual behavior should be reported to a healthcare professional promptly. If neuropsychiatric events occur, the risks and benefits of continuing treatment should be evaluated.

### **Drug Interactions**<sup>38,39,40,41</sup>

Amantadine undergoes enhanced elimination with coadministration of urine acidifying drugs. Coadministration of quinine or quinidine with amantadine was shown to reduce the renal clearance of amantadine by approximately 30 percent. Agents with anticholinergic effects may potentiate the anticholinergic adverse effects of amantadine. Administration of amantadine with thioridazine can cause increased tremor in elderly patients with Parkinson's disease.

Administration of agents in this class with Influenza Virus Vaccine Live (FluMist<sup>®</sup>) has not been evaluated. Because of the potential interference between the antivirals and FluMist, it is advisable that FluMist not be administered until 48 hours after cessation of anti-influenza antiviral therapy. Anti-influenza antivirals should not be administered until two weeks after the

FluMist vaccine administration unless medically necessary. Trivalent inactivated influenza vaccine can be administered at any time relative to use of drugs in this category.

No other drug interactions are expected with zanamivir or oseltamivir.

**Adverse Effects**

Drug	Headache	Nausea	Dizziness	Abd. Pain	Vomiting	Diarrhea
amantadine (Symmetrel) <sup>42</sup>	1-5	5-10	5-10	nr	0.1-1	1-5
oseltamivir (Tamiflu) <sup>43</sup> 75 mg twice daily n=724; placebo n=716	2 (2)	10 (6)	2 (3)	2 (2)	9 (3)	7 (10)
rimantadine (Flumadine) <sup>44</sup> n=1,027	1.4 (1.3)	2.8 (1.6)	1.9 (1.1)	1.4 (0.8)	1.7 (0.6)	0.3-1
zanamivir (Relenza) <sup>45</sup> 10 mg twice daily n=1,132 adults; placebo n=1,520	2 (3)	3 (3)	2 (<1)	<1.5	1 (2)	3 (4)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

In the treatment of influenza, vomiting was the most common adverse effect in children receiving oseltamivir (15 percent versus nine percent in the placebo group).<sup>46</sup> Vomiting is also the most common adverse event in children undergoing prophylaxis for influenza with oseltamivir.

The most common adverse effect in children receiving zanamivir was ear, nose, and throat infections. These occurred at a rate of five percent for both zanamivir- and placebo-treated patients.<sup>47</sup>

Amantadine may also cause other adverse events such as insomnia, hallucinations, confusion, orthostatic hypotension, peripheral edema, and dry mouth.<sup>48</sup>

**Special Populations**<sup>49,50,51,52</sup>

Pediatrics

For the treatment and prophylaxis of uncomplicated influenza A viral infections, amantadine is indicated for children as young as one year old. Rimantadine is indicated for the prophylaxis of influenza A infections in children ages one year to 16 years old, however, treatment with rimantadine is limited to patients age 17 years and older.



For the current influenza season 2009-2010, the CDC interim recommendations state that most healthy persons who develop an illness consistent with influenza or who appear to be recovering from influenza do not need antiviral medications for treatment or prophylaxis for known or suspected 2009 H1N1 influenza A infections.<sup>53</sup> Early empiric treatment with oseltamivir (Tamiflu) or zanamivir (Relenza) should be considered for persons with suspected or confirmed influenza who require hospitalization and/or have progressive, severe, or complicated illness, regardless of previous health status, and/or with risk factors for severe illness.<sup>54</sup> The risk factors for severe illness, according to the CDC, are the same medical conditions in adults and in children. Children less than five years of age are at higher risk for complications secondary to 2009 H1N1 influenza, especially children less than two years of age. According to the American Academy of Pediatrics, children at higher risk for complications include those with neurological disorders, chronic respiratory diseases, moderate to profound intellectual disability or developmental delay, deficiencies in immune function or conditions which require medications or treatments that result in significant immune deficiencies, congenital heart disease or significant metabolic disorders.<sup>55</sup>

Zanamivir has been approved for prevention of influenza in children as young as five years and is approved for the treatment of influenza for children ages seven years and older. The limitation of zanamivir is the dose administration technique of the inhaler.

Emergency Use Authorization of oseltamivir for treatment and prophylaxis of 2009 H1N1 influenza has been granted by the FDA for children less than one year of age.<sup>56</sup> Oseltamivir is not FDA-approved for children less than one year of age. Age-based dosing is recommended, but weight-based dosing is being considered for some premature or low-weight infants in investigational studies.

### oseltamivir (Tamiflu) versus placebo in children

Oseltamivir was studied in a randomized, double-blind, placebo-controlled trial with 695 children ages one to 12 years with fever and history of cough or corzya of less than 48 hours of duration.<sup>57</sup> Patients were randomized to oseltamivir 2 mg/kg twice daily or placebo for five days. Sixty-five percent of children (n=465) were found to have influenza. Oseltamivir reduced the median duration of illness by 36 hours (26 percent) in the influenza-infected children compared to placebo (101 hours versus 137 hours, p<0.0001). Oseltamivir reduced cough, corzya, and duration of fever. New diagnoses of acute otitis media were also reduced in the oseltamivir group (12 versus 21 percent, respectively). Use of antibiotics was significantly lower in the influenza-infected oseltamivir group compared to the influenza-infected placebo group (31 versus 41 percent, respectively, p=0.03). Oseltamivir group experienced more emesis than placebo group.

### zanamivir (Relenza) versus placebo in children

A double-blind, randomized, placebo-controlled, parallel-group, multicenter study enrolled children, five to 12 years of age, with influenza-like symptoms for no more than 36 hours.<sup>58</sup> Patients were randomized to zanamivir 10 mg twice daily or placebo for five days. Symptoms were recorded on diary cards twice daily during treatment, nine days after treatment, and potentially an additional 14 days if symptoms persisted. Of the 471 children enrolled in the study, 346 (73 percent) patients were influenza-positive by culture, serology, or polymerase chain reaction. Of those with confirmed infection, 65 percent had influenza A and 35 percent had influenza B. Zanamivir reduced the median time to symptom alleviation by 1.25 days compared with placebo among patients with confirmed influenza infection (p<0.001).

Zanamivir-treated patients returned to normal activities significantly faster and took significantly fewer relief medications than placebo-treated patients. Zanamivir was well-tolerated.

Pregnancy

All agents in this class are Pregnancy Category C.

Pregnant women are at a higher risk for severe complications and death from influenza. In the updated interim recommendations from the CDC, treatment with oseltamivir or zanamivir is recommended for pregnant women or women who are up to two weeks postpartum (including following pregnancy loss) with suspected or confirmed influenza.<sup>59</sup> Treatment can be given during any trimester of pregnancy. Duration of treatment is five days; however, longer courses of antiviral therapy may be considered for patients requiring hospitalization.

Geriatrics

Amantadine accumulates in patients with renal impairment and in patients over age 65 years. Dosage adjustments are listed in the Dosages section.

Rimantadine elimination is reduced in patients over age 64 years. An increase in central nervous system and gastrointestinal adverse effects are seen at the standard doses in geriatric patients receiving 200 or 400 mg of rimantadine. Dosage adjustments are listed in the Dosages section.

No dosage adjustment is required for oseltamivir or zanamivir in the geriatric population.

**Dosages**

Drug/ Dosage Forms	Treatment of influenza		Prophylaxis of influenza	
	Adults	Pediatrics	Adults	Pediatrics
amantadine (Symmetrel) <sup>60</sup> 100 mg tablet; 50 mg/5 mL syrup	For Influenza A only 200 mg daily (>12 years)  Therapy to continue for 24-48 hours after resolution of signs and symptoms	For Influenza A only 1-9 years: 4.4-8.8 mg/kg daily up to 150 mg daily  9-12 years: 100 mg twice daily  Therapy to continue for 24-48 hours after resolution of signs and symptoms	200 mg daily for 10 days (>12 years)	1-9 years: 4.4-8.8 mg/kg daily up to 150 mg daily for 10 days  9-12 years: 100 mg twice daily for 10 days
oseltamivir (Tamiflu) <sup>61</sup> 30, 45, 75 mg capsules; 12 mg/1 mL oral suspension	75 mg twice daily for five days (≥13 years)  Initiate therapy within 2 days of onset of symptoms.	>1 to <13 years: < 15 kg: 30 mg twice daily; 15-23 kg: 45 mg twice daily; 23-40 kg: 60 mg twice daily; > 40 kg: 75 mg twice daily  Emergency Use Authorization for children <1 year old: < 3 months: 12 mg twice daily for 5 days 3-5 months: 20 mg twice daily for 5 days 6-11 months: 25 mg twice daily for 5 days	75 mg daily for 10 days (≥13 years)  Initiate therapy within 2 days of exposure.	>1 to < 13 years: < 15 kg: 30 mg daily for 10 days; 15-23 kg: 45 mg daily for 10 days; 23-40 kg: 60 mg daily for 10 days; > 40 kg: 75 mg daily for 10 days  May give for up to six weeks for community outbreak.  Emergency Use Authorization for children <1 year old: < 3 months: not recommended 3-5 months: 20 mg once daily for 10 days 6-11 months: 25 mg once daily for 10 days
rimantadine (Flumadine) <sup>62</sup> 100 mg tablet	For Influenza A only 100 mg twice daily for seven days (≥17 years)	--	100 mg twice daily (≥17 years)	1 to 9 years: 5 mg/kg daily up to 150 mg daily  For 10 to 16 years of age, use adult dosage
zanamivir (Relenza) <sup>63</sup> 5 mg diskhaler	Two inhalations (10 mg) twice daily for 5 days  Initiate therapy within 2 days of onset of symptoms.	≥7 years: Two inhalations (10 mg) twice daily for 5 days	Two inhalations (10 mg) once daily for 10 days (household setting) or 28 days (community outbreaks)	≥5 years: Two inhalations (10 mg) once daily for 10 days (household setting) or 28 days (community outbreaks)

Amantadine is given as 100 mg twice daily for Parkinsonism and drug-induced extra-pyramidal reactions.

**Dosage Adjustments**

Drug/ Dosage Forms	Treatment of influenza		Prophylaxis of influenza	
	Disease state/concurrent condition	Recommended dosage adjustment	Disease state/concurrent condition	Recommended dosage adjustment
amantadine (Symmetrel) <sup>64</sup>	Patients > 65 years  Consider dose reduction for the following: Congestive heart failure, peripheral edema, orthostatic hypotension	100 mg daily or 50 mg twice daily	Patients > 65 years  Consider dose reduction for the following: Congestive heart failure, peripheral edema, orthostatic hypotension	100 mg daily or 50 mg twice daily
	CrCl 30-50 mL/min/1.73m <sup>2</sup>	200 mg on first day and 100 mg each day thereafter	CrCl 30-50 mL/min/1.73m <sup>2</sup>	200 mg on first day and 100 mg each day thereafter
	CrCl 15-29 mL/min/1.73m <sup>2</sup>	200 mg on first day followed by 100 mg on alternate days	CrCl 15-29 mL/min/1.73m <sup>2</sup>	200 mg on first day followed by 100 mg on alternate days
	CrCl <15 mL/min/1.73m <sup>2</sup> and hemodialysis	200 mg every seven days	CrCl <15 mL/min/1.73m <sup>2</sup> and hemodialysis	200 mg every seven days
oseltamivir (Tamiflu) <sup>65</sup>	Severe renal impairment (estimated CrCl 10-30 mL/min)	75 mg once daily for five days  No recommendations are available for patients with ESRD on hemodialysis or CAPD	Severe renal impairment (estimated CrCl 10-30 mL/min)	75 mg every other day or 30 mg once daily for 10 days  No recommendations are available for patients with ESRD on hemodialysis or CAPD
rimantadine <sup>66</sup>	Severe hepatic dysfunction	100 mg daily	Severe hepatic dysfunction	100 mg daily
	Renal insufficiency (CrCl 5 to 29 mL/min)		Renal insufficiency (CrCl 5 to 29 mL/min)	
	Renal failure (CrCl≤10 mL/min)		Renal failure (CrCl≤10 mL/min)	
	Elderly nursing home patients		Elderly nursing home patients	
zanamivir (Relenza) <sup>67</sup>	Not recommended for patients with airway diseases such as chronic obstructive pulmonary disease and asthma			

CrCl = creatinine clearance; ESRD = end stage renal disease; CAPD = continuous ambulatory peritoneal dialysis

### ***Clinical Trials***

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled trials performed in the United States comparing oral and inhaled agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Due to changes in resistance and practice patterns over time, studies conducted more than ten years ago were excluded. Because of the paucity of active controlled trials of the antiviral agents used for treatment and prophylaxis of influenza, studies that were placebo-controlled, randomized trials in humans using antiviral agents for the treatment or prevention of influenza were included. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

### ***Influenza - Treatment***

#### oseltamivir (Tamiflu) versus placebo

A randomized, double-blind study was performed in 629 healthy nonimmunized adults in the United States with febrile illness of less than 36 hours duration.<sup>68</sup> Patients were randomized to receive oseltamivir 75 mg or 150 mg or matching placebo twice daily. In the 374 patients infected with influenza, median duration of illness was shorter in the oseltamivir 75 mg (71.5 hours;  $p < 0.001$  versus placebo) and 150 mg groups (69.9 hours;  $p = 0.006$  versus placebo) compared to placebo (103.3 hours). There was no difference observed between the two active treatment regimens. Secondary complications such as bronchitis and sinusitis occurred more frequently in the placebo group (15 percent) than the oseltamivir groups (seven percent;  $p = 0.03$ ). Additionally, oseltamivir-treated patients returned to usual activities two to three days earlier than placebo-treated patients ( $p \leq 0.05$ ). Nausea and vomiting occurred more frequently in the oseltamivir groups (combined incidence of 18 and 14.1 percent, respectively;  $p = 0.002$ ) compared to placebo (7.4 and 3.4 percent;  $p < 0.001$ ).

A randomized, double-blind, controlled trial was conducted in 726 previously healthy nonimmunized adults with febrile influenza-like illness of up to 36 hours duration.<sup>69</sup> Patients were assigned to oseltamivir 75 mg, oseltamivir 150 mg, or placebo twice daily for five days. Infection was confirmed in 66 percent of patients. Compared to placebo (median duration 116.5 hours), the duration of illness, the primary endpoint, was 29 hours shorter in the oseltamivir 75 mg group (median duration 87.4 hours;  $p = 0.02$ ) and 35 hours shorter in the oseltamivir 150 mg group (median duration 81.8 hours;  $p = 0.01$ ). The effect of oseltamivir was apparent within 24 hours of the start of treatment. In patients treated within 24 hours of symptom onset, symptoms were alleviated in 74.5 hours in the oseltamivir 75 mg group, in 70.7 hours in the oseltamivir 150 mg group and in 117.5 hours in the placebo group ( $p \leq 0.02$  for both active treatments compared to placebo). Oseltamivir was associated with lower symptom scores, less viral shedding, and improved health, activity, and sleep quality. Oseltamivir was well tolerated.

### zanamivir (Relenza) versus placebo

In a double-blind trial, 417 adults with influenza-like illnesses of less than 48 hours duration were randomized to zanamivir 6.4 mg intranasal spray plus 10 mg by inhalation, zanamivir 10 mg inhalation plus placebo spray, or placebo by both routes twice daily for five days.<sup>70</sup> Sixty-three percent of patients (n=262) had confirmed influenza virus infection. In the confirmed influenza infections, the median length of time to alleviation of all symptoms was one day shorter (four versus five days) in the group given both zanamivir doses (p=0.02) and for those patients receiving inhalation zanamivir (p=0.05) compared to those on both placebo doses. For patients initiating therapy within 30 hours of onset of symptoms, the resolution of symptoms with either of the zanamivir groups was significantly earlier than the placebo group (four days versus seven days, p≤0.01).

A randomized, double-blind, placebo-controlled study was conducted in 455 patients aged 12 years and older with influenza-like symptoms of less than 36 hours.<sup>71</sup> Patients were randomly assigned to 10 mg inhaled zanamivir (n=227) or placebo (n=228) twice daily for five days. Patients were asked to record symptoms on diary cards four times daily during treatment and twice daily for nine days after treatment. Zanamivir relieved influenza symptoms a median of 1.5 days earlier in the intention-to-treat (p=0.011) and influenza-positive populations (p=0.004), and two days earlier in patients who were febrile at entry. In high-risk patients treated with zanamivir, symptoms were alleviated a median of 2.5 days earlier (p=0.048), fewer had complications (p=0.004), and fewer used complication-associated antibiotics (p=0.025) compared with placebo. Adverse event profiles were similar for zanamivir and placebo.

In a double-blind trial, 27 otherwise healthy adult patients were randomized to zanamivir 10 mg twice daily for five days or matching placebo.<sup>72</sup> Treatment was started within the first or second day of a flu-like illness. After 12 hours of treatment (e.g., one dose), median virus titers changed by -1.0 log<sub>10</sub> TCID<sub>50</sub>/mL in the zanamivir group compared with +0.42-log<sub>10</sub> change in the placebo group (p=0.08). This was associated with a 4.5 day (47.4 percent) reduction in the median time to alleviation of all significant flu symptoms in the zanamivir recipients (p=0.03 after adjusting for the initial virus titer and the time between onset of symptoms and treatment). Resistance to zanamivir was not detected in virus isolates.

In a randomized, double-blind trial, 356 patients aged 12 years and older were recruited within two days of onset of typical influenza symptoms.<sup>73</sup> Patients were randomized to receive inhaled zanamivir 10 mg twice daily for five days or matching placebo. Influenza was laboratory-confirmed in 277 (78 percent) of the patients; 32 (nine percent) patients were considered high-risk (elderly or with underlying medical conditions). The primary endpoint, time to alleviation of clinically significant symptoms of influenza, was significantly reduced by zanamivir compared to placebo (5 and 7.5 days, respectively; p<0.001). Zanamivir was well tolerated.

### oseltamivir (Tamiflu) and zanamivir (Relenza)

Although the study was conducted in an open-label manner, it has been included due to a lack of other direct comparative data. In a Japanese study, the effectiveness of zanamivir with oseltamivir for influenza A and B were compared in 1,113 patients during the 2006-2007 influenza season.<sup>74</sup> The duration of fever (≥ 37.5° C) after the first dose was less with zanamivir (31.8 hrs) compared to oseltamivir (35.5 hours; p<0.05) in patients with influenza A. For patients with influenza B, fever duration after starting zanamivir therapy (35.8 hrs) was significantly shorter than that of oseltamivir (52.7 hrs; p<0.001). By multiple regression analysis,

therapy (zanamivir or oseltamivir) was the major determinant affecting the duration of fever for influenza B.

### ***Influenza - Prophylaxis***

#### oseltamivir (Tamiflu) versus placebo

A study compared the efficacy of oseltamivir in prevention of household contacts acquiring influenza from the index case. A total of 955 household contacts of people with influenza were enrolled in a preventative, double-blind study and randomized to oseltamivir 75 mg once daily or placebo for seven days.<sup>75</sup> Randomization occurred by household within 48 hours of symptom onset of the index case of influenza. The index case patients did not receive therapy in the study. The overall protective efficacy of oseltamivir against clinical influenza was 89 percent for individuals (95% confidence interval [CI], 67-97 percent;  $p<0.001$ ) and 84 percent for households (95% CI, 49-95 percent;  $p<0.001$ ). Gastrointestinal adverse events were similar in both groups (oseltamivir, 9.3 percent; placebo, 7.2 percent).

In a double-blind, placebo-controlled, parallel-group, multicenter study, 548 frail, elderly nursing home occupants (mean age 81 years, >80 percent vaccinated for influenza) were randomized to prophylaxis with oseltamivir 75 mg or placebo once daily for six weeks, beginning when influenza was detected locally.<sup>76</sup> The administration of oseltamivir resulted in a 92 percent reduction in the incidence of laboratory-confirmed clinical influenza compared with placebo (0.4 and 4.4 percent, respectively;  $p=0.002$ ). In vaccinated subjects, influenza was confirmed in 0.5 percent of oseltamivir patients and five percent of patients randomized to placebo ( $p=0.003$ ). Oseltamivir use was also associated with a significant reduction in the incidence of secondary complications (0.4 percent versus 2.6 percent for placebo;  $p=0.037$ ). Oseltamivir was well tolerated with a similar incidence of adverse events, including gastrointestinal effects, occurring in both groups.

Two identical, double-blind, randomized trials located in the US enrolled a total of 1,559 healthy, non-immunized adults (18 to 65 years old) to receive either oseltamivir 75 mg once or 75 mg twice daily or placebo for six weeks during the peak of influenza outbreak.<sup>77</sup> For the combined studies, 38 patients developed influenza-like illness with 19 of those patients having laboratory confirmation. The rate of influenza was 1.2 and 1.3 percent for the oseltamivir 75 once daily and 75 mg twice daily groups, respectively, whereas the placebo group had 4.8 percent with influenza ( $p<0.001$  and  $p=0.001$  for comparison to once daily and twice daily oseltamivir groups, respectively). For the culture-proven influenza, the rate of protective efficacy was 87 percent for oseltamivir compared to 2.9 percent of the placebo-treated group (95% CI, 65 to 96 percent,  $p<0.001$ ). Oseltamivir had more frequent nausea and vomiting (12.1 and 14.6 for nausea; 2.5 and 2.7 percent for vomiting) compared to placebo of 7.1 and 0.8 percent.

#### zanamivir (Relenza) versus placebo

A total of 1,107 healthy adults were randomized to receive zanamivir 10 mg once daily or matching placebo for four weeks in a double-blind manner at the start of the influenza outbreak.<sup>78</sup> Zanamivir was 67 percent efficacious (95% CI, 39 to 83 percent,  $p<0.001$ ) in preventing laboratory-confirmed clinical influenza meeting the case definition and 84 percent efficacious (95% CI, 55 to 94 percent;  $p=0.001$ ) in preventing laboratory-confirmed illnesses with fever. All influenza infections occurring during the season, with or without symptoms, were prevented with an efficacy of 31 percent (95% CI, four to 50 percent,  $p=0.03$ ). Adverse events did not differ between the groups.

Prior to influenza season, 799 families with two to five members and at least one child who was five years of age or older were enrolled in a double-blind, placebo-controlled study.<sup>79</sup> If an

influenza-like illness developed in one member, all family members aged five years and older were randomly assigned to receive either inhaled zanamivir or placebo. The family member with the index illness was treated with either zanamivir or placebo twice daily for five days, and the other family members received either zanamivir or placebo once daily as prophylaxis for ten days. The proportion of families with at least one initially healthy household contact in whom influenza developed (the primary endpoint) was significantly lower in the zanamivir group than in the placebo group (four versus 19 percent;  $p < 0.001$ ). Zanamivir provided protection against both influenza A and influenza B. Among the subjects with index cases of laboratory-confirmed influenza, the median duration of symptoms was 2.5 days shorter in the zanamivir group than in the placebo group (5 versus 7.5 days;  $p = 0.01$ ). Viral resistance to zanamivir was not identified in this study. Zanamivir was well tolerated.

After close contacts with index cases of influenza-like illnesses, 575 subjects were randomized to receive one of four prophylactic regimens in a double-blind manner: placebo, intranasal zanamivir, inhaled zanamivir and inhaled plus intranasal zanamivir, each given for five days.<sup>80</sup> Of 25 subjects (four percent) who developed symptomatic influenza during the five days of prophylaxis, nine (36 percent) were in the placebo group, eight (32 percent) were in the intranasal zanamivir group, three (12 percent) were in the inhaled zanamivir group, and five (20 percent) were in the inhaled plus intranasal zanamivir group ( $p = \text{NS}$  for all comparisons to placebo).

A double-blind, randomized study evaluated inhaled zanamivir for the prevention of influenza in families.<sup>81</sup> Once a person with a suspected case of influenza was identified (index patient), treatment of all other household members (contacts) five years and older was initiated. Contacts received either 10 mg zanamivir or placebo inhaled once daily for 10 days. Index cases were not treated with antivirals in the trial. In total, 487 households were enrolled with 1,291 contacts randomly assigned to receive prophylaxis. Four percent of zanamivir versus 19 percent of placebo households had at least one contact who developed symptomatic, laboratory-confirmed influenza, representing 81 percent protective efficacy (95% CI, 64 to 90 percent,  $p < 0.001$ ). In the intent-to-treat population, contacts with laboratory-confirmed influenza were significantly lower in the zanamivir group (seven and 17 percent for the zanamivir and placebo groups, respectively; 59 percent protective efficacy; 95% CI, 44 to 70,  $p < 0.001$ ). Protective efficacy was also high for individuals (82 percent) and against both influenza types A and B (78 and 85 percent, respectively, for households). Zanamivir was well tolerated.

In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, the efficacy and safety of zanamivir for the prevention of influenza in community-dwelling patients who were at high risk for developing complications of influenza were evaluated.<sup>82</sup> The study was conducted in the 2000-2001 influenza season. To be enrolled, patients were able to use the Diskhaler device and were able to take the first dose of study medication within five days of laboratory-confirmed local influenza activity. Patients ( $n = 3,363$ ) were randomized to receive inhaled zanamivir 10 mg or placebo once daily for 28 days. The proportion of randomized subjects who developed symptomatic influenza during prophylaxis was significantly lower in those patients receiving zanamivir (4/1,678 versus 23/1,685; relative risk 0.17; [95% CI, 0.07 to 0.44,  $p < 0.001$ ]). Zanamivir provided a protective efficacy of 83 percent. Significantly fewer complications were observed in the zanamivir-treated patients (1/1,678 versus 8/1,685; relative risk 0.12 [95% CI, 0.002 to 0.73;  $p = 0.042$ ]). Influenza-like illness was reported in nine percent in the zanamivir-treated patients and ten percent in the placebo-treated patients. Adverse effects were similar between the groups with the most common reports being headache, cough, throat and tonsil discomfort/pain. The incidences of viral respiratory infections or ear, nose, and throat infections were similar between the two groups. No resistance to zanamivir was identified in the study.



Meta-analyses

The World Health Organization (WHO) evaluated the available evidence and developed a summary of efficacy of antivirals in the recent pharmacological management of influenza document updated in February 2010.<sup>83,84</sup> A summary of observational data for the treatment of ill and severely ill patients with 2009 H1N1 influenza with antivirals are included in the latest WHO report.

amantadine and rimantadine<sup>85,86,87,88</sup>

A systematic review showed that amantadine is superior to placebo in terms of a reduction in duration of fever for both adults and children, with a decrease in fever duration of one day for adults (MD=-0.99; 95% CI: -1.26 to -0.71) and fewer cases of fever for children. No statistically significant difference was demonstrated between amantadine and placebo in the occurrence of adverse events in the randomized trials.

The use of rimantadine for the treatment of influenza is based on two systematic reviews. The first review included three placebo controlled trials of rimantadine in adults and the second review included one placebo controlled trial of rimantadine in children. Rimantadine is superior to placebo, with a reduction in duration of fever for adults of greater than one day (MD=-1.24; 95% CI: -1.71 to -0.76) and fewer cases of fever in children. No statistically significant difference was demonstrated between rimantadine and placebo in the occurrence of adverse events.

*Adults*

A 2006 meta-analysis evaluated the prevention and treatment efficacy in symptomatic and asymptomatic influenza in healthy adults.<sup>89</sup> Of the 51 included trials that evaluated either prevention or treatment of asymptomatic or symptomatic influenza, amantadine prevented 61 percent of the symptomatic influenza A cases but with a significant discontinuation rate due to adverse effects.<sup>90</sup> Rimantadine had fewer data but similar effects. In symptomatic influenza, efficacy rates of oseltamivir 75 mg and 150 mg daily were 61 and 73 percent, respectively whereas zanamivir was 62 percent. For post-exposure prevention, oseltamivir was associated with 58.5 percent reduction within households and 68 to 89 percent for contacts of index cases. Symptom duration was shorter by one to two days with both oseltamivir and zanamivir when therapy was started within 36 to 48 hours of onset.<sup>91</sup> Oseltamivir was associated with nausea. Both oseltamivir and zanamivir reduced nasal viral shedding; however, amantadine did not. In asymptomatic influenza, antivirals had no effect. Another 2003 meta-analysis found that oseltamivir was associated with a reduction in lower respiratory tract complications, antibiotic use, and hospitalizations related to influenza in both healthy and at risk patients.<sup>92</sup>

A 2009 systematic review included randomized placebo controlled studies of neuraminidase inhibitors in otherwise healthy adults exposed to naturally occurring influenza.<sup>93</sup> A total of 20 trials were included. In the four trials evaluating prophylaxis, the neuraminidase inhibitors had no effect against influenza-like illness or asymptomatic influenza. The efficacy of oseltamivir 75 mg daily against symptomatic laboratory confirmed influenza was 61 percent (risk ratio 0.39; 95% CI, 0.18 to 0.85). Inhaled zanamivir 10 mg daily was 62 percent efficacious (risk ratio 0.38; 95% CI, 0.17 to 0.85). In postexposure prophylaxis trials, oseltamivir had an efficacy of 58 percent (95% CI, 15 to 79) and 84 percent in two trials of households. Zanamivir performed similarly. For treatment, the hazard ratios for time to alleviation of influenza-like illness symptoms were in favor of treatment : 1.20 (95% CI, 1.06 to 1.35) for oseltamivir and 1.24 (95% CI, 1.13 to 1.36) for zanamivir. Regarding lower respiratory tract complications, evidence

suggests oseltamivir did not reduce influenza related complications (risk ratio 0.55; 95% CI, 0.22 to 1.35).

### *Children*

A systematic review of double-blind, randomized, controlled trials comparing the neuraminidase inhibitors with placebo in children less than 12 years of age evaluated trials published through 2005.<sup>94</sup> A total of three trials involving 1,500 children with influenza were included with 977 having laboratory-confirmed influenza. Oseltamivir reduced the median duration of illness by 26 percent (36 hours) in healthy children with laboratory-confirmed influenza ( $p < 0.0001$ ). The reduction was only 7.7 percent (10 hours) in 'at risk' or asthmatic children ( $p = 0.54$ ). Zanamivir reduced the median duration of illness by 24 percent (1.25 days) in healthy children with laboratory-confirmed influenza ( $p < 0.001$ ). No data in 'at risk' children were available. Only oseltamivir produced a significant reduction in the complications of influenza (particularly otitis media), although there was a trend to benefit for zanamivir. Adverse events profile of zanamivir was no worse than placebo, but vomiting was more common in children treated with oseltamivir.

A 2009 systematic review evaluated the effects of the neuraminidase inhibitors in treatment of children ( $\leq 12$  years old) with seasonal influenza and prevention of transmission to children in households.<sup>95</sup> Published and unpublished data were considered. A total of four randomized controlled trials with 1,766 children evaluated treatment with oseltamivir or zanamivir in the community setting with confirmed or clinically suspected influenza. Three randomized trials with 863 children evaluated postexposure prophylaxis (one trial for oseltamivir, two trials for zanamivir). The median time to resolution of symptoms or return to normal activities or both was reduced by 0.5 to 1.5 days, which was a significant finding in only two trials. A ten day duration of postexposure prophylaxis with zanamivir or oseltamivir resulted in an eight percent (95% CI, 5 to 12) decrease in the incidence of symptomatic influenza. Based on only one trial, oseltamivir did not reduce asthma exacerbations and oseltamivir was not associated with a reduction in overall use of antibiotics (risk difference -0.3, 95% CI, -0.13 to 0.01). Zanamivir was well tolerated, but oseltamivir was associated with an increased risk of vomiting (0.05, 95% CI, 0.02 to 0.09, number needed to harm=20).

### **Summary**

Vaccination is the primary method of preventing influenza infection.

Agents approved for influenza prevention and treatment include amantadine (Symmetrel), rimantadine (Flumadine), oseltamivir (Tamiflu), and zanamivir (Relenza). The CDC currently does not recommend the use of amantadine or rimantadine for the treatment or prophylaxis of influenza A due to viral resistance.

Most healthy persons who develop suspected or confirmed 2009 H1N1 influenza or seasonal influenza that present with an uncomplicated febrile illness generally do not require antiviral treatment according to the CDC. The CDC recommends treatment of 2009 influenza A (H1N1) in 'at risk' adults and children with either oseltamivir or zanamivir. Treatment should be initiated as early as possible because studies show that treatment initiated early (e.g., within 48 hours of illness onset) is more likely to provide benefit.

Zanamivir uses a complex administration device for inhalation and should not be used in patients with pre-existing respiratory disorders. For the treatment of influenza B, either oseltamivir or zanamivir are recommended.

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