

Indiana Medicaid Therapeutics Committee **Therapeutic Class Review Summary**

Therapeutic Class:

Antiviral (Influenza) Agents

Overview:

Influenza occurs at epidemic rates each year and is the leading cause of respiratory illness in the United States with the majority of complications, hospitalizations, and deaths occurring in the elderly. Vaccination has been the cornerstone for prophylaxis and is recommended annually for immunocompromised persons and those with comorbidities such as chronic pulmonary, cardiovascular, and chronic metabolic diseases. Illness due to influenza in the general population results in increased time off from work and loss of productivity. Recognition of the clinical and economic impact of influenza worldwide has resulted in increased research for alternative methods of prevention and treatment.

Pharmacological interventions have been developed to specifically target viral proteins that facilitate influenza infection of the host. The two classes of antiviral influenza agents are ion channel inhibitors and neuraminidase inhibitors. The ion channel inhibitors, amantadine and rimantadine, inhibit M2 protein which allows hydrogen ions to enter into the cell resulting in the acidification needed for viral replication. The neuraminidase inhibitors oseltamivir and zanamivir inhibit viral neuraminidase necessary for aggregation of viral particles. Amantadine was first introduced into the market in 1966 for the treatment of influenza A. Ten years later, amantadine also gained FDA approval for chemoprophylaxis of influenza. Rimantadine, pharmacologically related to amantadine, was marketed in 1993. Although trials have shown clinical efficacy of ion channel inhibitors, *Monto et al* reports that the use of these agents have been limited due to the concern for resistance and the need to ensure that the virus being treated is caused by influenza A. *Hayden et al* further explains that oral rimantadine may be preferable to amantadine for treating influenza A virus infections due to its therapeutic efficacy combined with its lower potential for central nervous system (CNS) side effects. Recently, resistance to influenza A viruses has been reported in the United States with use of the M2 ion channel inhibitors; therefore these agents are currently not recommended as monotherapy. Additionally, the neuraminidase inhibitors, oseltamivir and zanamivir, both introduced in 1999, are FDA approved to treat influenza A and B; however, in 2007-08, a significant increase in the prevalence of oseltamivir resistance was reported among influenza A (H1N1) viruses worldwide. Though the majority of influenza A (H1N1) viruses have been susceptible to oseltamivir during the 2009-2010 influenza season, possible resistance to oseltamivir is still a concern. Therefore, zanamivir or the combination of oseltamivir with either rimantadine or amantadine is recommended when treatment with oseltamivir alone is inappropriate.

Self-injury and delirium have been reported as postmarketing events with use of the neuraminidase inhibitors. These events occurred primarily among pediatric patients in Japan; however, the relative contribution of the neuraminidase inhibitors to these incidents is unknown. All antiviral influenza agents are indicated for prophylaxis of influenza. Caution should be

exercised when using zanamivir because it has been associated with bronchospasms in patients with a history of airway disease. Clinical studies, such as the IMPACT trial, have shown improved effectiveness in the treatment of influenza when oseltamivir and zanamivir were initiated ≤ 48 hours after the onset of symptoms. Specific dosage recommendations and precautions must be considered when using ion channel and neuraminidase inhibitors in children, elderly, and patients with renal and hepatic impairment.

Vaccinations are the most cost effective therapy in the elderly and other patients with comorbidities. According to the *Advisory Committee on Immunization Practices*, the cost-utility of vaccinations improved with increasing age and among those with chronic medical conditions. Chemoprophylaxis with influenza agents may benefit persons at high risk who are vaccinated after influenza activity has begun and persons who provide care to those at high risk for influenza complications. However, further study is needed to provide rationale for use of these agents in immunocompromised patients. The antiviral influenza agents may be considered in this patient population.

Generic Name	Trade Name	Dosage Form	Manufacturer	Generic
Amantadine	Symmetrel®	100-mg capsules, tablets 50 mg/5-mL syrup	Endo, various	Y
Oseltamivir	Tamiflu®	30-, 45-, and 75-mg capsules (blister package of 10) 12-mg/mL powder for oral suspension	Hoffman-LaRoche	N
Rimantadine	Flumadine®	100-mg tablets	Forest, various	Y
Zanamivir	Relenza®	Powder for oral inhaler (Rotadisk®) 5 mg/blister	GlaxoSmithKline	N

Summary:

Amantadine is the least expensive antiviral influenza drug available today, while novel neuraminidase inhibitors are the most expensive agents. Amantadine, although proven clinically efficacious, is associated with notable CNS side effects. Rimantadine is associated with fewer side effects; however, like amantadine, it is only active against influenza A virus. Resistance to influenza A viruses has been reported in the United States with the use of the M2 ion channel inhibitors and their use is generally not recommended. However, oseltamivir resistance has been detected among influenza A (H1N1) viruses worldwide; therefore, zanamivir or the combination of oseltamivir with either rimantadine or amantadine is recommended when treatment with oseltamivir alone is inappropriate. The neuraminidase inhibitors are active against both influenza A and B virus and are proven to be efficacious with less severe gastrointestinal side effects such as nausea and vomiting.



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Currently, comparative clinical trials of the efficacy and safety of ion channel inhibitors and neuraminidase inhibitors are limited. Selection of an antiviral agent to prevent or treat influenza should be based on each drug's spectrum of activity, side effects and ease of dosage administration; therefore, one ion channel inhibitor and one neuraminidase inhibitor should be considered on the formulary. Antiviral agents should not be substituted for the suggested annual influenza vaccine.