Therapeutic Class Overview
Antivirals, Influenza

INTRODUCTION

- Influenza is an infectious respiratory illness caused by the influenza A and influenza B viruses. Influenza epidemics occur annually in the United States, typically from late fall to early spring. Although the majority of infected individuals recover without complications, some cases of influenza result in severe illness or death *(Grohskopf et al 2016)*.
- The virus is primarily transmitted through direct contact large-particle respiratory droplets from an infected individual's coughs and sneezes. It is also spread through contact with surfaces contaminated by infected respiratory droplets. Adults begin to shed virus 1 day prior to symptom onset, and they remain contagious for 5 to 7 days after falling ill *(Centers for Disease Control and Prevention [CDC] 2016[a])*.
- Signs and symptoms of uncomplicated influenza illness include fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. Complications of influenza infection include sinusitis, otitis media, pneumonia, sepsis, and exacerbation of chronic medical conditions. Elderly adults, young children, pregnant women, and patients with chronic medical conditions have a higher risk of developing complications from influenza *(CDC 2016[b])*.
- Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. Antiviral prescription medications are also available for influenza prophylaxis and treatment; however, antiviral chemoprophylaxis is not a substitute for annual influenza vaccination *(Grohskopf et al 2016)*.
- Initiation of antiviral therapy to treat influenza is recommended as early as possible for patients with confirmed or suspected influenza who are hospitalized, have severe, complicated, or progressive illness, or are at higher risk for influenza complications *(Fiore et al 2011)*.
- Two classes of antiviral medications are available and will be reviewed. The adamantanes include amantadine and Flumadine (rimantadine). The neuraminidase inhibitors include Rapivab (peramivir), Relenza (zanamivir), and Tamiflu (oseltamivir).
- Although the adamantanes are active against influenza A virus, resistance is high amongst currently circulating virus strains. The adamantanes lack activity against influenza B virus. Therefore, amantadine and rimantadine are not recommended for treatment or chemoprophylaxis during the current influenza season *(CDC 2017)*.
- The neuraminidase inhibitors are active against both influenza A and influenza B viruses. Rapivab (peramivir), Relenza (zanamivir), and oseltamivir are the only antivirals recommended for the current influenza season in the United States *(CDC 2017)*.
- Circulating influenza viruses are constantly evolving, and drug-resistant influenza virus strains have been reported. Prescribers should refer to influenza drug susceptibility patterns and treatment effects when selecting an antiviral agent *(CDC 2017)*.
- Medispan class: Antiparkinson, Dopaminergics and Influenza Agents. The only agent from the Antiparkinson, Dopaminergics category that will be included in this review is amantadine for the influenza indication.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
amantadine	✔
Flumadine (rimantadine)	✔
Rapivab (peramivir)	-
Relenza (zanamivir)	-
Tamiflu (oseltamivir)	✔

(*Drugs@FDA 2017*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication[1]	amantadine[2]	Flumadine (rimantadine)	Rapivab[3] (peramivir)	Relenza[4] (zanamivir)	Tamiflu[5] (oseltamivir)
Prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus	✔				
Prophylaxis and treatment of illness caused by various strains of influenza A virus in adults (17 years and older)		✔			
Prophylaxis against influenza A virus in children (1 to 16 years of age)		✔			
Treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than 2 days			✔		
Prophylaxis of influenza in adults and pediatric patients aged 5 years and older				✔	
Treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients aged 7 years and older who have been symptomatic for no more than 2 days				✔	
Prophylaxis of influenza A and B in patients 1 year and older					✔
Treatment of acute, uncomplicated illness due to influenza A and B infection in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours					✔

[1] The changing of viruses over time is a limitation of use for antivirals. Emergence of resistance substitutions could decrease drug effectiveness. Other factors, such as changes in viral virulence, may also diminish clinical benefit of antivirals. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when selecting an antiviral.

[2] Amantadine is also indicated in the treatment of parkinsonism and drug-induced extrapyramidal reactions.

[3] Limitations of use for Rapivab (peramivir):

- Efficacy is based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled.
- Efficacy could not be established in patients with serious influenza requiring hospitalization.

[4] Limitations of use for Relenza (zanamivir):

- Not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) due to risk of serious bronchospasm.
- Has not been proven effective for treatment of influenza in individuals with underlying airways disease.
- Has not been proven effective for prophylaxis of influenza in the nursing home setting.

[5] Limitations of use for Tamiflu (oseltamivir):

- Not recommended for patients with end-stage renal disease not undergoing dialysis.

(Prescribing information: amantadine capsules 2017, amantadine oral solution 2015, amantadine tablets 2017, Flumadine 2010, Rapivab 2016, Relenza 2016, Tamiflu 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Adamantanes

- Clinical trials have demonstrated that the adamantanes are effective in both the prophylaxis and treatment of influenza A virus *(Bryson et al 1980, Crawford et al 1988, Dolin et al 1982, Hall et al 1987, Hayden et al 1989, Jackson et al 2011, Jefferson et al 2006[a], Jefferson et al 2006[b], Monto et al 1995, Reuman et al 1989)*.
- One systematic review assessed the efficacy and safety of adamantanes in healthy adults by analyzing 20 prophylaxis and 13 treatment randomized trials comparing amantadine or rimantadine with placebo. For prophylaxis, amantadine was 61% better than placebo at reducing influenza risk (P<0.001). Although rimantadine was 72% better than placebo at preventing influenza, statistical significance was not achieved. There was significant heterogeneity between the prophylaxis trials, and only a small sample size was available for rimantadine compared to amantadine. For treatment, amantadine and rimantadine both reduced the duration of fever by one day. Both agents caused gastrointestinal side effects, but amantadine caused significantly more adverse effects in the central nervous system than rimantadine *(Jefferson et al 2006[a])*.
- Influenza A virus resistance to amantadine and rimantadine has developed over the years. During the 2009 to 2010 influenza season, 100% of the 18 influenza H3N2 viruses tested in the United States were resistant to adamantanes. Similarly, 99.8% of the pandemic H1N1 viruses tested were resistant to adamantanes. Due to influenza A virus resistance and lack of activity against influenza B virus, the adamantanes are not recommended for the current influenza season *(CDC 2010[b], CDC 2017)*.

Neuraminidase inhibitors

- The neuraminidase inhibitors have demonstrated efficacy for their respective indications. Relenza (zanamivir) inhalation and oral oseltamivir are effective in both the prophylaxis and treatment of influenza A and B. Clinical trials have demonstrated a reduction in laboratory-confirmed influenza, illness, fever duration, secondary complications, and household contacts with influenza infection *(Aoki et al 2003, Chik et al 2004, Cooper et al 2003, Fry et al 2014, Halloran et al 2007, Hayden et al 1997, Hayden et al 1999, Hayden et al 2000, Hayden et al 2004, Hedrick et al 2000, Hiba et al 2011, Kaiser et al 2003, Kawai et al 2005, Kawai et al 2006, Lin et al 2006, MIST Study Group 1998, Monto et al 1999[a], Monto et al 1999[b], Monto et al 2002, Nicholson et al 2000, Peters et al 2001, Reuman et al 1989, Singh et al 2003, Treanor et al 2000, Turner et al 2003, Wang et al 2012, Welliver et al 2001, Whitley et al 2001)*.
- One systematic review analyzed 20 oseltamivir and 26 Relenza (zanamivir) randomized, placebo-controlled trials in order to better define their efficacy and safety. In prophylaxis trials, the risk of symptomatic influenza was reduced by 3.05% in patients treated with oseltamivir compared to placebo and 1.98% in patients treated with Relenza (zanamivir) compared to placebo. In adults, the time to first alleviation of symptoms was reduced by 0.7 days (P<0.0001) in patients receiving oseltamivir compared to placebo and 0.6 days (P<0.00001) in patients receiving Relenza (zanamivir) compared to placebo. Oseltamivir significantly reduced the time to alleviation of symptoms in non-asthmatic children and decreased the incidence of self-reported pneumonia. Relenza (zanamivir) significantly reduced the risk of bronchitis in adults with influenza. Neither treatment was a significant improvement over placebo in time to symptom alleviation in asthmatic children or risk of hospitalizations, otitis media, or sinusitis. Many studies included were at a high risk of selection bias due to inadequate reporting and a high risk of attrition bias due to selective reporting. All trials were sponsored by the manufacturers *(Jefferson et al 2014)*.
- Rapivab (peramivir) intravenous (IV) infusion is approved for the treatment of influenza A and B in adults. The primary endpoint for the main clinical trial supporting Food and Drug Administration (FDA)-approval of Rapivab (peramivir) was time to alleviation of symptoms. The trial evaluated 296 previously healthy adults presenting with the onset of influenza-like illness within the previous 48 hours and a positive influenza rapid antigen test. In this multicenter, double-blind, placebo-controlled clinical trial, patients were randomized to Rapivab (peramivir) 300 mg, 600 mg, or placebo as a single IV dose. Acetaminophen use was permitted. Patients self-reported body temperature, symptoms, and resumption of activities over 14 days. The primary endpoint, median time to alleviation of symptoms, was significantly earlier with Rapivab (peramivir) 300 mg (59.1 hours) and 600 mg (59.9 hours) compared to placebo (81.8 hours; both P=0.0092). There was no significant difference in the incidence of all adverse events in patients receiving Rapivab (peramivir)

compared to placebo. Diarrhea was the most common adverse event, occurring in 14.1%, 15.2% and 17% of the Rapivab (peramivir) 300 mg, 600 mg, and placebo groups, respectively *(Kohno et al 2010)*.

- Although studies have evaluated Rapivab (peramivir) in hospitalized patients and in children, both of these populations are not included in the FDA-approved labeling *(De Jong et al 2014, Ison et al 2014, Ison et al 2013, Sugaya et al 2012)*. The Phase 3 clinical trial of Rapivab (peramivir) in hospitalized influenza patients failed to meet its primary endpoint of reducing the time to clinical resolution compared to placebo. There are no clinical endpoints that have been validated for clinical trials of neuraminidase inhibitors treating hospitalized patients with influenza *(FDA 2014)*. In 2009, the United States issued an Emergency Use Authorization (EUA) program allowing Rapivab (peramivir) for the treatment of suspected or confirmed 2009 H1N1 influenza A virus infection in hospitalized patients *(Birnkrant and Cox 2009)*. Patients eligible for treatment were hospitalized, unable to tolerate or unresponsive to other available antivirals, or lacked a dependable oral or inhalation drug delivery route. The Public Health Emergency determination for the 2009 H1N1 influenza pandemic expired on June 23, 2010 *(CDC 2010[a])*.
- Numerous placebo-controlled trials have demonstrated the efficacy of neuraminidase inhibitors individually, but head-to-head trials directly comparing the agents are limited. One randomized, double-blind, placebo-controlled safety trial compared the use of oseltamivir, Relenza (zanamivir), and placebo in 390 healthy adults for influenza chemoprophylaxis over 16 weeks. The study showed that both treatments were well tolerated compared to placebo, and there were no discontinuations due to adverse events *(Anekthananon et al 2013)*.
- A Phase 3 multinational, multicenter, double-blind, randomized, noninferiority trial compared a single dose of 300 or 600 mg IV Rapivab (peramivir) to 5 days of oral oseltamivir in 1,091 patients with seasonal influenza. The primary endpoint, time to alleviation of influenza symptoms, had a median of 78.0 hours in patients receiving 300 mg of Rapivab (peramivir), 81.0 hours in patients receiving 600 mg of Rapivab (peramivir), and 81.8 hours in patients receiving oseltamivir. Both strengths of Rapivab (peramivir) were noninferior to oseltamivir with a noninferiority margin of 0.170. There was no significant difference between treatments in the incidence of complications of influenza infection *(Kohno et al 2011)*.
- Observational studies comparing the clinical efficacy of Rapivab (peramivir), Relenza (zanamivir), and oseltamivir in treating influenza have demonstrated within-class variation in the time to alleviation of influenza symptoms. The lack of robust data from randomized, head-to-head trials prevents the recommendation of one neuraminidase inhibitor over another. Local and seasonal susceptibility trends, route of administration, and patient-specific factors such as age and compliance should be taken into account when selecting an agent for antiviral drug therapy *(Kawai et al 2008, Takemoto et al 2013)*.
- While influenza virus strains resistant to specific neuraminidase inhibitors have emerged, overall resistance remains low. According to surveillance data on seasonal influenza virus strains, the rate of resistance to oseltamivir is 1 to 3% and resistance to Relenza (zanamivir) is less than 1% *(Li et al 2015)*.

CLINICAL GUIDELINES

- Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. All individuals six months of age and older should receive an influenza vaccination each year, unless contraindicated. The live attenuated intranasal influenza vaccine is not recommended during the 2016 to 2017 influenza season due to low effectiveness. Prophylactic antiviral administration is not a substitute for early influenza vaccination *(Grohskopf et al 2016)*.
- Amantadine and rimantadine are not recommended for antiviral treatment or prophylaxis of influenza A virus strains in the United States due to high rates of resistance *(American Academy of Pediatrics [AAP] 2016, Fiore et al 2011, CDC 2017)*.
- The antivirals recommended by the CDC for the current influenza season include oseltamivir, Relenza (zanamivir) and Rapivab (peramivir). Routine or widespread use of antivirals for chemoprophylaxis is not recommended due to concerns for viral resistance. Oseltamivir and Relenza (zanamivir) are recommended for post-exposure prophylaxis in patients who are severely immunosuppressed and in patients at a high risk for influenza complications who are either not a candidate for vaccination or received their annual vaccination less than 2 weeks prior to exposure *(CDC 2017)*.
- Treatment of influenza with antiviral therapy is recommended as early as possible for patients with confirmed or suspected influenza who are hospitalized, have severe, complicated, or progressive illness, or are at a high risk for complications *(CDC 2017)*.
- Populations at a high risk for influenza complications and recommended to receive antiviral treatment include children younger than 2 years old, adults age 65 and above, pregnant or postpartum women, American Indians, Alaska Natives,

obese patients with a body mass index (BMI) of 40 kg/m² and above, patients younger than 19 years old receiving long-term treatment with aspirin, residents of nursing homes, and patients with immunosuppression, chronic disorders (eg, pulmonary, cardiovascular, renal, hepatic, hematological and metabolic), or neurologic conditions *(CDC 2017)*.

- Antiviral therapy works best when administered within 48 hours of symptom onset. Treatment initiation should not be delayed for the results of diagnostic testing. Early administration of antivirals may shorten the duration of fever, reduce the risk of influenza-related complications such as otitis media and pneumonia, reduce death in hospitalized patients, and decrease the duration of hospitalization in hospitalized children *(CDC 2017)*.

SAFETY SUMMARY

- Common adverse events with adamantanes include headache, anorexia, dry mouth, and agitation.
- Amantadine and rimantadine should be used with caution in patients with epilepsy due to an increased risk for seizures.
- Amantadine has anticholinergic effects and is contraindicated in patients with untreated angle closure glaucoma. There have also been reports of death from overdose and suicide attempts with amantadine.
- Common adverse events with neuraminidase inhibitors include nausea, vomiting, and headache. The most common adverse effect with Rapivab (peramivir) is diarrhea.
- All three neuraminidase inhibitors have labelled warnings for neuropsychiatric events such as hallucinations and delirium. Patients should be monitored for signs of abnormal behavior.
- Oseltamivir and Rapivab (peramivir) have warnings for serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome.
- Relenza (zanamivir) has a warning for bronchospasm and should not be used in patients with asthma or chronic obstructive pulmonary disease. It is also contraindicated in patients with milk protein allergies.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
amantadine	Capsules, oral solution, tablets	Oral	Once daily or twice daily Adults: 200 mg once daily or 100 mg twice daily Pediatric patients: 1 to 9 years: 4.4 to 8.8 mg/kg/day not to exceed 150 mg per day 9 to 12 years: 100 mg twice daily The safety and efficacy of amantadine in newborn infants and infants below the age of 1 year have not been established.	Should be taken for 10 days following a known exposure. If using in conjunction with vaccine until antibody response, then take for 2 to 4 weeks. Treatment of illness should be started within 24 to 48 hours of symptom onset and continued for 24 to 48 hours after symptoms disappear. For adult patients intolerant to 200 mg daily dose because of central nervous system or other toxicities: 100 mg daily dose Because amantadine is primarily excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of amantadine should be reduced in patients with renal impairment and in individuals who are 65

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				years of age or older according to the following: For CrCl=30 to 50 mL/min: 200 mg 1st day, then 100 mg daily For CrCl=15 to 29 mL/min: 200 mg 1st day, then 100 mg on alternate days For CrCl<15 mL/min and HD: 200 mg every 7 days For patients ≥65 years: 100 mg once daily The dose of amantadine may need reduction in patients with congestive heart failure, peripheral edema, or orthostatic hypotension.
Flumadine (rimantadine)	Tablets	Oral	Twice daily **Adults** Treatment: 100 mg twice daily for 7 days Prophylaxis: 100 mg twice daily **Pediatric patients** Prophylaxis in patients 1 to 9 years: 5 mg/kg/day, not to exceed 150 mg per day 10 to 16 years: Refer to the adult dose	Treatment of illness should be started within 48 hours of symptoms. A suspension can be made from the tablets and is stable for 14 days. Dose adjustment in patients ≥65 years: 100 mg once daily Dose adjustment in patients with CrCl<29 mL/min: 100 mg daily Dose adjustment in patients with severe hepatic dysfunction: 100 mg daily
Rapivab (peramivir)	Injection	IV	One time (within 2 days of onset of influenza symptoms)	A single dose administered by IV infusion for a minimum of 15 minutes. Dose adjustment in patients with CrCl=30 to 49 mL/min: 200 mg Dose adjustment in patients with CrCl=10 to 29 mL/min: 100 mg HD: Administer after dialysis
Relenza (zanamivir)	Inhalation powder (in blisters)	Oral inhalation	Once daily or twice daily, depending on the indication	The 10-mg dose is provided by 2 inhalations (one 5-mg blister

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
		via Diskhaler device	Treatment (≥7 years): 10 mg twice daily for 5 days Prophylaxis in household setting (≥5 years): 10 mg once daily for 10 days Prophylaxis in community outbreak (adults and adolescents): 10 mg once daily for 28 days	per inhalation). Patients scheduled to use an inhaled bronchodilator at the same time as Relenza should use their bronchodilator before taking Relenza. If Relenza is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional. Due to the low systemic bioavailability of Relenza following oral inhalation, no dosage adjustments are necessary in patients with renal Impairment; however, the potential for drug accumulation should be considered.
Tamiflu (oseltamivir)	Capsules, powder for oral suspension	Oral	Once daily or twice daily, depending on the indication **Patients ≥13 years** Treatment: 75 mg twice daily for 5 days Prophylaxis: 75 mg once daily for at least 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak. In immunocompromised patients, may be continued for up to 12 weeks. **Patients <13 years** Treatment: • 2 weeks to <1 year: 3 mg/kg twice daily for 5 days • 1 to 12 years: 30 to 75 mg twice daily for 5 days Prophylaxis: • 1 to 12 years: 30 to 75 mg once daily for 10 days. During a community	Start treatment within 48 hours of symptom onset or close contact with infected individual. Taking with food may enhance tolerability. In an emergency, a suspension can be made from capsules. Dosage adjustment is recommended for patients with a CrCl between 10 and 60 mL/minute and for patients with ESRD undergoing routine HD or CAPD. Not recommended for patients with ESRD not undergoing dialysis. No dosage adjustment for mild to moderate hepatic impairment. Safety not evaluated in patients with severe hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			outbreak, can continue for up to six weeks (or up to 12 weeks in immuno-compromised patients).	

CAPD=continuous ambulatory peritoneal dialysis; CrCl =creatinine clearance; ESRD=end stage renal disease; HD=hemodialysis
*See the current prescribing information for full details

CONCLUSION

- The first line of protection against influenza is vaccination. All individuals six months of age and older without contraindications should receive yearly influenza vaccination *(AAP 2016, Fiore et al 2011, Grohskopf et al 2016)*.
- Antivirals are available for the prevention and treatment of influenza. Overall, the adamantanes and neuraminidase inhibitors have demonstrated safety and efficacy for their respective indications. However, amantadine and rimantadine are not currently recommended due to high rates of resistance in circulating influenza virus strains *(CDC 2017)*.
- Relenza (zanamivir) and oseltamivir are both effective in preventing influenza but are not substitutes for annual vaccination. They are recommended as post-exposure chemoprophylaxis in patients with a high risk for influenza complications who are not sufficiently protected by vaccination *(Fiore et al 2011, CDC 2017, Harper et al 2009, Panel on Opportunistic Infections 2013)*. Rapivab (peramivir) is not approved or recommended for influenza prophylaxis *(CDC 2017)*.
- Rapivab (peramivir), Relenza (zanamivir), and oseltamivir effectively treat influenza by reducing the duration of fever and illness. Initiation of treatment is recommended as soon as possible for patients with suspected influenza who are hospitalized, severely ill, or at high risk for influenza complications *(Fiore et al 2011, AAP 2016, CDC 2017, Harper et al 2009, Panel on Opportunistic Infections 2013)*.
- Limited within-class comparisons prevent the recommendation of one neuraminidase inhibitor over another. Factors to consider when selecting an antiviral agent include the route of administration, seasonal and geographical susceptibility trends, and patient-specific factors such as age and compliance *(Takemoto et al 2013)*.
- The most common adverse events with amantadine and rimantadine are headache, anorexia, dry mouth, and agitation. The adamantanes are associated with an increased risk for seizures.
- The most common adverse events with Relenza (zanamivir) and oseltamivir are headache, nausea, and vomiting. Diarrhea is the most common adverse event with Rapivab (peramivir). The neuraminidase inhibitors have a labelled warning for neuropsychiatric events such as delirium and abnormal behavior leading to injury.

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