

## Appendix A

### **Oseltamivir (Tamiflu®) and Zanamivir (Relenza®) Prophylaxis and Treatment Recommendations**

This appendix replaces pages 37 to 43 in *A Guide to the Control of Respiratory Infection Outbreaks in Long-Term Care Homes, October 2004*.

The H3 and H1 influenza subtypes currently circulating in Ontario are resistant to amantadine but susceptible to oseltamivir (Tamiflu®) and zanamivir (Relenza®). These antivirals appear to be equally effective in the treatment and prophylaxis of influenza during institutional influenza outbreaks. Oseltamivir is the drug of choice for both treatment and prophylaxis for residents of long-term care homes. Many residents are cognitively impaired and as a result, have difficulty coordinating their breathing to inhale zanamivir correctly or have medical contraindications to zanamivir use. Unvaccinated staff who require treatment or prophylaxis may use either zanamivir or oseltamivir. Zanamivir is also an option for persons who cannot tolerate oseltamivir as stand-alone therapy.

Resistance patterns in strains of influenza can change quickly. For this reason, it is important that public health units, long-term care homes and other institutions review their outbreak management protocols each fall, and use the most recent recommendations for treatment and prophylaxis. In the event that antiviral resistance is identified during an influenza season, notification will follow from public health units regarding related antiviral recommendations.

Antivirals for treatment and prevention of influenza in residents of long-term care homes are reimbursed by the Ontario Drug Benefit (ODB) Program only if an influenza outbreak is declared by the local Medical Officer of Health or designate. Currently, the only available format of oseltamivir that is reimbursed by the ODB Program is the 75 mg capsule. Zanamivir is only reimbursed when the predominant circulating strain is resistant to oseltamivir. If such an event arises, communication from the province will outline the parameters for reimbursement.

**Table 1: Oseltamivir (Tamiflu®) Prophylaxis and Treatment Recommendations**

<b>PROPHYLAXIS<sup>1</sup></b>		
Adults (≥ 13 years of age) • with no known renal disease OR • renal disease and creatinine clearance > 30 mL/min	75 mg orally once daily	14 days or until the outbreak is declared over <sup>2</sup>
Adults (≥ 13 years of age) • with known renal disease and creatinine clearance of 10-30 mL/min	75 mg orally every second day <sup>3</sup> OR 30 mg orally once daily	Until the outbreak is declared over
Adults (≥ 13 years of age) • undergoing hemodialysis or whose creatinine clearance <10 mL/min OR • undergoing continuous ambulatory peritoneal dialysis or whose creatinine clearance <10 mL/min	Low flux hemodialysis: 30 mg orally after every second session <sup>4</sup>  High flux hemodialysis: 75 mg orally after each dialysis session  Continuous ambulatory peritoneal dialysis: 30 mg orally once per week <sup>4</sup>	
Children (1 to 12 years of age)	≤15 kg: 30 mg orally once daily >15 kg – 23 kg: 45 mg orally once daily >23 kg – 40 kg: 60 mg orally once daily >40 kg: 75 mg orally once daily	
<b>TREATMENT</b>		
Adults (≥ 13 years of age) • with no known renal disease OR • renal disease and creatinine clearance > 30 mL/min	75 mg orally twice daily	5 days
Adults (≥ 13 years of age) • with known renal disease and creatinine clearance of 10-30 mL/min	75 mg orally once daily	5 days
Adults (≥ 13 years of age) • undergoing hemodialysis or whose creatinine clearance <10 mL/min OR • continuous ambulatory peritoneal dialysis or whose creatinine clearance <10 mL/min	Low flux hemodialysis: 30 mg orally after every second session <sup>4</sup>  High flux hemodialysis: 75 mg orally after each dialysis session  Continuous ambulatory peritoneal dialysis: 30 mg orally once per week <sup>4</sup>	5 days
Children (1 to 12 years of age)	≤15 kg: 30 mg orally twice daily >15 kg – 23 kg: 45 mg orally twice daily >23 kg – 40 kg: 60 mg orally twice daily >40 kg: 75 mg orally twice daily	5 days

### Oseltamivir: Additional Important Information

Available Format	30 mg, 45 mg, 75 mg capsule <sup>3</sup> , Powder for oral suspension (12 mg/mL when reconstituted) <sup>5</sup>
Drug Interactions	Probenecid may increase concentrations of one of the active metabolites of oseltamivir.
Contraindications	None
Potential Side-effects	Nausea and vomiting occurs in approximately 2.5-10% of all people. It is usually associated with the first dose. It can be effectively minimized by giving oseltamivir with a snack or immediately after a meal.
Pregnancy and Lactation	Oseltamivir should be used during pregnancy and lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant. There is insufficient data currently available regarding possible toxic effects on the fetus. One study suggests that both oseltamivir and oseltamivir carboxylate are detectable in human breast milk <sup>10</sup> .

**Table 2: Zanamivir (Relenza®) Prophylaxis and Treatment Recommendations**

PROPHYLAXIS		
Persons ≥ 7 years of age	Two 5 mg inhalations (10 mg) once daily	For institutional outbreaks: minimum of 2 weeks, including in vaccinated persons, and up to 1 week after the last known case was identified. <sup>8</sup>
		For community outbreaks: 28 days <sup>9</sup>
TREATMENT		
Persons ≥ 7 years of age	Two 5 mg inhalations (10 mg) twice daily	5 days

### Zanamivir: Additional Important Information

Available Format	5 mg powder for inhalation in blister pack. <sup>1</sup> <b>Zanamivir must be used with a Diskhaler device. Do not use for nebulization. MAY RESULT IN FATALITY.</b> One disk contains 4 puffs (2 doses). Each disk is inserted into the Diskhaler device that punctures the disk, dropping the powder into a well, which is then ready for inhalation.
Drug Interactions	No known drug interactions <sup>1</sup>
Contraindications	May exacerbate wheezing in asthma or chronic obstructive pulmonary disease (COPD). Many long-term care residents have difficulty coordinating the inhalation required. Anyone who has wheezing immediately after a dose should discontinue therapy.
Potential Side-effects	Dosage adjustment is not required in the elderly. No dosage adjustment is recommended for persons with impaired kidney function, given a 5-day course of treatment.

### References

1. If respiratory symptoms develop in a patient on prophylaxis with oseltamivir, the dose should be changed to the therapeutic dose and continued for a total of five (5) days, starting from the day when the therapeutic dose was first given.
2. Oseltamivir prophylaxis should be continued until the outbreak is declared over; there are no recommended minimum days of prophylaxis (reimbursement through the ODB Program is limited to 6 weeks).
3. Currently, only the 75 mg capsule of oseltamivir is reimbursable through the ODB Program.
4. Gin/Aoki endorsement of the Robson (Nephrol Dial Transplant 2006) dosing regimen:
  - Hemodialysis: 30 mg orally after every second session
  - Continuous ambulatory peritoneal dialysis: 30 mg orally once per week

5. Some pharmacies may compound an oral suspension from the capsules with a different final strength than the commercially-available product. The label must be carefully checked to ensure that the correct dose is administered.
6. Zanamivir is reimbursed by the ODB Program for residents only when the predominant circulating strain is resistant to oseltamivir.
7. [http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adrv10n4\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adrv10n4_e.html) Canadian Adverse Drug Reaction Newsletter by Health Canada. Volume 10 Number 4 October 2000.
8. Centers for Disease Control and Prevention, 2010-2011 Influenza Antiviral Medications: A Summary for Clinicians
9. Compendium of Pharmaceuticals and Specialties, 2010
10. Wentges-van Holthe et al. Int J Infect Dis 2008;12:451.

**Appendix B**  
**National Microbiology Laboratory (NML) Antiviral Susceptibility Testing Results**

**Table 1. NML Strain Characterization Completed on Influenza Isolates in Canada, Sept 1 to Dec 2, 2010**

	Province													TOTAL			
	NFL	PEI	NS	NB	QUE	ONT	MAN	SASK	ALTA	BC	YT	NT	NU				
<u>Influenza A (H3N2)</u> (see notes)																	
A/Perth/16/2009-like	0	0	0	0	1	17	1	0	2	3	0	0	0	0	0	0	24
<u>Influenza A (H1N1)</u> (see notes)																	
A/California/07/2009-like	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
<u>Influenza B</u> (see notes)																	
B/Brisbane/60/2008-like	0	0	0	0	1	2	0	0	0	1	0	0	0	0	0	0	4

Notes:

- A/Perth/16/2009 (H3N2) is the recommended H3N2 component for the 2010-2011 northern hemisphere influenza vaccine.
- B/Brisbane/60/2008-like virus which belongs to the B/Victoria/02/87 lineage is the recommended influenza B component for the 2010-2011 influenza vaccine
- A/California/07/2009 is the recommended H1N1 component for the 2010-2011 northern hemisphere influenza vaccine

**Table 2. NML Osteltamivir Susceptibility Assay Completed on Influenza Isolates in Canada, Sept 1 to Dec 2, 2010\***

	Province																		TOTAL			
	(R: Resistant, S: Susceptible)																					
	NFLD	PEI	NS	NB	QUE	ONT	MAN	SASK	ALTA	BC	YT	NT	NU	R		S						
	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S				
<u>Influenza A (H3N2)</u>	0	0	0	0	0	1	0	14	0	1	0	0	0	2	0	3	0	0	0	0	21	
<u>Influenza B</u>	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	1	0	0	0	0	3	
<u>Pandemic Influenza A</u>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Appendix B. National Microbiology Laboratory Antiviral Susceptibility Testing Results.  
MOHLTC, Public Health Division, Public Health Protection and Prevention Branch, December 13, 2010.

Table 3. NML Zanamivir Susceptibility Assay Completed on Influenza Isolates in Canada From Sept 1 to Dec 2, 2010\*

	Province (R: Resistant, S: Susceptible)														TOTAL												
	NFLD	PEI	NS	NB	QUE	ONT	MAN	SASK	ALTA	BC	YT	NT	NU														
	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S									
Influenza A (H3N2)	0	0	0	0	0	0	0	0	1	0	14	0	1	0	0	0	2	0	3	0	0	0	0	0	0	21	
Influenza B	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	3
Pandemic Influenza A	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Table 4. NML Amantadine Susceptibility Assay Completed on Influenza Isolates in Canada From Sept 1 to Dec 2, 2010\*

	Province (R: Resistant, S: Susceptible)														TOTAL													
	NFLD	PEI	NS	NB	QUE	ONT	MAN	SASK	ALTA	BC	YT	NT	NU															
	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S										
Seasonal Influenza A (H1N1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Influenza A (H3N2)	0	0	0	0	0	0	0	0	0	1	0	0	17	0	1	0	0	0	3	0	3	0	3	0	0	1	26	0
Pandemic Influenza A	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

\*Influenza and Respiratory Viruses Section, National Microbiology Laboratory (NML)  
Public Health Agency of Canada, Canadian Sciences Centre for Human and Animal Health

## Appendix C

### Neuraminidase Inhibitors: Oseltamivir (Tamiflu®) and Zanamivir (Relenza®)

Neuraminidase inhibitors, such as oseltamivir and zanamivir, are a class of antiviral agents that are active against both influenza A and influenza B. They are approved by Health Canada for prophylaxis and/or treatment of influenza in adults and children (>1 year of age), whereas zanamivir is approved for prophylaxis and/or treatment of people 7 years of age and older. Dosing schedules and other key details about oseltamivir and zanamivir are provided in Appendix A.

Oseltamivir is recommended as the first-line antiviral for prophylaxis and treatment during confirmed institutional influenza outbreaks.

While zanamivir is approved for treatment and prophylaxis in Canada, its prophylactic use in outbreaks has yet to be determined. Zanamivir is administered by inhalation and may be more difficult to administer to frail or confused elderly patients. In addition, it may cause breathing problems or worsen underlying chronic respiratory disease (i.e. asthma or chronic obstructive pulmonary disease).

#### What are the licensed indications for prescribing oseltamivir (Tamiflu®) and zanamivir (Relenza®)?

- Oseltamivir has been approved for treatment and prophylaxis of influenza A and influenza B in persons one year of age and older.<sup>1</sup>
- When used for treatment, oseltamivir is approved for those who have been symptomatic for no more than two days (48 hours).
- Zanamivir is approved in Canada for the treatment of influenza A and influenza B in persons seven years of age and older, who have been symptomatic for less than two days (48 hours).
- Zanamivir has also been approved by Health Canada for use in the *prevention* (prophylaxis) of influenza in adults and children seven years of age and older.

#### How effective are oseltamivir (Tamiflu®) and zanamivir (Relenza®) for prophylaxis of influenza?

- Oseltamivir has been successfully used as prophylaxis along with vaccination and infection control measures to control outbreaks of influenza in long-term care homes. One study found that oseltamivir was 92% effective in preventing laboratory-confirmed clinical influenza illness among elderly individuals in residential care.<sup>2</sup> Prophylactic use of zanamivir for control of institutional outbreaks has not been well studied.<sup>3</sup>

- In two trials of post-exposure prophylaxis, the relative efficacy of oseltamivir in preventing symptomatic, laboratory-confirmed influenza was 58% and 89% compared with controls.<sup>3</sup>
- In two trials of post-exposure prophylaxis, the relative efficacy of zanamivir in preventing symptomatic, laboratory-confirmed influenza was 79% and 81% compared with placebo.<sup>3</sup>

**How effective are oseltamivir (Tamiflu®) and zanamivir (Relenza®) for treatment of influenza?**

- When administered as soon as possible and within 48 hours of illness onset, oseltamivir and zanamivir can reduce the duration of uncomplicated influenza illness.
- The effect of oseltamivir and zanamivir on secondary complications of influenza depends on the population being treated.
  - In a study of 10 clinical trials involving 3,564 subjects (ages 13-97 years), oseltamivir treatment reduced the risk of pneumonia and hospitalization by approximately 50%. The study population included healthy unimmunized persons as well as persons at-risk of complications due to influenza.<sup>4</sup>
  - A 2006 Cochrane systematic review of studies (involving primarily healthy subjects 14-60 years of age) found oseltamivir treatment to be effective in preventing lower respiratory tract complications, such as bronchitis and pneumonia. Zanamivir was also shown to prevent secondary complications.<sup>1</sup>
  - There is preliminary evidence that oseltamivir can prevent complications of influenza in children (particularly otitis media), however, further research is needed to determine if the drugs are helpful in children more at risk of complications due to underlying chronic medical conditions.<sup>5</sup>

**Please refer to the Compendium of Pharmaceuticals and Specialties Product Monographs for a complete list of oseltamivir and zanamivir side effects, precautions, contraindications, and potential drug interactions.**

**What are the side-effects of oseltamivir (Tamiflu®)?<sup>6</sup>**

- The most frequently reported side effects are nausea and vomiting. They are usually associated with the first dose and may be reduced by taking the medication with food.
- Less common side effects include abdominal pain and headache.
- In children, vomiting (15%), abdominal pain (4.7%), epistaxis (3.1%) and conjunctivitis (1%), were more common in those treated with oseltamivir than in those treated with placebo.
- Allergic skin rashes, anaphylaxis, facial swelling, liver toxicity and

elevated liver enzymes have been reported in association with taking oseltamivir, but a causal relationship has not yet been established.

- There have been post-marketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including oseltamivir and zanamivir. Since these events were reported voluntarily during clinical practice, estimates of frequency cannot be made, but they appear to be uncommon based on usage data for oseltamivir and zanamivir. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of antiviral medications to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuro-psychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient. For more information please visit the following websites:  
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm095044.htm>  
or  
<http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM186224.pdf>

**What are the side effects of zanamivir (Relenza®)?<sup>7</sup>**

- Bronchospasm and declines in respiratory function have been reported.
- Respiratory arrests and deaths have occurred in patients taking zanamivir and a contribution from zanamivir cannot be ruled out in these cases.
- Zanamivir should be discontinued in anyone developing bronchospasm or a decline in respiratory function; immediate treatment and hospitalization may be required.

**When is oseltamivir (Tamiflu®) contra-indicated? What are the warnings and precautions which should be taken into account when prescribing oseltamivir (Tamiflu®)?<sup>6</sup>**

Oseltamivir should NOT be taken in the following situations:

- Known hypersensitivity to any of the components of the product.
- Child is less than one year of age.
- Hereditary fructose insufficiency.

In addition, physicians should consider the following WARNINGS and PRECAUTIONS prior to prescribing oseltamivir:

- The safety of oseltamivir in infants less than one year of age has not

been established, and therefore the drug should not be given to children under one year of age.

- Tamiflu should not be used by mothers who are nursing children under one year of age due to the potential risk to the nursing infant.
- Elevated liver enzymes and hepatotoxicity have been reported in individuals taking oseltamivir. The safety of oseltamivir has not been established for individuals with hepatic impairment, and no manufacturer dosing recommendations are available for individuals on dialysis or with creatinine clearance  $\leq 10$  ml/min (See Appendix A).
- The safety of oseltamivir in pregnant women has not been studied. The drug should not be used in these circumstances unless the benefit outweighs the potential risk to the fetus.
- Allergic reactions have been reported in post-marketing surveillance, however it is not possible to estimate frequency or establish a causal relationship with oseltamivir. Reactions reported have included dermatitis, rash, eczema, urticaria, (and very rarely erythema multiforme, Stevens-Johnson-Syndrome and toxic epidermal necrolysis).

**NOTE:** Use of antibiotics is not a contraindication to the use of antivirals.

**When is zanamivir (Relenza<sup>®</sup>) contra-indicated? What are the warnings and precautions which should be taken into account when prescribing zanamivir (Relenza<sup>®</sup>)?**<sup>7</sup>

Zanamivir should NOT be taken in the following situations:

- Known hypersensitivity to zanamivir or any of its components, including LACTOSE or MILK PROTEIN.

In addition, physicians should consider the following WARNINGS and PRECAUTIONS prior to prescribing zanamivir:

- Zanamivir is not generally recommended for patients with severe underlying chronic pulmonary disease or severe asthma because of the risk of serious adverse events. If zanamivir is given to such patients, close monitoring and availability of medical care is required as described in the product monograph.
- The safety of zanamivir in pregnant women has not been studied. The drug should not be used in pregnancy unless the benefits outweigh the potential risks to the fetus.
- It is not known whether zanamivir is excreted in human breast milk; therefore caution should be exercised in giving it to nursing women.
- The safety of zanamivir has not been established for individuals who are immuno-compromised or who have chronic illnesses (including hepatic impairment, severe renal insufficiency), however, at therapeutic doses, systemic exposure to zanamivir is limited.

- Allergic-like reactions (facial/oropharyngeal edema, bronchospasm, dyspnea, urticaria, skin rashes, anaphylaxis) have been reported in post-marketing surveillance. Zanamivir should be discontinued and appropriate treatment sought if such reactions occur.
- Safety and effectiveness have not been established for pediatric patients less than seven years of age.

### **How are oseltamivir (Tamiflu®) and zanamivir (Relenza®) formulated?**

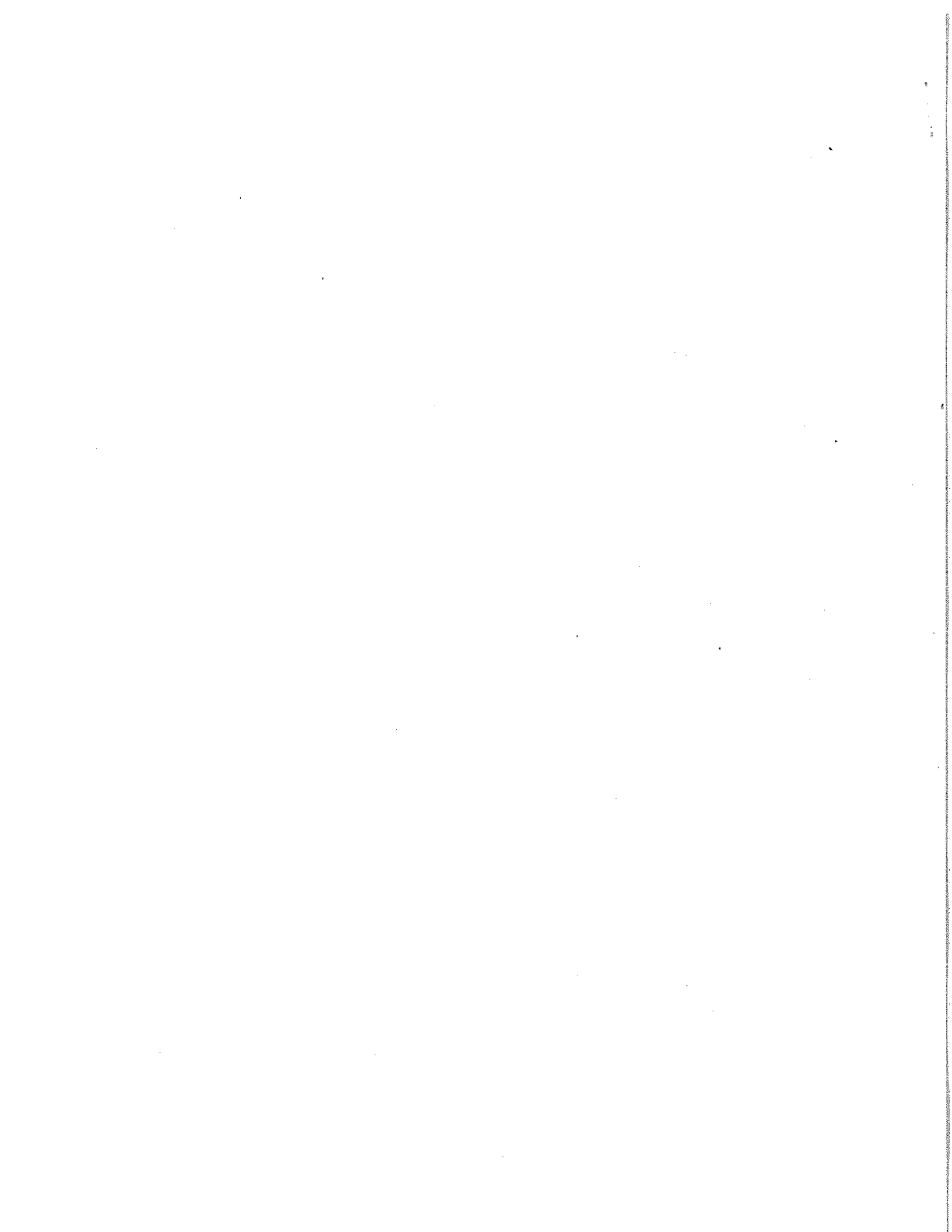
**Oseltamivir** is administered orally. It is available as a 75 mg capsule, or a powder that can be reconstituted into an oral suspension at 12 mg/ml.

**Zanamivir** is an inhaled powder. It is packaged as a "Rotadisk," which is a circular foil disk with 4 blisters, each containing 5 mg of Zanamivir. The rotadisk is inserted into a Diskhaler® device that punctures the disk, dropping the powder into a well, so that it is ready for inhalation. Each inhalation contains 5 mg of zanamivir.

**Please refer to Appendix A for the dosing of oseltamivir (Tamiflu®) and zanamivir (Relenza®).**

### **References**

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3. National Advisory Committee on Immunization. Statement on Influenza Vaccination for the 2007-2008 Season. *CCDR* 2007 July 1;33:1-38.
4. Kaiser L, Wat C, Mills T, et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med.* 2003;163(14):1667-1672.
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## Appendix D

### M2 Ion Channel Inhibitor: Amantadine

**Amantadine is NOT currently recommended for prophylaxis or treatment of influenza due to its adverse side effects and the emergence of amantadine resistance.**

In recent years resistance to amantadine has been high, especially for influenza A/H3N2, which has led to a recommendation that it not be used for influenza treatment or prevention.

