

Therapeutic Class ReviewSM

Antivirals – oseltamivir (Tamiflu[®]) and zanamivir (Relenza[®])

September 2006

Products for Review:

oseltamivir (Tamiflu[®]) [Roche]

zanamivir (Relenza[®]) [GSK]

Dossier Provided by Manufacturer: Yes

Dossier Evaluation: Tamiflu: 1

Relenza: 2

1- dossier w/missing components

2- all components present, except pharmacoeconomic model

3- all components present (comprehensive)

Available Therapeutic Alternatives:

Preferred/formulary	Non-preferred/non-formulary
<i>Treatment and prevention of influenza:</i>	
M2 inhibitors:	Neuraminidase inhibitors:
amantadine (Symmetrel [®]) [generic]	oseltamivir (Tamiflu [®]) [Roche]
rimantadine (Flumadine [®]) [generic]	zanamivir (Relenza [®]) [GSK]
<i>Prevention only:</i>	
influenza vaccine – covered under medical benefit	

Reason for Review:

- Re-review the formulary status of oseltamivir (Tamiflu) and zanamivir (Relenza), two antivirals used for the treatment and prevention of influenza, because of:
 - Concerns with resistance of influenza virus to amantadine and rimantadine.
 - Lack of treatment options for avian influenza ("bird flu").

Executive Summary:

Influenza	Avian influenza ("bird flu")
<ul style="list-style-type: none">• 10-20% of world's population affected each year.• Human contact is the primary mode of infection.• Influenza A is responsible for the majority of influenza cases.• Vaccination considered the primary strategy for preventing influenza and its complications.	<ul style="list-style-type: none">• As of May 2006, 206 confirmed cases reported to the World Health Organization.• Transmission between humans is very limited at present.• No treatment currently available. (A vaccine is currently under development).

- There is a renewed interest in oseltamivir (Tamiflu) and zanamivir (Relenza) due to:
 - Growing concerns of a worldwide influenza pandemic.
 - Resistance of influenza to amantadine and rimantadine.
 - International and federal agencies recommending their potential use in treating patients with bird flu.
 - Active stockpiling of oseltamivir (Tamiflu) in preparation for potential outbreaks of the bird flu.
- Oseltamivir (Tamiflu) and zanamivir (Relenza) are promoted as superior to amantadine and rimantadine because:
 - They have activity against both influenza A and influenza B.
 - Resistance is less likely.
 - They decrease viral shedding and therefore transmission of influenza.
- The utility of oseltamivir (Tamiflu) and zanamivir (Relenza) is limited by the:
 - Uncertainty as to whether these agents prevent serious influenza-related complications and reduce mortality in high-risk patients.
 - Uncertain clinical relevance of decreasing the duration of symptoms by 1 day.
 - Short timeframe for initiation (within 24 to 48 hours of first symptoms) necessary for presumed benefit.
 - Emergence of resistance due to frequent use. (There are case reports of resistance to oseltamivir (Tamiflu) reported in children who were treated with Tamiflu for "bird flu").
 - High cost of these agents.

Evidence

Efficacy

- Oseltamivir (Tamiflu) and zanamivir (Relenza):
 - Reduced the duration of symptoms of influenza by 1 day (from about 6 to 5 days).
 - Provided no benefit in the time it took patients with influenza to return to normal activity levels.
- There are no head-to-head trials that evaluate the efficacy of oseltamivir (Tamiflu) and zanamivir (Relenza) relative to other available influenza interventions (flu shot, amantadine, rimantadine).
- Current CDC surveillance reports a high rate of resistance (92%) of the influenza A virus to amantadine and rimantadine. (Use of these medications for treatment or prevention of influenza in the United States is currently not recommended).

- There are no head-to-head trials that compare the efficacy or effectiveness of oseltamivir (Tamiflu) or zanamivir (Relenza), and influenza vaccine in the prevention of influenza.

Avian Influenza

- There is no evidence for oseltamivir (Tamiflu) or zanamivir (Relenza) regarding their efficacy in the treatment and prevention of avian influenza ("bird flu").
 - Potential for efficacy is based on in vitro virological data and extrapolation from use in treating and preventing ordinary human influenza.

Safety

	Oseltamivir (Tamiflu)	Zanamivir (Relenza)
Adverse Event Incidence	<ul style="list-style-type: none"> ▪ Nausea and vomiting most predominant. ▪ Number needed to harm for 1 patient to experience nausea or vomiting over 5 days = 10 patients. 	<ul style="list-style-type: none"> ▪ Overall incidence similar to placebo. ▪ Unknown statistical significance.

Consideration in subpopulations:

	Oseltamivir (Tamiflu)	Zanamivir (Relenza)
Pediatrics:	Safety and efficacy in children < 1 year of age has not been demonstrated.	Safety and efficacy in children < 7 years of age has not been demonstrated.
Geriatrics:	Safety and efficacy has been established in elderly nursing home residents for up to 42 days in prevention trials.	No overall differences in safety or efficacy were observed between elderly and young patients. However, two trials in nursing home residents failed to demonstrate efficacy. Assistance with the inhaler device may be required in this population.
Race, gender, ethnicity:	No information available.	

Conclusions

- Zanamavir (Relenza) is non-preferred/non-formulary because:
 - Influenza vaccine is the gold standard for influenza prevention.
 - Minimal changes in outcomes in influenza treatment.
 - No evidence of efficacy in use in 'bird flu' patients.
 - Addition may encourage overuse, increasing the likelihood of developing resistance.
- Oseltamivir (Tamiflu) is preferred/formulary to provide a second-line alternative when the flu vaccine is not an option.

Products

Drug Products	FDA approval ^a	FDA approved indications	Usual Dose/Route	Cost ^b	Potential Off-label Uses ^c
amantadine* (Symmetrel [®]) ¹	11/1980	<ul style="list-style-type: none"> ▪ Prevention of symptoms caused by infection with influenza type A virus. ▪ Treatment of symptoms caused by infection with influenza type A virus. ▪ Treatment of parkinsonism. ▪ Treatment of drug-induced extrapyramidal reactions. 	<p><u>Adult:</u> 100 mg po BID or 200 mg po QD x 10 days.</p> <p><u>Pediatric:</u> 1 to 9 yo: 4.4 to 8.8 mg/kg/day; NTE 150 mg/day (x 10 days) 9 to 12 yo: 100 mg po BID</p> <p>For treatment of influenza A virus infection, amantadine should be started within 24 to 48 hours after symptoms begin and continued for 24 to 48 hrs after symptoms disappear.</p>	\$7	Abnormal gait, cocaine withdrawal, drug-induced dyskinesia, Freidreich's ataxia, chronic hepatitis C, multiple sclerosis, nocturnal enuresis, poliomyelitis
oseltamivir (Tamiflu [®]) ²	10/1999	<ul style="list-style-type: none"> ▪ Treatment of uncomplicated illness due to influenza infection in patients \geq 1 yo who have been symptomatic \leq 2 days. ▪ Prevention of influenza in patients \geq 1 yo. 	<p><u>Adult (treatment):</u> 75 mg po BID x 5 days</p> <p><u>Adult (prevention):</u> 75 mg po QD for \geq 10 days</p> <p><u>Pediatric (treatment x 5 days):</u> \leq 15 kg: 30 mg BID > 15 to 23 kg: 45 mg BID > 23 to 40 kg: 60 mg BID > 40 kg: 75 mg BID</p> <p><u>Pediatric (prevention x 10 days):</u> \leq 15 kg: 30 mg QD > 15 to 23 kg: 45 mg QD > 23 to 40 kg: 60 mg QD > 40 kg: 75 mg QD</p>	\$84	Avian influenza
rimantadine* (Flumadine [®]) ³	9/1993	<ul style="list-style-type: none"> ▪ Prevention of symptoms caused by infection with influenza type A virus. ▪ Treatment of symptoms caused by infection with influenza type A virus. 	<p><u>Adult (treatment):</u> 100 mg po BID x 7-10 days</p> <p><u>Adult (prevention):</u> 100 mg po BID x 5-10 days (up to 85 days)</p> <p><u>Pediatric: (prevention only):</u> < 10 yo: 5 mg/kg/day divided BID; NTE 150 mg/d \geq 10 yo: use adult dose</p>	\$26 (10 days)	Parkinson's disease
zanamivir (Relenza) ⁴	7/1999	<ul style="list-style-type: none"> ▪ Prevention of influenza in adult and pediatric patients 5 years of age and older. ▪ Treatment of uncomplicated acute illness due to influenza A and B virus in patients \geq 7 years of age who have been symptomatic for no more than 2 days. 	<p><u>Adult (treatment):</u> 10 mg (2 inh) BID x 5 days</p> <p><u>Adult (prevention):</u> 10 mg (2 inh) QD x 10 days</p> <p><u>Pediatric (treatment):</u> \geq 7 yo: 10 mg (2 inh) BID x 5 days</p> <p><u>Pediatric (prevention):</u> \geq 5 yo: 10 mg (2 inh) QD x 10 days.</p>	\$67	Avian influenza

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Cost estimate based on AWP (average wholesale price) listed in First Data Bank or MAC (maximum allowable cost) as of June 2006.

^c As listed in © 1974 - 2005 Thomson MICROMEDEX database or as referenced.

* Amantadine and rimantadine should not be used for the treatment or prophylaxis of influenza A in the United States for the 2005-2006 influenza season due to resistance, according to the Centers for Disease Control (Centers for Disease Control, 2006).

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