# Antivirals, Herpes Simplex Virus (HSV)
# Therapeutic Class Review (TCR)

**October 25, 2021; rev. October 24, 2022**



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## FDA-APPROVED INDICATIONS

| Drug | Manufacturer | FDA-Approved Indications |
|---|---|---|
| acyclovir (Zovirax®)[1,2,3] | generic, Mylan | ▪ Treatment of herpes zoster (shingles)<br>▪ Treatment of varicella (chickenpox) in patients > 2 years old<br>▪ Treatment of genital herpes simplex (initial and recurrent episodes) |
| buccal acyclovir (Sitavig®)[4] | EPI Health | ▪ Treatment of recurrent herpes labialis (cold sores) in immunocompetent adults |
| famciclovir[5] | generic | ▪ Treatment of herpes zoster (shingles)<br>▪ Treatment and suppression of recurrent genital herpes in immunocompetent adults<br>▪ Treatment of recurrent episodes of orolabial or genital herpes infections in HIV-infected patients<br>▪ Treatment of recurrent herpes simplex labialis (cold sores) in immunocompetent adults |
| valacyclovir (Valtrex®)[6] | generic, GlaxoSmithKline | ▪ Treatment of herpes zoster (shingles)<br>▪ Treatment of genital herpes<br>– Immunocompetent patients with initial or recurrent episode<br>– Suppression in immunocompetent or HIV-infected patients<br>– Reducing heterosexual transmission to susceptible partners<br>▪ Treatment of herpes labialis (cold sores) in patients ≥ 12 years old)<br>▪ Treatment of varicella (chickenpox) in immunocompetent patients 2 to 18 years old |

## OVERVIEW

According to the Centers for Disease Control and Prevention (CDC) sexually transmitted infections (STI) surveillance, herpes simplex virus (HSV) remains one of the most prevalent of sexually transmitted infections in the United States (US).[7,8] HSV is most often transmitted by people unaware they have infection and/or who are asymptomatic. HSV shedding can occur when the patient is asymptomatic. There are 2 types of herpes simplex virus, HSV-1 and HSV-2. HSV-1 usually establishes latency in the trigeminal ganglion lesions on the lower lip or face. HSV-2 resides in the sacral ganglion at the base of the spine and produces lesions and/or viral shedding in the genital area. However, it is possible to have either virus affecting either region, as well as other areas. HSV-2 infections are the most common cause of genital ulceration in the US. HSV-2 seroprevalence is more common in women and non-Hispanic African Americans. HSV-2, by causing genital ulcerations, has been found to increase the risk of acquiring human immunodeficiency virus (HIV).[9]

HSV infections are chronic, life-long infections. Management of genital herpes includes counseling and methods to reduce transmission, such as use of condoms, avoidance of sexual activity during infection recurrences, and suppressive antiviral therapy. Antivirals do not eradicate HSV.[10] They are used to treat and partially control the signs and symptoms of infection during initial and recurrent herpes episodes. These agents are also given as daily suppressive therapy to reduce the frequency of episodes.

The 2021 CDC STI recommendations for genital herpes do not indicate a preference for any of the 3 oral agents (acyclovir, famciclovir, valacyclovir) either for initial or recurrent episodes.[11] Chronic suppressive therapy for patients with frequent recurrences may include any 1 of the 3 oral agents

according to the CDC STI guidelines. Oral antiviral therapy is preferred over topical antiviral therapy. Topical treatment with antivirals offers minimal clinical benefit, and its use is discouraged.

Varicella-zoster virus (VZV) causes an acute, localized infection commonly known as chickenpox.[12] After this acute infection, VZV lies dormant in the dorsal root ganglia for many years before potentially re-emerging to cause herpes zoster, commonly known as shingles. Approximately 1 in 3 persons will develop herpes zoster during their lifetime, resulting in an estimated 1 million episodes in the US annually, with about half of all cases occurring in patients ≥ 60 years of age. About 10% to 18% of these patients will develop postherpetic neuralgia (PHN); likelihood of occurrence and its severity increases at ≥ 60 years.[13]

Reactivation of VZV may be due to aging, stress, or immunosuppression.[14] The virus spreads along nerve tracts, causing pain or a burning sensation followed by a painful, blistering rash. The infection may spontaneously disappear after 2 to 4 weeks and rarely recurs. Relief of pain may be all that is required. In severe cases of shingles, nerve palsy, continued neuralgia, or blindness as a result of eye lesions caused by VZV, may persist after the acute infection disappears. The goal of treatment of herpes zoster is to reduce pain in immunocompetent patients and stop viral replication in immunocompromised patients and those with ophthalmic herpes zoster.[15] Antivirals reduce the duration of viral shedding and development of new lesions and promote healing of the rash. The effect of antivirals on the development of postherpetic neuralgia are less clear; however, several meta-analyses and clinical trials have demonstrated that antivirals significantly reduce the duration or incidence of prolonged pain.[16,17,18,19] Risk factors for postherpetic neuralgia include older age, female gender, presence of prodromal symptoms, greater rash severity, and greater acute pain severity.[20] Guidance for the management of herpes zoster support the use of any of the 3 agents for first line therapy.[21,22] Clinical guidance was released in 2018 by the CDC Advisory Committee on Immunization Practices (ACIP) regarding the use of shingles vaccines. As of November 2020, the 2-dose recombinant zoster vaccine (Shingrix®) is the only shingle vaccine available in the US and is recommended in adults ≥ 50 years of age; live attenuated zoster vaccine (Zostavax®) is no longer available in the US as of November 2020.[23,24] In their 2022 recommendations for the use of recombinant zoster vaccine in immunocompromised adults (Shingrix), ACIP recommends 2 doses of the vaccine for prevention of herpes zoster and related complications in immunodeficient or immunosuppressed adults aged ≥ 19 years.[25]

## PHARMACOLOGY[26,27,28,29,30,31]

| Drug | Mechanism of Action |
|---|---|
| acyclovir (Zovirax, Sitavig) | ▪ Acyclovir is an acyclic analogue of the natural nucleoside, guanosine; it is activated via monophosphorylation by HSV-induced thymidine kinase; selective affinity results in the activation and concentration of acyclovir in virus-infected cells over normal cells; 2 additional phosphorylations result in acyclovir triphosphate, a substrate for and preferential inhibitor of viral, rather than cellular, DNA polymerase; it binds to HSV DNA polymerase, is incorporated into viral DNA, and thereby inhibits viral DNA replication<br>▪ Acyclovir has *in vitro* inhibitory activity against HSV-1, HSV-2, VZV, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) |
| famciclovir | ▪ Famciclovir is a pro-drug; it is the diacetyl 6-deoxy analog of the active antiviral compound, penciclovir; penciclovir is phosphorylated into a monophosphate form that is converted into penciclovir triphosphate; viral DNA synthesis and replication are inhibited by penciclovir<br>▪ Famciclovir has inhibitory activity against HSV-1, HSV-2, VZV, and EBV |
| valacyclovir (Valtrex) | ▪ Valacyclovir is the L-valyl ester prodrug of acyclovir and is rapidly converted to acyclovir, which has affinity for the viral enzyme thymidine kinase encoded by HSV and VZV; therefore, valacyclovir has similar viral inhibitory activity as acyclovir |

## PHARMACOKINETICS[32,33,34,35,36,37]

| Drug | Bioavailability (%) | Half-Life (hr) | Metabolism | Excretion (%) |
|---|---|---|---|---|
| acyclovir (Zovirax) | 10-20 | 2.5-3.3 | ≥ 1 metabolite | Renal: 62-91<br>Fecal: minimal |
| famciclovir | 77 | 2.3 for penciclovir | 1 active – penciclovir; 3 inactive | Renal: 73<br>Fecal: 27 |
| valacyclovir (Valtrex) | 55 | 2.5-3.3 | Rapidly converted to acyclovir | Renal: 46<br>Fecal: 47 |

In pharmacokinetic studies, buccal acyclovir (Sitavig) was undetectable at 5 hours (had a delayed appearance) and did not reach concentration levels needed for systemic antiviral activity.

## CONTRAINDICATIONS/WARNINGS[38,39,40,41,42,43]

Acyclovir (Zovirax, Sitavig) and valacyclovir (Valtrex) are contraindicated in patients with hypersensitivity to acyclovir. Famciclovir is contraindicated in patients with known hypersensitivity to the product, its components, or penciclovir cream (Denavir®).

Renal failure, in some cases resulting in death, has been observed with acyclovir and valacyclovir therapy. Thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), which has resulted in death, has occurred in immunocompromised patients receiving acyclovir or valacyclovir, including patients with advanced HIV disease, patients having undergone allogenic bone marrow transplant, and renal transplant. Cases of acute renal failure have been reported in patients with underlying renal disease who have received inappropriately high doses of famciclovir for their level of renal function. Dosage reduction is recommended when administering famciclovir to patients with renal impairment.

Central nervous system (CNS) adverse effects, such as agitation, hallucinations, confusion, and encephalopathy, may occur in elderly patients (with or without reduced renal function) and in patients

with underlying renal disease who receive higher than recommended doses of valacyclovir for their level of renal function. Use with caution in elderly patients and reduce dosage in patients with renal impairment. Valacyclovir should be discontinued if CNS adverse effects occur.

CNS adverse effects, such as dizziness, confusion, and hallucinations, as well as thrombocytopenia, palpitations, and abnormal liver function tests, have been observed in post-marketing studies with famciclovir. Dermatological and tissue disorders such as urticaria, Stevens-Johnson syndrome, and angioedema were also associated with famciclovir usage in post-marketing analysis.

Caution should also be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible CNS symptoms, such as those that have been reported in patients treated with intravenous acyclovir. Adequate hydration should be maintained.

## DRUG INTERACTIONS[44,45,46,47,48,49]

Co-administration of probenecid with intravenous acyclovir (Zovirax) has been shown to increase the mean acyclovir half-life and the area under the concentration-time curve (AUC). Urinary excretion and renal clearance were correspondingly reduced. No drug interactions are expected with buccal acyclovir (Sitavig) due to its low dose and minimal systemic absorption.

Concurrent use with probenecid or other drugs significantly eliminated by active renal tubular secretion may result in increased plasma concentrations of penciclovir, the active metabolite of famciclovir.

No clinically significant drug interactions have been observed with valacyclovir (Valtrex).

## ADVERSE EFFECTS[50,51,52,53,54,55]

| Drug | Headache | Nausea | Dizziness | Abdominal Pain | ⇧ AST | Diarrhea |
|---|---|---|---|---|---|---|
| acyclovir (Zovirax)<br>400 mg twice daily<br>n=586 continuous treatment<br>(n=589 intermittent treatment of occurrences) | reported<br>(2.2) | 4.8<br>(2.4) | reported | nr | reported | 2.4<br>(2.7) |
| buccal acyclovir (Sitavig)<br>50 mg buccal tablet given as a single dose | 3<br>(3) | nr | 1<br>(1) | nr | nr | nr |
| famciclovir<br>125 mg daily to 1 gm twice daily | 13.5-22.7<br>(5.4-17.8) | 2.5-12.5<br>(3.6-11.6) | nr | 0-1.1<br>(1.2-3.4) | 2.3<br>(1.2) | 4.9-7.7<br>(1.2-4.8) |
| valacyclovir (Valtrex)<br>500 mg twice daily to<br>1 gm 3 times daily | 11-38<br>(8-14) | 4-15<br>(5-8) | 2-4<br>(1-2) | 3-11<br>(2-6) | 1-4.1<br>(0-3) | nr |

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. AST = aspartate aminotransferase

In clinical studies for the treatment of herpes labialis in adolescents with valacyclovir, the adverse effects most commonly reported were headache (17%) and nausea (8%). In pediatric patients (ages 1

month to 12 years of age), adverse effects reported in pharmacokinetic and safety studies of valacyclovir included diarrhea (5%), pyrexia (4%), dehydration (2%), herpes simplex (2%), and rhinorrhea (2%). In clinical trials for buccal acyclovir (Sitavig), administration site irritation and pain were both reported in about 1% of the population.

## SPECIAL POPULATIONS[56,57,58,59,60,61]

### Pediatrics

#### *Herpes Infections*

Intravenous acyclovir (Zovirax) has been shown to be safe in pediatric patients, but safety and effectiveness of oral formulations of acyclovir in children < 2 years of age have not been established. Safety and effectiveness of buccal acyclovir (Sitavig) have not been established in pediatric patients. The ability of pediatric patients to follow the application instructions has not been evaluated. Due to the potential for choking, use of buccal acyclovir in younger children is not recommended.

Safety and efficacy in children < 18 years of age have not been established for famciclovir.

Valacyclovir (Valtrex) is approved for the treatment of herpes labialis episodes in children ≥ 12 years of age.

#### *Varicella Infections*

Acyclovir is approved for the treatment of varicella in children ≥ 2 years of age. The use of acyclovir for the treatment of varicella in children has decreased since the arrival of the varicella vaccine for the prevention of varicella infections in children.

Valacyclovir is approved for the treatment of chickenpox in children ages 2 to 18 years. Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) can be prepared from the 500 mg caplets; acyclovir is available as an oral suspension.

### Geriatric

Elderly patients are more likely to have reduced renal function and require dose reduction. Elderly patients are also more likely to have increased renal or CNS adverse events with valacyclovir and acyclovir. In clinical studies assessing the efficacy of famciclovir in treating herpes zoster, there were no differences in overall adverse effects between younger and older patients. Thus, there are no suggested dosage adjustments in geriatric patients treated with famciclovir. Yet, caution should be taken when administering all HSV agents to elderly patients due to decreased renal function associated with age.

### Pregnancy

Acyclovir capsule and tablet are Pregnancy Category B. Previously Pregancy Category B, labeling for acyclovir oral suspension (Zovirax), buccal acyclovir (Sitavig), and valacyclovir was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) to descriptive text and advise that there have been no identified risks of major birth defects with acyclovir or valacyclovir in published studies or with acyclovir on miscarriage or adverse maternal or fetal outcomes, but data regarding miscarriage or adverse maternal or fetal outcomes with valacyclovir are insufficient. Likewise, famciclovir was also assigned Pregnancy Category B; however, its labeling also was updated in

compliance with the PLLR and now contains descriptive text. Available data with famciclovir in pregnant women have not identified a drug-associated risk adverse fetal or maternal outcomes, major birth defects, or miscarriage.

Prevention of neonatal exposure to herpes requires the avoidance of contracting genital HSV during the third trimester and avoidance of exposure of the infant to active herpetic lesions during delivery.[62] Safety data for agents in this category are not robust; the majority of data are with acyclovir.

### Patients with Human Immunodeficiency Virus (HIV)

Patients with HIV may have severe and prolonged episodes of HSV lesions.[63] In general, HSV shedding is more common in patients with HIV. The CDC recommends any 1 of the 3 agents for daily suppressive therapy in patients infected with HIV. Resistance of HSV to all of these drugs is higher in immunocompromised patients (6% to 7%) than in immunocompetent patients (< 0.5%).[64,65,66]

### Renal Impairment

All systemic products in this category require dose and/or interval adjustments for renal impairment.

## DOSAGES[67,68,69,70,71,72]

### FDA-Approved Dosages

| Drug/ Dosage Forms | Initial genital herpes | Recurrent genital herpes | Chronic suppressive genital herpes | Herpes zoster | Herpes labialis (cold sores) | Varicella |
|---|---|---|---|---|---|---|
| acyclovir (Zovirax*)<br>200 mg capsule (generic only);<br>400 mg, 800 mg tablets (generic only);<br>200 mg/5 mL suspension | 200 mg 5 times per day for 10 days | 200 mg 5 times per day for 5 days | 400 mg twice daily for up to 12 months | 800 mg 5 times per day for 7 to 10 days | -- | 2 years and older: Less than 40 kg: 20 mg/kg per dose orally 4 times daily for 5 days<br>40 kg and up: 800 mg 4 times a day for 5 days |
| acyclovir (Sitavig)<br>50 mg buccal tablet | -- | -- | -- | -- | 50 mg buccal tablet applied to upper gum, and allowed to adhere and dissolve throughout day (within 1 hour of symptom onset and before the appearance of any signs of herpes labialis lesions) | -- |

*FDA-Approved Dosages (continued)*

| Drug/ Dosage Forms | Initial genital herpes | Recurrent genital herpes | Chronic suppressive genital herpes | Herpes zoster | Herpes labialis (cold sores) | Varicella |
|---|---|---|---|---|---|---|
| famciclovir 125 mg, 250 mg, 500 mg tablets | -- | 1 gm twice daily for 1 day<br>For HIV+ patients, 500 mg twice daily for 7 days for genital herpes | 250 mg twice daily for up to 12 months | 500 mg 3 times daily for 7 days | 1,500 mg as a single dose<br>For HIV+ patients, 500 mg twice daily for 7 days for orolabial herpes | -- |
| valacyclovir (Valtrex) 500 mg, 1,000 mg tablets | 1 gm twice daily for 10 days | 500 mg twice daily for 3 days | 500 mg to 1 gm daily<br>For HIV+ patients, 500 mg twice daily<br>For reduction of heterosexual transmission: 500 mg daily | 1 gm 3 times daily for 7 days | ≥ 12 years: 2 gm every 12 hours for 1 day | Ages 2 to <18 years: 20 mg/kg 3 times daily for 5 days; not to exceed 1 gm 3 times daily |

## 2021 CDC Recommended Dosages for Genital HSV Infections[73]

| Drug | Initial genital herpes | Recurrent genital herpes | Chronic suppressive genital herpes |
|---|---|---|---|
| acyclovir (Zovirax) | 400 mg 3 times daily for 7 to 10 days | 800 mg twice daily for 5 days<br>OR<br>800 mg 3 times daily for 2 days | 400 mg twice daily |
| | | For HIV+ patients, 400 mg 3 times daily for 5 to 10 days | For HIV+ patients, 400 mg to 800 mg twice to 3 times daily |
| famciclovir | 250 mg 3 times daily for 7 to 10 days | 125 mg twice daily for 5 days<br>OR<br>1 gm twice daily for 1 day<br>OR<br>500 mg for 1 dose, then 250 mg twice daily for 2 days | 250 mg twice daily |
| | | For HIV+ patients, 500 mg twice daily for 5 to 10 days | For HIV+ patients, 500 mg twice daily |
| valacyclovir (Valtrex) | 1 gm twice daily for 7 to 10 days | 500 mg twice daily for 3 days<br>OR<br>1 gm once daily for 5 days | 500 mg* to 1 gm daily |
| | | For HIV+ patients, 1 gm twice daily for 5 to 10 days | For HIV+ patients, 500 mg twice daily |

* Valacyclovir 500 mg daily for suppressive therapy may be less effective than other regimens in patients with high frequency recurrences (>10 episodes per year).

# CLINICAL TRIALS

## Search Strategy

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, comparative, controlled trials performed in the United States comparing oral agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. 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% 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 and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

## Herpes Zoster – Uncomplicated

### *acyclovir (Zovirax)*

Acyclovir has been shown to be effective in the treatment of chickenpox in at least 2 double-blind placebo-controlled studies in normal children ages 2 to 16 years that were conducted in the early 1990s prior to the availability of the varicella vaccine for children.[74,75] Treatment in both studies began within 24 hours of rash onset and was given as acyclovir 20 mg/kg 4 times daily for 5 to 7 days. Children ages 12 to 16 years received 10 mg/kg 4 times daily orally for 5 to 7 days. Beneficial effects of acyclovir included earlier defervescence, fewer varicella lesions, and absence of new lesions after 3 days of acyclovir, and accelerated crusting and healed stages. No differences in disease complications were noted in either study. Acyclovir was well tolerated in the children with no serious adverse effects reported.

### *acyclovir (Zovirax) versus famciclovir*

In a double-blind, parallel-group study, 55 immunocompetent adults with acute uncomplicated herpes zoster were randomized to treatment with famciclovir 250 mg 3 times daily or acyclovir 800 mg 5 times daily.[76] Treatment was initiated within 72 hours of onset of the zoster rash and was continued for 7 days. Famciclovir was as effective as acyclovir for healing the cutaneous lesion, as indicated by the time to full crusting (11 days with famciclovir, 10 days with acyclovir; p=0.761) and loss of acute phase pain (famciclovir 20 days, acyclovir 27 days; p=0.683). Both groups experienced loss of vesicles on day 6. Loss of ulcers occurred in 1 day in both groups. Loss of crusts were similar between the 2 groups (acyclovir 27 days; famciclovir 20 days; p=0.558). Famciclovir was well tolerated and had a more favorable adverse event profile compared to acyclovir. Constipation, hematuria, and glycosuria were the most commonly reported adverse events. The dose of famciclovir used in this study is 50% lower than the approved dosage for this indication.

Another double-blind study compared the clinical efficacy of acyclovir 800 mg 5 times daily and famciclovir 750 mg once daily, 500 mg twice daily, or 250 mg 3 times daily in the treatment of acute uncomplicated herpes zoster in immunocompetent adults.[77] Patients (n=559) presented within 72 hours after rash onset and were randomized to famciclovir 750 mg daily, 500 mg twice daily, or 250 mg 3 times daily or acyclovir 800 mg 5 times daily. All patients were given treatment for 7 days. Complete healing was assessed at 4 weeks or whenever completed healing occurred. Healing was defined as time to full crusting of lesions, loss of vesicles, cessation of new lesion formation, and a 50% reduction in affected skin. Healing and loss of acute pain were similar among the 4 groups. The development of postherpetic neuralgia was not assessed in this study. Headache was the most commonly reported adverse effect. Five discontinuations were reported with both famciclovir and acyclovir. The doses of famciclovir used in this study are one-third to one-half lower than the dose recommended for this indication.

***acyclovir (Zovirax) versus valacyclovir (Valtrex)***

A randomized, double-blind, multicenter trial evaluated the safety and efficacy of acyclovir and valacyclovir in the treatment of herpes zoster in 1,141 immunocompetent adults.[78] Patients presented within 72 hours of onset of rash. Patients were randomized into 1 of 3 groups: valacyclovir 1 gm 3 times daily for 7 or 14 days or acyclovir 800 mg 5 times daily for 7 days. The primary outcome parameters were the succession of pain, time to cessation of new lesion formation and/or increase in lesion area, and time to greater than 50% crusting or healed rash. Valacyclovir treatment for 7 or 14 days significantly accelerated the resolution of pain (p=0.001 and p=0.03, respectively) compared with acyclovir treatment. Median cessation of pain was 38 and 44 days, respectively, with valacyclovir 7- or 14-day treatments compared to 51 days with acyclovir. No significant differences in time to cessation of new lesions and or increase in lesion area were reported among the groups: valacyclovir 7-day versus acyclovir (hazard ratio [HR], 1.03 [95% CI, 0.89 to 1.2]); valacyclovir 14-day versus acyclovir (HR, 0.99 [95% CI, 0.85 to 1.14]); valacyclovir 7- versus 14-day (HR, 1.05 [95% CI, 0.91 to 1.21]). No significant differences in the time to greater than 50% crusting or healing lesions were reported among the groups: valacyclovir 7-day versus acyclovir (HR, 1 [95% CI, 0.87 to 1.16]); valacyclovir 14-day versus acyclovir (HR, 1.02 [95% CI, 0.88 to 1.18]); valacyclovir 7- versus 14-day (HR, 0.98 [95% CI, 0.85 to 1.14]). Valacyclovir 14-day group had a shorter duration of abnormal sensations compared to acyclovir (HR, 1.27 [95% CI, 1.07 to 1.52]). All other groups were similar. No significant differences in pain intensity, quality of life, or unpleasantness were reported among the groups. Valacyclovir 7- and 14-day groups had a similar percentage of patients reporting pain after 6 months (19.9% and 18.6%, respectively) that was significantly lower than the percentage reporting the same in the acyclovir group (25.7%; valacyclovir versus acyclovir, p=0.02). No differences in adverse drug events were observed among the groups.

***famciclovir versus valacyclovir (Valtrex)***

A study compared the clinical efficacy of valacyclovir 1 gm 3 times per day to famciclovir 500 mg 3 times a day for 7 days in the treatment of acute uncomplicated herpes zoster. [79] A total of 597 outpatients, aged 50 years and older, who had herpes zoster were enrolled in a double-blind, randomized trial. The primary outcome was complete cessation of zoster-related pain. The occurrence of postherpetic neuralgia was also assessed. Secondary endpoints included time to cessation of zoster-associated abnormal sensations, pain intensity, rash healing, and lesion dissemination. No difference in resolution of zoster related pain were seen in this comparison of valacyclovir (42 days) and famciclovir

(49 days; HR, 1.02 [95% CI, 0.84 to 1.23]). Postherpetic neuralgia was similar in both groups (HR, 1.01 [95% CI, 0.84 to 1.23]). No differences were reported with any of the secondary endpoints including time to cessation of zoster-associated abnormal sensations, pain intensity, rash healing (p=0.26), and lesion dissemination. Headache and nausea were the most common events reported for each agent.

## Herpes zoster – Immunocompromised Patients

***acyclovir (Zovirax) versus famciclovir***

In a randomized, double-blind, multicenter study, 148 patients (ages 12 years and older) with clinical evidence of localized herpes zoster received either oral famciclovir 500 mg 3 times daily or acyclovir 800 mg 5 times daily for 10 days.[80] The efficacy and safety of famciclovir were evaluated for the treatment of herpes zoster in patients who were immunocompromised following bone marrow transplant (BMT) or solid organ transplantation or oncology treatment. An equivalent percentage of patients in the famciclovir and acyclovir groups, 77% and 73%, respectively, reported new lesion formation while on therapy. The median time to cessation of new lesions was 3 days with acyclovir and 4 days with famciclovir. The median time to full crusting was 8 days for famciclovir and 9 days for acyclovir (HR, 1.26 [95% CI, 0.88 to 1.82]). The median time to complete healing was 20 days with famciclovir and 21 days with acyclovir (HR, 0.98 [95% CI, 0.67 to 1.42]). The median time to loss of acute pain was 14 and 17 days for famciclovir and acyclovir, respectively (HR, 0.71 [95% CI, 0.71 to 1.75]). In summary, there were no significant differences between the groups in the median time to cessation of new lesion formation, full crusting, complete healing of lesions, or loss of acute phase pain. Treatment with famciclovir was well tolerated with a safety profile comparable to that of acyclovir.

## Herpes Zoster – Ophthalmic

***acyclovir (Zovirax) versus famciclovir***

Famciclovir and acyclovir were compared in a randomized, double-blind trial with 454 patients with ophthalmic herpes zoster involving the trigeminal nerve.[81] Therapy was famciclovir 500 mg 3 times daily or acyclovir 800 mg 5 times daily for 7 days. Ocular manifestations of ophthalmic zoster were similar in the 2 groups (famciclovir, 58% versus acyclovir, 58.2%). There was no difference in visual acuity loss either. Both therapies were well tolerated.

***acyclovir (Zovirax) versus valacyclovir (Valtrex)***

A multicenter, double-blind study enrolled 110 immunocompetent patients with ophthalmic herpes zoster diagnosed within 72 hours of skin eruption.[82] Patients were randomized to treatment with valacyclovir 1 gm 3 times daily or acyclovir 800 mg 5 times daily, each with matching placebo control. Ocular complications of ophthalmic herpes zoster were similar in the valacyclovir and acyclovir treatment groups with the main complications being conjunctivitis (54% and 52%), superficial keratitis, stromal keratitis (both 13%), and uveitis (13% and 17%). Pain duration and severity and outcome of skin lesions were similar between groups. Pain was reported after 1 month in 25% of the valacyclovir group and 31% in the acyclovir group. Three percent of each group reported pain at week 24. Both valacyclovir and acyclovir produced similar outcomes for skin lesions. Total healing (100%) was reported in 83% and 87% of the valacyclovir and acyclovir groups, respectively, at day 14. The most

frequent adverse events were vomiting and edema of the eyelids or face, which occurred in 3% to 5% of patients.

## Genital Herpes Simplex – Initial Episode

### *acyclovir (Zovirax) versus valacyclovir (Valtrex)*

A multicenter, randomized, double-blind clinical trial compared 10-day regimens of valacyclovir 1 gm twice daily and acyclovir 200 mg 5 times daily in the treatment of 643 healthy adults with first-episode genital herpes.[83] Patients were enrolled if symptoms had presented in less than 72 hours prior to enrollment. Patients received the randomized therapy plus a matching placebo. Patients (n=24) who had antibodies to HSV-1 and HSV-2 were excluded from the analysis since this represented a recurrent infection. Time to healing of all lesions and the duration of viral shedding were the primary outcome parameters. Valacyclovir and acyclovir did not differ significantly in efficacy with respect to duration of viral shedding (three days in both groups), portion of patients forming new lesions, duration of pain, maximum number of lesions, and time to loss of all symptoms. Adverse experiences were generally infrequent and mild and were comparable in the two treatment groups.

## Genital Herpes Simplex – Recurrent

### *acyclovir (Zovirax) versus famciclovir*

Two hundred and four patients with recurrent genital herpes were randomized in a double-blind, double-placebo, parallel-design study to famciclovir 125 mg twice daily or acyclovir 200 mg 5 times daily.[84] The mean time to complete healing of lesions was 5.1 days for famciclovir and 5.4 days for acyclovir (p=not significant [NS]). There were no differences detected in the proportion of patients having complete healing at the different days of evaluation, as well as in the duration until the complete resolution of all the symptoms. The frequency, nature, and severity of adverse events did not differ between the two treatment groups.

### *acyclovir (Zovirax) versus valacyclovir (Valtrex)*

In a double-blind study, 739 patients with a history of recurrent genital HSV infection were randomized to receive either oral valacyclovir 500 mg twice daily or acyclovir 200 mg 5 times daily for 5 days for treatment of their next recurrent episode.[85] Patients self-initiated therapy at the first signs and/or symptoms of the HSV recurrence, then were assessed in clinic on 5 occasions over 7 days, then twice weekly thereafter until lesions had healed. The time to healing of all lesions and the duration of all signs and symptoms were the primary endpoints. Duration of episode which was the time from treatment initiation to complete resolution of all signs and symptoms was similar between valacyclovir (4.7 days) and acyclovir (4.6 days [HR, 0.93; 95% CI, 0.79 to 1.08; p=0.34]). Lesion healing time was similar between valacyclovir (4.4 days) and acyclovir (4.5 days [HR, 0.96; 95% CI, 0.8 to 1.14]). The percentages of patients in whom all HSV cultures were negative were similar in the valacyclovir and acyclovir groups at 59% and 54%, respectively. There was no difference in the ability of each drug to prevent the development of vesicular/ulcerative lesions (HR, 1.08; 95% CI, 0.82 to 1.42). Duration and severity of pain were similar between the 2 groups (HR, 0.93; 95% CI, 0.78 to 1.06). The safety profiles of valacyclovir and acyclovir were comparable with adverse experiences being infrequent and generally mild. In patient-initiated therapy, acyclovir 200 mg 5 times daily and valacyclovir 500 mg twice daily

provide similar time to healing all lesions and reduce the development of new lesions in recurrent genital HSV infections.

In a multicenter, double-blind study, 1,200 people with recurrent genital HSV infections were randomized to self-initiated oral therapy with valacyclovir 1 gm twice daily, acyclovir 200 mg 5 times daily, or placebo for 5 days.[86] The primary endpoints included the length of the episode and time to lesion healing. Secondary endpoints included duration and severity pain and discomfort, viral shedding, and proportion of aborted episodes. Valacyclovir (median duration until herpetic resolution 4.8 days; HR, 1.66 [95% CI, 1.33 to 2.01]) and acyclovir (4.8 days; HR, 1.71 [95% CI, 1.41 to 2.06]) significantly reduced the length of time of episode compared to placebo (5.9 days). Median healing times were significantly earlier with valacyclovir (4.8 days; HR, 1.88 [95% CI, 1.53 to 2.32]) and acyclovir (4.8 days; HR, 1.9 [95% CI, 1.55 to 2.34]) compared to placebo (6 days). Pain duration was shorter in both active treatment groups (both $p<0.05$), and viral shedding stopped earlier in patients on active treatment (both $p<0.001$). Both active treatments reduced the severity of pain and discomfort compared to placebo on day three (valacyclovir, $p<0.001$; acyclovir, $p=0.001$). Aborted episodes occurred more frequently with valacyclovir (25.9%) and acyclovir (24.8%) than placebo (19.8%), although this did not achieve statistical significance. The safety profiles of valacyclovir and acyclovir were comparable. Valacyclovir and acyclovir reduce the length of a genital HSV episode and reduced the time to healing compared to placebo. The dose of valacyclovir studied in this trial is twice the dosage recommended by the CDC for this patient population.[87]

Over a 52-week period, a study examined the dose-response relationship of once-daily valacyclovir for the suppression of genital HSV infections in 1,479 immunocompetent patients with frequently recurring infections.[88] Twice-daily acyclovir and valacyclovir were also evaluated. In the randomized, double-blind study, patients were randomized to valacyclovir 250, 500, or 1,000 mg once daily or 250 mg twice daily, acyclovir 400 mg twice daily, or placebo for 1 year. All patients had a history of at least 6 recurrences of genital herpes per year. Suppressive therapy was discontinued for at least three months prior to enrollment. Episodic therapy with valacyclovir was given for 5 days for recurrences. The primary endpoint was the time to first recurrence of genital HSV infection which was defined as number of days since randomization until first onset of lesions. No significant difference between active treatments for suppression HSV recurrences was demonstrated (all tested comparisons, p=NS); all were significantly more effective than placebo at suppressing HSV recurrences (all comparisons versus placebo; $p<0.01$). All valacyclovir treatment groups had longer time to first recurrence compared to placebo. Acyclovir was not tested versus placebo but numerically looked to favor acyclovir. The percentage of patients without recurrences were reported as follows: 48% of valacyclovir 1 gm daily group, 40% of valacyclovir 500 mg daily group, 50% of valacyclovir 250 mg twice daily group, 22% of valacyclovir 250 mg daily group, 49% acyclovir group, and 5% of the placebo group. Patients with more than 10 recurrences had a lower rate of response to suppression overall. These patients are best treated with valacyclovir 1 gm daily, valacyclovir 250 mg twice daily, or acyclovir 400 mg twice daily. Patients with less than 10 recurrences per year had a similar response rate with valacyclovir 500 mg or 1 gm once daily or 250 mg twice daily or acyclovir 400 mg twice daily. Adverse events were generally mild, infrequent, and similar in nature to placebo. The most common adverse event reported in all groups was headache.

In a double-blind, three-period crossover trial, the efficacy in suppression of shedding of genital HSV in 69 immunocompetent patients was compared.[89] Patients received valacyclovir 500 mg twice daily,

acyclovir 400 mg twice daily, or placebo for 7-week time periods in random order. Daily genital mucosal swabs were collected from the patients. HSV was detected at least once in 90% of patients by culture and 98% by DNA polymerase chain reaction (PCR). Genital HSV shedding detected by culture was detected in 86% while on placebo, 12% while on valacyclovir and 24% while on acyclovir (both p<0.01). By PCR detection, HSV shedding was detected in 93%, 65%, and 76% while on placebo, valacyclovir, and acyclovir, respectively (valacyclovir versus placebo, p<0.001; acyclovir versus placebo, p=0.01). Antiviral therapy significantly reduced the HSV shedding compared to placebo by both culture and PCR detection methods with no significant differences in frequency or quantity of HSV shedding between the 2 antivirals. The geometric mean number of HSV DNA detected PCR copies/mL decreased from $10^{5.2}$ for placebo to $10^{3.9}$ and $10^{3.6}$ with valacyclovir and acyclovir, respectively (both p<0.001 versus placebo). The levels of valacyclovir and acyclovir suppression of HSV DNA were similar. Valacyclovir was associated with a significant decrease in the frequency of total HSV shedding by both viral culture (relative risk [RR], 0.03 [95% CI, 0.01 to 0.07]; p<0.001) and PCR (RR, 0.18 [95% CI, 0.12 to 0.26]; p<0.001) compared to placebo. A similar decrease in the frequency of total HSV shedding was observed with acyclovir compared with placebo (RR, 0.05 [95% CI, 0.03 to 0.1] for culture and RR, 0.2 [95% CI, 0.15 to 0.28] for PCR; p<0.001 for both). Days with genital lesions were reported in 2.8% for valacyclovir (p<0.001), 3.1% with acyclovir (p<0.001), and 22.1% with placebo.

***famciclovir versus valacyclovir (Valtrex)***

In a multicenter, multinational, double-blind, parallel-group study, 1,179 adults with a history of recurrent genital herpes were randomized to receive either single-day famciclovir 1 gm (administered twice daily) versus 3-day valacyclovir 500 mg (administered twice daily).[90] Patients initiated treatment within 6 hours after a recurrence. Single-day famciclovir therapy was non-inferior to 3-day valacyclovir therapy in reducing time to healing of all genital herpes lesions (median time to healing, 4.25 days versus 4.08 days, respectively). There was no significant difference in time to resolution of symptoms associated with recurrence. The overall incidence of adverse events was similar (23.2% for the famciclovir group versus 22.3% for the valacyclovir group). Additionally, the median time to next recurrence from treatment initiation was 33.5 days for famciclovir and 38 days for valacyclovir.[91] No drug resistance to penciclovir, the active metabolite of famciclovir, was observed at baseline nor did any develop by the time of the next recurrence. The study had no placebo arm, typing of viral isolates was not performed, and viral resistance testing was restricted to penciclovir only.

Two randomized, double-blind, placebo-controlled studies comparing daily famciclovir 250 mg bid with valacyclovir 500 mg daily were performed. Study 1 randomized 320 participants and compared the clinical effect of the drugs given for 16 weeks, and study 2 enrolled 70 HSV-2 seropositive subjects and compared the virologic effect of the drugs given for 10 weeks.[92] In study 1, the time to first recurrence was similar in famciclovir and valacyclovir recipients (HR, 1.17; 95% CI, 0.78 to 1.76), but time to first virologically confirmed recurrence was shorter among famciclovir recipients (HR, 2.15; 95% CI, 1 to 4.6). In study 2, HSV was detected on 3.2% of days among famciclovir recipients and 1.3% of days among valacyclovir recipients (RR, 2.33; 95% CI, 1.18 to 4.89). Valacyclovir appear to be somewhat better than famciclovir for suppression of genital herpes and associated shedding.

## Genital Herpes Simplex – Reduced Transmission

***valacyclovir (Valtrex) versus placebo***

A randomized, double-blind study evaluated the effectiveness of valacyclovir in reducing the risk of transmission of genital herpes in heterosexual, monogamous discordant couples (n=1,484 couples).[93] The patients with HSV-2 were randomized to valacyclovir 500 mg once daily or placebo for 8 months. Of the participating couples, 78.1% completed the study. Over 70% of the source partners reported taking at least 95% of the prescribed doses. Immunocompetent, heterosexual, monogamous couples with 1 clinically infected with HSV-2 and the other susceptible to HSV-2 were eligible for participation. The patient with recurrent genital herpes must have had fewer than 10 episodes per year, over 18 years of age, and use of daily antiviral therapy outside the study protocol was not permitted. The inclusion criteria for the susceptible partner were an age of 18 years or older and HSV-2 seronegativity. Both partners were required to be immunocompetent and in good health, and the couple was required to use effective contraception. Acquisition of HSV-2 infection was defined as the isolation of HSV-2 in culture, the detection of HSV-2 DNA, or HSV-2 seroconversion in the susceptible partner during the course of the trial. Clinically symptomatic genital herpes infection in the susceptible partner was a primary outcome of the study. A total of 41 new HSV-2 and four HSV-1 infections were acquired during the course of the study in the susceptible partners. Of these 45 new infections, 14 were from sexual partners receiving valacyclovir and 31 were from partners receiving placebo. Of the 20 symptomatic acquisitions of HSV-2, 16 occurred among the 741 partners of placebo recipients (2.2%), as compared with four among the 743 partners of valacyclovir recipients (0.5%) (RR, 0.25; 95% CI, 0.08 to 0.74; p=0.01). HSV-2 had been acquired by 27 of the susceptible partners of placebo recipients (3.6%) as compared with 14 of the susceptible partners of valacyclovir recipients (1.9%) (HR, 0.52; 95% CI, 0.27 to 0.99; p=0.04). HSV-2 shedding occurred on 3.3% and 0.9% of the days among the valacyclovir-treated women and men, respectively, as compared with 11.4% and 9.2% of the days among placebo-treated women and men. Adverse effects were similar between the valacyclovir- and placebo-treated patients. Valacyclovir 500 mg daily reduces the transmission of genital herpes in immunocompetent, heterosexual, monogamous couples with one clinically infected with HSV-2 and the other susceptible to HSV-2.

## Herpes Labialis

There are no direct comparative trials with the oral antivirals for the treatment or prevention of herpes labialis. All agents in this category have been shown to prevent and treat oral HSV lesions in placebo-controlled studies.

A number of double-blind trials with acyclovir for oral herpes have been completed.[94,95] The early trials with acyclovir from the 1980s were generally small populations and open-label.[96,97] Buccal acyclovir (Sitavig), in a double-blinded placebo controlled trial, was shown to reduce the median duration of oral herpetic episodes by one-half day as compared to placebo.[98] Famciclovir has also been shown to be effective and safe in the prevention and treatment of oral HSV infections and in the HIV-positive population.[99, 100, 101, 102] Valacyclovir has been studied in a variety of dosage regimens for the treatment of recurring oral HSV infections including a simple 2 dose regimen.[103,104]

## META-ANALYSES

Acyclovir has been shown to reduce fever earlier in acute varicella infection in otherwise healthy children and adolescents according to a systematic review that included data through June 2005.[105] Studies were randomized controlled studies in children through age 18 years. Three studies were included. Acyclovir reduced the number of days with fever (-1.1 days; 95% CI, -1.3 to -0.9) and reduced the maximum number of lesions (-76 lesions; 95% CI, -145 to -8). Complications with chickenpox and adverse effects were clinically important differences between acyclovir and placebo.

A meta-analysis compared the clinical efficacies of the different oral antiviral drugs prescribed prophylactically to suppress recurrent genital herpes.[106] A total of 14 randomized clinical trials were selected, including a total of 6,158 patients. The global relative risk of developing at least 1 recurrence during the study was reduced by 47% (95% CI, 45 to 49) in antiviral drug groups compared with the placebo. The best evaluated regimens, with comparable efficacies, were acyclovir 400 mg twice daily, valacyclovir 250 mg twice daily, famciclovir 250 mg twice daily, and valacyclovir 500 mg once daily. The analysis confirmed high clinical efficacy of all agents for the prevention of recurrent genital herpes.

## SUMMARY

The oral agents which are approved for herpes infections include acyclovir (Zovirax, Sitavig), famciclovir, and valacyclovir (Valtrex). Based on available data, all of the agents have similar efficacy and adverse effects.

The 2021 Centers for Disease Control and Prevention (CDC) sexually transmitted infections (STI) treatment guidelines for genital herpes do not recommend any 1 of these 3 agents over another for the treatment of initial or recurrent episodes of genital HSV infections. Chronic suppressive therapy for patients with frequent recurrences may include any 1 of the 3 agents; however, famciclovir may be slightly less effective for suppression of viral shedding in genital herpes.

Acyclovir (Zovirax), famciclovir, and valacyclovir agents have similar efficacy for the treatment of herpes zoster (shingles), and recent guidelines support the use of any of the 3 agents for first-line therapy.

All oral agents in this class have demonstrated safety and effectiveness in the treatment of herpes labialis. Acyclovir (Sitavig) offers a buccal tablet formulation, with minimal systemic absorption, to treat oral herpetic lesions. It has not been compared to other oral formulations.

Both acyclovir (Zovirax) and valacyclovir are approved for the treatment of varicella (chickenpox).

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# Antivirals, Influenza
# Therapeutic Class Review (TCR)

**January 2, 2023**



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## FDA-APPROVED INDICATIONS

| Drug | Manufacturer | FDA-Approved Indications |
|---|---|---|
| baloxavir marboxil (Xofluza®)[1] | Genentech | ▪ Treatment of acute, uncomplicated influenza in patients who have been symptomatic for ≤ 48 hours and who are:<br>– aged ≥ 5 years and are otherwise healthy<br>– aged ≥ 12 years and are at high risk of developing influenza-related complications<br>▪ Postexposure prophylaxis of influenza in patients ≥ 5 years of age following contact with an individual who has influenza |
| oseltamivir (Tamiflu®)[2] | generic, Roche Labs, Genentech | ▪ Treatment of acute, uncomplicated illness due to influenza A and B infection in patients ≥ 2 weeks of age who have been symptomatic for ≤ 48 hours<br>▪ Prophylaxis of influenza A and B in patients ≥ 1 year of age |
| rimantadine (Flumadine®)[3] | Amneal, Caraco | ▪ Treatment of illness caused by influenza A virus in adults (≥ 17 years of age)<br>▪ Prophylaxis of influenza A virus in patients ≥ 1 year of age |
| zanamivir (Relenza®)[4] | GlaxoSmithKline | ▪ Treatment of acute uncomplicated influenza A and B infections in patients ≥ 7 years of age who have been symptomatic for ≤ 2 days<br>▪ Prophylaxis of influenza in patients ≥ 5 years of age<br>– Not recommended for treatment or prophylaxis for influenza for patients with underlying airways diseases due to risk of bronchospasm<br>– Not proven effective for treatment in patients with underlying airways diseases<br>– Not proven effective for prophylaxis of influenza in nursing home residents |

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 1 to 2 days.

Influenza viruses change over time. Emergence of drug resistance could decrease drug effectiveness. Prescribers should consider the most current available drug susceptibility information for influenza and treatment effects when deciding whether to use antiviral therapy.

Due to increased drug resistance and its additional indications for Parkinson's disease and drug-induced extrapyramidal reactions, amantadine is no longer included in this class review. Rimantadine (Flumadine) is not recommended to be used for influenza prophylaxis due to resistance and is therefore, no longer reviewed here, but will remain listed as it is still available and FDA-approved for this indication.

Peramivir (Rapivab®) is approved for the treatment of acute uncomplicated influenza in patients ≥ 6 years and older who have been symptomatic for no more than 2 days.[5] Notably, data for its use is stronger in patients with influenza A compared to influenza B due to fewer cases of influenza B enrolled in its clinical trials. In addition, efficacy is not established in patients with serious influenza requiring hospitalization. Since the focus of the review is on self-administered medications and the peramivir is administered by intravenous infusion, it is not included in this review.

Use of zanamivir for treatment of influenza has not proven to reduce the risk of transmission of influenza to others.

Antiviral treatment for influenza is not a substitute for annual vaccination for influenza.

# OVERVIEW

Influenza (flu) is a common illness affecting most people at least once in their lifetime. Influenza is most often self-limiting; however, very young, elderly, or immunocompromised patients are predisposed to secondary complications with potential fatalities.[6,7] Incubation period ranges from 1 to 4 days. Symptoms include abrupt onset of fever, myalgia, headache, malaise, and respiratory signs and symptoms, including non-productive cough, sore throat, and rhinitis. Children may also experience otitis media, nausea, and vomiting. Uncomplicated influenza illness typically resolves after 3 to 7 days for most patients; however, cough and malaise can persist for more than 2 weeks.

The influenza viruses that cause epidemic human disease are influenza A and B, which are separated into subtypes (for A viruses) and lineages (for B viruses).[8] Influenza A viruses are categorized as hemagglutinin (HA) or neuraminidase (NA) based on 2 different surface antigens, while influenza B viruses are separated into 2 distinct genetic lineages; Yamagata and Victoria.

While timing of the onset, peak, and end of influenza activity varies from season to season, in the United States (US), influenza season occurs in the fall and winter with activity peaking between December and February.[9] Activity can last as late as May.

## Vaccination

Influenza vaccination is the primary method for preventing influenza and the severe complications associated with influenza.[10] Since 2010, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) has recommended an annual influenza vaccination for all people ≥ 6 months of age, who do not have contraindications, at the beginning of flu season.[11]

For the 2022-2023 season, inactivated influenza vaccines, recombinant influenza vaccine, and live attenuated influenza vaccine (LAIV) are available.[12] All available vaccines for the 2022-2023 season are quadrivalent formulations. Each year, seasonal influenza vaccines are designed to protect against the 4 predominant groups of flu Type A and B viruses.[13] Vaccine virus components are chosen based on which flu viruses caused illness during the prior flu season, the extent to which those viruses are circulating prior to the upcoming season, the potential efficacy of the previous season's vaccines against those viruses, and the ability of vaccine viruses to provide cross-protection across subtype/lineage. Current vaccines available in the US target an influenza A(H1) virus, an influenza A(H3) virus, an influenza B/Yamagata lineage virus, and an influenza B/Victoria lineage virus.

## Treatment

There are 4 FDA-approved antiviral drugs recommended by CDC for the treatment of outpatients during the 2022-2023 season: oseltamivir (Tamiflu), zanamivir (Relenza), baloxavir (Xofluza), and peramivir (Rapivab).[14] Adamantanes (amantadine and rimantadine) are not recommended for use in the US due to resistance to these drugs by many influenza A influenza B viruses.

Studies indicate that early antiviral treatment can reduce the risk of complications from influenza, such as pneumonia, respiratory failure, and death.[15] Empiric antiviral treatment, without waiting for laboratory confirmation, is recommended as early as possible for any patient with confirmed or suspected influenza who has severe, complicated, or progressive illness; is hospitalized; or is at high risk for influenza complications. In addition, empiric antiviral treatment of non-high-risk outpatients with

suspected influenza can be started based on clinical judgement without an office visit. According to the CDC, oseltamivir (oral or enterically-administered) is the recommended antiviral for outpatients with complications or progressive illness, or those who are hospitalized. There are not sufficient data for zanamivir (Relenza), peramivir (Rapivab), or baloxavir marboxil (Xofluza) in non-hospitalized patients with severe influenza. Co-infection with influenza A or B viruses and SARS-CoV-2 can occur and should be considered, particularly in hospitalized patients with severe respiratory disease.

Patient groups at high risk for influenza complications include children < 5 years of age, particularly those < 2 years of age; adults ≥ 65 years; women who are pregnant or postpartum (within 2 weeks after delivery); residents of nursing homes and other long-term care facilities; and patients from certain racial and ethnic groups (non-Hispanic Black, Hispanic or Latino, American Indian, and Alaskan Natives).[16] Additional people at high risk include those with asthma; neurological and neurodevelopmental conditions (e.g., cerebral palsy, epilepsy, stroke, intellectual disability, spinal cord injury); chronic lung disease (e.g., chronic obstructive pulmonary disease [COPD], cystic fibrosis); heart disease; blood disorders (e.g., sickle cell disease); endocrine disorders (e.g., diabetes mellitus); kidney disorders; liver disorder; metabolic disorders (e.g., inherited metabolic disorders and mitochondrial disorders); weakened immune system due to disease or medication (e.g., HIV/AIDS, cancer, chronic steroids); age < 19 years receiving long-term aspirin therapy; and those who are morbidly obese (body mass index ≥ 40). It is imperative for clinicians to consider a patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, when making antiviral treatment decisions for high-risk outpatients.

Pregnant women are at a higher risk for severe complications and death from influenza. The CDC recommends treatment with oseltamivir or zanamivir for pregnant women or women who are up to 2 weeks postpartum (including following pregnancy loss) with suspected or confirmed influenza, the preferred treatment being oseltamivir.[17] Treatment can be given during any trimester of pregnancy. The CDC does not recommend baloxavir marboxil (Xofluza) for treatment of pregnant women or breastfeeding mothers as there are no available efficacy or safety data in this population.

In the outpatient setting, antiviral treatment can also be considered for any previously healthy, symptomatic patient not at high risk for influenza complications, who is diagnosed with confirmed or suspected influenza, if treatment can be initiated within 48 hours of illness onset.[18] For acute uncomplicated influenza, baloxavir marboxil (Xofluza), oseltamivir (Tamiflu), peramivir (Rapivab), or zanamivir (Relenza) may be used for treatment. Studies show that treatment initiated early (e.g., within 48 hours of illness onset) is more likely to provide benefit. The decision to treat should be based patient clinical presentation consistent with influenza and on epidemiologic factors.[19] Treatment should not be delayed pending laboratory confirmation of influenza even to distinguish from SARS-CoV-2 infection.[20] In the setting of an antiviral medication shortage however, the CDC urges prioritization of antiviral treatment for those with laboratory-confirmed influenza who are at highest risk for severe disease and who test positive for influenza within 2 days of illness onset.[21]

In 2018, the Infectious-Diseases Society of America (IDSA) published updated guidelines regarding the management of influenza.[22] Treatment of suspected or confirmed influenza should be started as soon as possible in persons who are hospitalized with influenza; outpatients with severe or progressive illness, or at high risk of complications; children < 2 years of age; adults ≥ 65 years of age; and pregnant and

postpartum (≤ 2 weeks from delivery) women. Treatment with antivirals can also be considered in select adults and children who are not at high risk of complications including outpatients with illness onset ≤ 2 days before presentation; symptomatic outpatients with high-risk household contacts; and symptomatic healthcare providers who care for high-risk patients. IDSA recommends oseltamivir, zanamivir, or peramivir for influenza treatment; no recommendations were made regarding baloxavir marboxil, as it was approved after the finalization of the guidelines. Longer than recommended durations of therapy may be considered in patients with a documented or suspected immunocompromising condition or those hospitalized for severe lower respiratory tract disease.

The American Academy of Pediatrics (AAP) recommends antiviral treatment as early as possible and beyond 48 hours of symptom onset in children hospitalized with suspected or confirmed influenza; children with severe, complicated, or progressive influenza; and children at high risk for complications.[23] Treatment may also be considered within 48 hours of symptom onset in non-high-risk children and children with household contacts younger than 6 months old or at high risk for complications. The AAP states that any licensed influenza vaccine that is appropriate for age and health status may be given. They do not prefer one product over another, including IIV or live attenuated influenza vaccine (LAIV). In addition, if 2 doses of vaccine is required in a given season, the doses do not need to be the same brand, and a combination of IIV and LAIV may be give, if appropriate for age and health status.

## Prophylaxis

According to the CDC, neuraminidase inhibitor antiviral medications are about 70% to 90% effective in preventing influenza and are useful adjuncts to influenza vaccination, but annual influenza vaccination is the best way to prevent influenza.[24] Because of the possibility of emergence of antiviral resistance viruses, widespread or routine use of antiviral medications for chemoprophylaxis is not recommended.

Antiviral chemoprophylaxis generally should be reserved for people at higher risk for influenza-related complications who have had contact with someone likely to have been infected with influenza.[25] Adults can shed influenza virus from the day before symptoms begin through 5 to 10 days after illness onset; however, shedding decreases rapidly by 3 to 5 days after illness onset. Children can shed influenza viruses for longer periods. Antivirals are not generally recommended if more than 48 hours have elapsed since the last contact with an infectious person.[26] An emphasis on early treatment and monitoring is an alternative to chemoprophylaxis after a suspected exposure for some people. Postexposure prophylaxis may be considered for the following patient groups: people at high risk of influenza complications during the first 2 weeks following vaccination; people with severe immune deficiencies or others who might not respond to influenza vaccination, such as people receiving immunosuppressive medications; people at high risk for complications from influenza who cannot receive influenza vaccine due to a contraindication; children at high risk for influenza complications when circulating virus strains are not well matched with the seasonal vaccines; and residents and unvaccinated staff of institutions, such as long-term care facilities, during influenza outbreaks in the institution.[27,28,29]

In the community setting, the IDSA also recommends preexposure and postexposure prophylaxis, using oseltamivir or zanamivir, in select individuals at high risk for influenza complications. Baloxavir marboxil was not yet approved for prophylaxis at the time of this guideline recommendation.

## PHARMACOLOGY[30,31,32]

| Drug Mechanism of Action | Mechanism of Action |
|---|---|
| baloxavir marboxil (Xofluza) | ▪ Baloxavir marboxil is a prodrug, which after oral administration, is converted to its active metabolite, baloxavir. It interferes with viral RNA transcription and blocks virus replication through inhibition of the polymerase acidic protein. Baloxavir is active against influenza A and B viruses.<br>▪ Baloxavir may be active against select oseltamivir-resistant strains and Avian strains (H7N9, H5N1), as suggested in non-clinical studies |
| oseltamivir (Tamiflu) | ▪ 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. |
| zanamivir (Relenza) | ▪ 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. |

### Viral Resistance

The CDC monitors viral resistance and responds to changes in resistance by publishing recommendations based on the incidence of viral resistance.[33,34] Because there were no significant changes in antiviral resistance patterns during 2021-2022 flu season, the 2022-2023 guidance on the use of influenza antiviral drugs has not changed; the majority of circulating influenza viruses are susceptible to oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapivab) and baloxavir marboxil (Xofluza). Due to high levels of resistance, amantadine and rimantadine are not recommended.

During the 2020-2021 and 2021-2022 seasons, only a small number of viruses were resistant to oseltamivir.[35] Oseltamivir works by binding to the influenza virus neuraminidase (NA) proteins and inhibiting their enzymatic activity, therefore, preventing the virus from spreading from infected cells to healthy cells. If the influenza virus' NA proteins change, oseltamivir can lose its ability to carry out its intended function, resulting in resistance. A genetic change to the virus known as the H275Y mutation results in oseltamivir resistance in A(H1N1)pdm09 flu viruses. The H275Y mutation also reduces the effectiveness of peramivir in viruses with this mutation.

## PHARMACOKINETICS[36,37,38]

| Drug | Bioavailability (%) | Half-Life (hr) | Metabolism | Excretion |
|---|---|---|---|---|
| baloxavir marboxil (Xofluza) | nr | 79.1 | 1 active metabolite – baloxavir | Predominantly feces |
| oseltamivir (Tamiflu) | 75 | 1-3 (parent); 6-10 (metabolite) | 1 active metabolite – oseltamivir carboxylate | Predominantly renal |
| zanamivir (Relenza) | 4–17 | 2.5–5.1 | No metabolites | Renally excreted |

nr = not reported

## CONTRAINDICATIONS/WARNINGS[39,40,41]

Baloxavir marboxil (Xofluza), oseltamivir (Tamiflu), and zanamivir (Relenza) are contraindicated in patients who have hypersensitivity to 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. Zanamivir should also not be used in patients with a history of allergic reaction to milk proteins.

A risk of serious bacterial infections may coexist with or occur as a complication of influenza. Baloxavir marboxil and oseltamivir have not been shown to prevent these complications. There is no evidence of efficacy of baloxavir marboxil, oseltamivir, zanamivir in any illness due to pathogens other than influenza viruses.

Patients < 5 years of age are at increased risk of treatment-emergent resistance to baloxavir marboxil compared with older individuals. Baloxavir marboxil is not indicated for use in this population.

Efficacy of oseltamivir for the treatment of influenza has not been established in patients with chronic cardiac disease and/or respiratory disease. 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; however, safety has been demonstrated for up to 12 weeks in this population.

Zanamivir is not recommended for treatment or prophylaxis of influenza in individuals with underlying airway diseases, such as asthma or COPD, due to risk of serious bronchospasm. Zanamivir should be discontinued in any patient who develops bronchospasm or respiratory difficulty; immediate treatment, including hospitalization, may be necessary. 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. Zanamivir must not be made into an extemporaneous solution for administration by nebulization or mechanical ventilation. Zanamivir inhalation powder must only be administered using the device provided.

### Neuropsychiatric Reactions

Hallucinations, delirium, and abnormal behavior have been reported with influenza infection. Neuropsychiatric reactions have been noted in postmarketing 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[42,43,44,45]

Concurrent administration of agents in this class with intranasal live attenuated influenza virus vaccine (FluMist®) 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 2 weeks after the FluMist vaccine administration unless medically necessary. Inactivated influenza vaccine can be administered at any time relative to use of drugs in this category.

Co-administration of baloxavir marboxil (Xofluza) with polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) should be avoided.

## ADVERSE EFFECTS[46,47,48]

| Drug | Headache | Nausea | Dizziness | Vomiting | Diarrhea |
|---|---|---|---|---|---|
| baloxavir marboxil (Xofluza)<br>n=1,440<br>placebo n=1,136 | 1<br>(1) | 2<br>(3) | nr | nr | 3<br>(4) |
| oseltamivir (Tamiflu)<br>75 mg twice daily<br>Treatment<br>n=2,464<br>placebo n=1,977<br>Prophylaxis<br>n=1,943<br>Placebo n=1,586 | <br><br>2<br>(2)<br><br>17<br>(16 | <br><br>10<br>(6)<br><br>8<br>(4) | <br><br>nr<br><br>nr | <br><br>8<br>(3)<br><br>2<br>(1) | <br><br>nr<br><br>nr |
| zanamivir (Relenza)<br>10 mg twice daily<br>n=1,132 adults;<br>placebo n=1,520 | 2<br>(3) | 3<br>(3) | 2<br>(< 1) | 1<br>(2) | 3<br>(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.

The adverse reactions reported in adolescents for baloxavir marboxil are similar to those reported in adults. The mostly frequently reported adverse events in children 5 to 11 years of age receiving baloxavir marboxil for the treatment of influenza were vomiting (5%) and diarrhea (5%). In a clinical trial evaluating baloxavir for postexposure prophylaxis, the safety profiles among children ≥ 5 years of age, adolescents, and adults were similar.

In the treatment of influenza, vomiting was the most common adverse effect in children receiving oseltamivir (15% versus 9% in the placebo group). Vomiting is also the most common adverse event in children undergoing prophylaxis for influenza with oseltamivir. Oseltamivir may be administered with or without food; however, drug tolerability may be increased for certain patients if taken with food.

The most common adverse effect in children receiving zanamivir was ear, nose, and throat infection occurring at a rate of 5% for both zanamivir-treated and placebo-treated patients.

## SPECIAL POPULATIONS[49,50,51]

### Pediatrics

Baloxavir marboxil (Xofluza) is approved for the treatment of influenza and for postexposure prophylaxis in children ≥ 5 years of age. Oseltamivir (Tamiflu) is approved for treatment of influenza in children 2 weeks of age and older and for prevention of influenza in children 1 year of age and older. Zanamivir (Relenza) is approved for prevention of influenza in children as young as 5 years and is approved for the treatment of influenza for children ages ≥ 7 years. The limitation of zanamivir use is the dose administration technique of the inhaler.[52]

### Pregnancy

Previously Pregnancy Category C, the labels for oseltamivir and zanamivir have been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and advise that while data are lacking to inform of any drug-related risk of adverse developmental outcomes, the limited available data suggest that oseltamivir and zanamivir are not associated with an increased risk of maternal and/or fetal adverse outcomes. Baloxavir marboxil labeling states that no pregnancy data is available to inform of a drug-associated risk to the fetus.

### Geriatrics

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

### Hepatic Impairment

Moderate hepatic impairment does not effect baloxavir marboxil pharmacokinetics; the effect of severe impairment has not been evaluated.

No dose adjustment for oseltamivir is required in patients with mild to moderate hepatic impairment. The impact of severe hepatic impairment on oseltamivir pharmacokinetics has not been established.

The pharmacokinetics of zanamivir have not been studied in patients with impaired hepatic function.

### Renal Impairment

Mild or moderate renal impairment do not appear to effect baloxavir marboxil pharmacokinetics; the effect of severe impairment has not been evaluated.

Oseltamivir dose and/or interval should be reduced in patients with an estimated creatinine clearance (CrCl) of 10 to 60 mL/minute or in patients with end stage renal disease (ESRD).

No dosage adjustments of zanamivir are required in patients with renal impairment; but safety and efficacy of the drug have not been documented in the presence of severe impairment.

## DOSAGES[53,54,55]

| Drug/ Dosage Forms | Treatment of influenza | | Prophylaxis of influenza | |
|---|---|---|---|---|
| | Adults | Pediatrics | Adults | Pediatrics |
| baloxavir marboxil (Xofluza)*<br><br>Tablets: 20 mg†, 40 mg, 80 mg | In patients weighing < 80 kg, a single dose of one 40 mg tablet is recommended<br>Patients weighing ≥ 80 kg should take a single dose of one 80 mg tablet | Ages ≥ 5 years<br>In patients weighing 20 kg to < 80 kg, a single dose of 40 mg is recommended<br>Patients weighing ≥ 80 kg should take a single dose of 80 mg | In patients weighing < 80 kg, a single dose of one 40 mg tablet is recommended<br>Patients weighing ≥ 80 kg should take a single dose one 80 mg tablet | Ages ≥ 5 years<br>In patients weighing 20 kg to < 80 kg, a single dose of 40 mg is recommended<br>Patients weighing ≥ 80 kg should take a single dose of 80 mg |
| oseltamivir (Tamiflu)<br><br>Capsules: 30 mg, 45 mg, 75 mg<br>Oral suspension: 6 mg/mL | 75 mg twice daily for 5 days<br>(≥ 13 years)<br>Initiate therapy within 2 days of onset of symptoms. | 2 weeks to 1 year:<br>3mg/kg twice daily<br>> 1 to < 13 years:<br>< 15 kg: 30 mg twice daily;<br>15-23 kg: 45 mg twice daily;<br>23-40 kg: 60 mg twice daily;<br>> 40 kg: 75 mg twice daily | 75 mg daily for 10 days<br>(≥ 13 years)<br>Initiate therapy within 2 days of exposure. | > 1 to < 13 years:<br>< 15 kg: 30 mg daily for 10 days;<br>15-23 kg: 45 mg daily for 10 days;<br>23-40 kg: 60 mg daily for 10 days;<br>> 40 kg: 75 mg daily for 10 days<br>May give for up to 6 weeks for community outbreak. |
| zanamivir (Relenza)<br><br>Inhalation powder or oral inhalation for use with Diskhaler™ device‡: 5 mg Rotadisk™ blister | Two inhalations (10 mg) twice daily for 5 days<br>Initiate therapy within 2 days of onset of symptoms. | ≥ 7 years:<br>Two inhalations (10 mg) twice daily for 5 days | 2 inhalations (10 mg) once daily for 10 days (household setting) or 28 days (community outbreaks) | ≥ 5 years:<br>2 inhalations (10 mg) once daily for 10 days (household setting) or 28 days (community outbreaks) |

* Product labeling includes an oral suspension formulation which is not currently marketed.

† Product labeling no longer includes the 20 mg tablet; however, this strength may be available until supply is depleted.

‡ Patients scheduled to use an inhaled bronchodilator at the same time as zanamivir (Relenza) should use their bronchodilator before taking zanamivir.

## 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 |
| oseltamivir (Tamiflu) | Renal impairment<br>*Moderate:* CrCl > 30-60 mL/min | 30 mg twice daily for 5 days | Renal impairment<br>*Moderate:* CrCl > 30-60 mL/min | 30 mg once daily |
| | *Severe:* CrCl > 10-30 mL/min | 30 mg once daily for 5 days | *Severe:* CrCl > 10-30 mL/min | 30 mg every other day |
| | *ESRD (hemodialysis):* CrCl ≤ 10 mL/min | 30 mg after hemodialysis cycles not to exceed 5 days | *ESRD (hemodialysis):* CrCl ≤ 10 mL/min | 30 mg after alternate hemodialysis cycles |
| | *ESRD (CAPD):* CrCl ≤ 10 mL/min | 30 mg immediately after a dialysis exchange | *ESRD (CAPD):* CrCl ≤ 10 mL/min | 30 mg once weekly after dialysis exchange |
| zanamivir (Relenza) | Not recommended for patients with airway diseases such as COPD 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 US 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 15 years ago were excluded, but due to the paucity of active-controlled trials, studies that were placebo-controlled, randomized trials in humans using antiviral agents for the treatment or prevention of influenza were included. Key approval studies for products remain in the review regardless of date published. 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% 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 and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

## Influenza – Treatment

## Children

***baloxavir marboxil (Xofluza) versus placebo***

The use of baloxavir marboxil in pediatric patients 12 years of age and older weighing at least 40 kg, is supported by the randomized, double-blind CAPSTONE-1 trial in which 118 otherwise healthy adolescents 12 to 19 years of age with acute uncomplicated influenza were randomized to receive either baloxavir (n=80) or placebo (n=38).[56,57] The study included patients from both the United States and Japan from December 2016 through March 2017. A single dose of baloxavir marboxil or placebo was administered within 48 hours of influenza symptom onset. The primary endpoint of median time to alleviation of symptoms in adolescents was 54 hours for baloxavir marboxil and 93 hours for placebo. The secondary endpoint of difference in the time to alleviation of symptoms (for baloxavir marboxil and placebo) was greater in patients who initiated therapy within 24 hours of symptom onset ($p<0.001$). Baloxavir marboxil resulted with significantly greater declines in infectious viral load than placebo. Reductions in susceptibility were observed in 9.7% of baloxavir marboxil patients in those with influenza A(H3N2).

The CAPSTONE-2 trial was a randomized, double-blind, placebo- and active-controlled trial to evaluate the efficacy and safety of a single oral dose of baloxavir marboxil compared with placebo or oseltamivir, in adult and adolescent subjects 12 years of age or older with influenza who were at high risk of developing influenza related complications.[58] The trial included 38 adolescents aged 12 to 17 years who were randomized and received either baloxavir marboxil (n=21) or placebo (n=17). The median time to improvement of influenza symptoms was similar for subjects who received baloxavir marboxil (188 hours) or placebo (191 hours) (n=13 and n=12, respectively). Adverse events reported in adolescents were similar to those reported in adults.

In miniSTONE-2, a placebo- and active-controlled, double-blind trial, children aged < 12 years with a clinical diagnosis of influenza were randomized 2:1 to receive a single dose of oral baloxavir (n=117) or oseltamivir (n=59) twice daily for 5 days.[59] All participants were screened within 48 hours of symptom onset. Patients in the baloxavir group weighing < 20 kg received a 2 mg/kg dose and those weighing ≥ 20 kg received a 40 mg dose. The primary endpoint assessed adverse events during the 5-day treatment period and a 24-day follow-up period. The overall incidence of adverse events and adverse events determined to be related to study drug were similar between the baloxavir group (46.1% and 2.6%, respectively) and the oseltamivir group (53.4% and 8.6%, respectively). The median duration of fever and all symptoms, as well as time to return to normal health and activity, were also similar between groups. Influenza virus titer was significantly reduced on day 2 (24 hours posttreatment) with baloxavir treatment compared with oseltamivir treatment (-3.59 versus -1.79 $\log_{10}$ median tissue culture infectious dose/mL, respectively). The median time to cessation of viral shedding by virus titer was also shorter for baloxavir by 51.6 hours compared with oseltamivir (24.2 hours [95% confidence interval (CI), 23.5 to 24.6] versus 75.8 hours [95% CI, 68.9 to 97.8]). Children aged 1 to < 5 years treated with baloxavir were found to have a higher prevalence of treatment-emergent resistance mutations (31.3%) compared with children 5 to < 12 years (14.6%).

***oseltamivir (Tamiflu) versus placebo***

Oseltamivir was studied in a randomized, double-blind, placebo-controlled trial with 695 children ages 1 to 12 years with fever and history of cough or coryza of less than 48 hours of duration.[60] Patients were randomized to oseltamivir 2 mg/kg twice daily or placebo for 5 days. Sixty-five percent of children (n=465) were found to have influenza. Oseltamivir reduced the median duration of illness by 36 hours (26%) in the influenza-infected children compared to placebo (101 hours versus 137 hours, p<0.0001). Oseltamivir reduced cough, coryza, and duration of fever. New diagnoses of acute otitis media were also reduced in the oseltamivir group (12% versus 21%, respectively). Use of antibiotics was significantly lower in the influenza-infected oseltamivir group compared to the influenza-infected placebo group (31% versus 41%, respectively, p=0.03). The oseltamivir group experienced more emesis than placebo group.

***zanamivir (Relenza) versus placebo***

A double-blind, randomized, placebo-controlled, parallel-group, multicenter study enrolled children, 5 to 12 years of age, with influenza-like symptoms for no more than 36 hours.[61] Patients were randomized to zanamivir 10 mg twice daily or placebo for 5 days. Symptoms were recorded on diary cards twice daily during treatment, 9 days after treatment, and potentially an additional 14 days, if symptoms persisted. Of the 471 children enrolled in the study, 346 (73%) patients were influenza-positive by culture, serology, or polymerase chain reaction. Of those with confirmed infection, 65% had influenza A and 35% 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.

## Adults

***baloxavir marboxil (Xofluza) versus oseltamivir (Tamiflu)***

In the active- and placebo-controlled CAPSTONE-1 trial, baloxavir was studied in 1,436 otherwise healthy patients 12 to 64 years of age weighing at least 40 kg in the US and Japan.[62,63] At enrollment, patients had influenza symptoms for no longer than 48 hours. Adults ages 20 to 64 years received baloxavir marboxil or placebo as a single oral dose on day 1 (plus oseltamivir-matched placebo) or oseltamivir twice a day for 5 days. Subjects weighing < 80 kg received baloxavir marboxil at a dose of 40 mg and subjects weighing ≥ 80 kg received an 80 mg dose. In the intention-to-treat infected population, the median time to alleviation of symptoms (primary endpoint) was 53.7 hours and 80.2 hours, for baloxavir marboxil and placebo, respectively (p<0.001). The difference in the time to alleviation of symptoms between the baloxavir marboxil group and the placebo group was greater in patients who initiated the trial regimen within 24 hours after symptom onset (median difference, 32.8 hours; p<0.001) than in those who initiated it later (median difference, 13.2 hours; p=0.008). There was no difference in the median time to alleviation of symptoms between baloxavir marboxil and oseltamivir (approximately 54 hours for both). Baloxavir marboxil resulted in significantly greater declines in infectious viral load than placebo and oseltamivir. Reductions in susceptibility were observed in 9.7% of baloxavir marboxil patients in those with influenza A(H3N2), which was the predominant virus identified among patients. Incidence of diarrhea of any grade was 3% with baloxavir marboxil, 2.1% with oseltamivir, and 4.5% with placebo; bronchitis was reported in 2.6%, 3.5%, and 5.5% among the 3 groups, respectively.

The CAPSTONE-2 trial was a randomized, double-blind, placebo- and active-controlled trial to evaluate the efficacy and safety baloxavir marboxil compared with placebo or oseltamivir, in adult and adolescent subjects 12 years of age or older with influenza who were at high risk of developing influenza related complications.[64] A total of 2,182 patients with signs and symptoms of influenza were randomized to receive a single oral dose of 40 mg or 80 mg of baloxavir marboxil (n=729), oseltamivir 75 mg twice daily for 5 days (n=725), or placebo (n=728). High risk health factors known to increase the risk of developing serious complications from influenza were based on those defined by the CDC. Most subjects had underlying asthma, chronic lung disease, diabetes, heart disease, morbid obesity, or were at least 65 years of age. Influenza was confirmed by RT-PCR in 1,158 patients of whom were included in the efficacy analysis (baloxavir marboxil n=385, placebo n=385, or oseltamivir n=388). In the patients that tested positive for one type/subtype of influenza virus, 50% had A/H3N2, 43% had type B, and 7% had A/H1N1. While there was a statistically significant difference in the median time to improvement of influenza symptoms reported with baloxavir marboxil (73 hours) compared to placebo (102 hours; p<0.001), there was no statistically significant difference compared to oseltamivir (81 hours). For subjects infected with type B virus, the median time to improvement of influenza symptoms was 75 hours in the baloxavir marboxil group (95% CI, 67-90) compared to 101 hours in the placebo group (95% CI, 83 to 116; p<0.001).

***oseltamivir (Tamiflu) versus placebo***

A randomized, double-blind study was performed in 629 healthy nonimmunized adults in the U.S. with febrile illness of less than 36 hours duration.[65] 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 2 active treatment regimens. Secondary complications, such as bronchitis and sinusitis, occurred more frequently in the placebo group (15%) than the oseltamivir groups (7%; p=0.03). Additionally, oseltamivir-treated patients returned to usual activities 2 to 3 days earlier than placebo-treated patients (p≤0.05). Nausea and vomiting occurred more frequently in the oseltamivir groups (combined incidence of 18 and 14.1%, respectively; p=0.002) compared to placebo (7.4 and 3.4%; 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.[66] Patients were assigned to oseltamivir 75 mg, oseltamivir 150 mg, or placebo twice daily for 5 days. Infection was confirmed in 66% 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≤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, 27 otherwise healthy adult patients were randomized to zanamivir 10 mg twice daily for 5 days or matching placebo.[67] Treatment was started within the first or second day of a flu-like

illness. After 12 hours of treatment (e.g., 1 dose), median virus titers changed by -1.0 log10 TCID50/mL in the zanamivir group compared with +0.42-log10 change in the placebo group (p=0.08). This was associated with a 4.5-day (47.4%) 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 2 days of onset of typical influenza symptoms.[68] Patients were randomized to receive inhaled zanamivir 10 mg twice daily for 5 days or matching placebo. Influenza was laboratory-confirmed in 277 (78%) of the patients; 32 (9%) 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.[69] The duration of fever (≥ 37.5° C) after the first dose was less with zanamivir (31.8 hours) 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 hours) was significantly shorter than that of oseltamivir (52.7 hours; 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

***baloxavir marboxil (Xofluza) versus placebo***

A double-blind, multicenter, placebo-controlled study evaluated the efficacy of baloxavir marboxil for the prevention of influenza in subjects who were household contacts of influenza-infected patients.[70,71] The study was conducted in Japan. The influenza-infected patients were required to have onset of symptoms for ≤ 48 hours, and the household contacts were required to have co-habited with the influenza-infected patient for ≥ 48 hours and be free of influenza symptoms. A total of 715 household contacts ≥ 5 years of age were randomized 1:1 and received a single oral dose of baloxavir (according to body weight) or placebo on day 1. The primary efficacy endpoint was the proportion of patients with laboratory-confirmed influenza virus infection and the presence of both fever (axillary body temperature ≥ 37.5°C) and ≥ 1 respiratory symptom (cough or nasal discharge/congestion) during the period from day 1 to day 10. Influenza infection was confirmed by reverse transcription-polymerase chain reaction (RTPCR) assay. There was a statistically significant reduction in the proportion of household contacts with confirmed influenza in the baloxavir marboxil group compared to the placebo group (2% [95% CI, 1 to 4] versus 13% [95% CI, 10 to 17], respectively; p<0.0001). In the cohort of subjects aged 5 to < 12 years, 4% treated with baloxavir had clinical influenza versus 14% in the placebo group. Adverse events were reported by 22.2% of subjects in the baloxavir group and 20.5% of those who received placebo; the most common were headache, hematuria, pharyngitis, and increases in ALT level.

***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 7 days.[72] 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% for individuals (95% confidence interval [CI], 67-97%; p<0.001) and 84% for households (95% CI, 49-95%; p<0.001). Gastrointestinal adverse events were similar in both groups (oseltamivir, 9.3%; placebo, 7.2%).

In a double-blind, placebo-controlled, parallel-group, multicenter study, 548 frail, elderly nursing home occupants (mean age 81 years, >80% vaccinated for influenza) were randomized to prophylaxis with oseltamivir 75 mg or placebo once daily for 6 weeks, beginning when influenza was detected locally.[73] The administration of oseltamivir resulted in a 92% reduction in the incidence of laboratory-confirmed clinical influenza compared with placebo (0.4 and 4.4%, respectively; p=0.002). In vaccinated subjects, influenza was confirmed in 0.5% of oseltamivir patients and 5% 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% versus 2.6% for placebo; p=0.037). Oseltamivir was well tolerated with a similar incidence of adverse events, including gastrointestinal effects, occurring in both groups.

***zanamivir (Relenza) versus placebo***

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.[74] 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 5 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 of 1,678 versus 23 of 1,685; relative risk 0.17; [95% CI, 0.07 to 0.44, p<0.001]). Zanamivir provided a protective efficacy of 83%. Significantly fewer complications were observed in the zanamivir-treated patients (1 of 1,678 versus 8 of 1,685; relative risk 0.12 [95% CI, 0.002 to 0.73; p=0.042]). Influenza-like illness was reported in 9% in the zanamivir-treated patients and 10% in the placebo-treated patients. Adverse effects were similar between the groups with the most common reports being headache, cough, and throat and tonsil discomfort/pain. The incidences of viral respiratory infections or ear, nose, and throat infections were similar between the 2 groups. No resistance to zanamivir was identified in the study.

# META-ANALYSES

## Adults and Children

A 2020 network meta-analysis conducted to assess the comparative efficacy and safety of baloxavir, compared baloxavir with oseltamivir, zanamivir, laninamivir (not approved in the US), and peramivir in both high-risk and uncomplicated (healthy) patients.[75] Thirty-two studies were included: 7 with high-risk patients, 13 with healthy patients and 14 studies with both healthy and high-risk patients. The studies included were randomized controlled trials conducted in patients ≥ 12 years of age. Analysis of 10 trials

including high risk patients demonstrated comparable time to alleviation of symptoms for all treatments. Mean decline in virus titer from baseline at 24 hours after treatment was significantly greater for baloxavir compared with oseltamivir and peramivir. The analysts concluded that baloxavir was significantly more effective than placebo regarding all outcomes except for risk of pneumonia. Baloxavir was associated with similar clinical efficacy and safety and superior antiviral activity compared to other antivirals in both high risk and uncomplicated patients.

A 2021 systemic review and meta-analysis of randomized controlled trials compared the clinical efficacy and safety of baloxavir with other anti-influenza agents or placebo in the treatment of influenza.[76] Three randomized controlled trials in both adults and children (baloxavir group, n=1,451; oseltamivir group, n=1,288; placebo group, n=1,032) were included. Baloxavir had an insignificantly shorter time to the alleviation of symptoms compared with oseltamivir (mean difference [MD], -1.29 h; 95% CI, -6.8 to 4.21; I2=0). Baloxavir had a significantly shorter time to the alleviation of symptoms than placebo (MD, -26.32 h; 95% CI, -33.78 to -18.86; I2=0). Compared to oseltamivir and placebo, baloxavir was associated with a significant decline in influenza virus titers and viral RNA load. These findings suggest that, compared to oseltamivir, baloxavir is as effective as oseltamivir clinically, with possibly a better virological response.

The efficacy and safety of oseltamivir, zanamivir, peramivir, laninamivir (not approved in the US), and baloxavir for the treatment of influenza among healthy adults and children were compared in a 2020 systematic review and network meta-analysis.[77] Twenty-six randomized controlled trials (n=11,897) that compared the use of these agents with each other or with placebo were included. Of all treatments compared with placebo in efficacy outcomes, zanamivir was associated with the shortest time to alleviation of symptoms (hazard ratio [HR], 0.67; 95% CI, 0.58 to 0.77), while baloxavir was associated with the lowest risk of influenza-related complications (risk ratio [RR], 0.51; 95% CI, 0.32 to 0.8) based on moderate-quality evidence. Also based on moderate-quality evidence, baloxavir was associated with the lowest risk of total adverse events (RR, 0.84; 95% CI, 0.74 to 0.96) compared with placebo. A similar network meta-analysis of 58 studies (n=22,250) evaluated the efficacy and safety of zanamivir, peramivir, oseltamivir, and laninamivir (not available in the US).[78] The surface under the cumulative ranking curve (SUCRA) was calculated based on time to alleviation of symptoms, incidence of nausea, and incidence of diarrhea. Peramivir (SUCRA = 82.6%), zanamivir (SUCRA = 64%), and oseltamivir (SUCRA = 55.1%) were found to be the top-ranking drugs for the treatment of influenza. In the pediatric population, only peramivir and zanamivir were associated with significant improvement in the time to alleviation of influenza symptoms.

A 2014 systematic review of 107 clinical studies analyzed the effects of zanamivir and oseltamivir on time to first alleviation of influenza symptoms, influenza outcomes, complications, hospitalizations and adverse events in adults and children. Oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours in adults (95% CI, 8.4 to 25.1 hours; p<0.0001) and by 29 hours in otherwise healthy children (95% CI, 12 to 47 hours; p=0.001); no effect was seen in asthmatic children. Zanamivir reduced the time to first alleviation of symptoms in adults by 0.6 days (95% CI, 0.39 to 0.81 days; p<0.00001); the effect in children was not significant. Zanamivir significantly reduced the risk of bronchitis in adult treatment trials (RD, 1.8%; 95% CI, 0.65 to 2.8), but not oseltamivir. Neither zanamivir nor oseltamivir significantly reduced the risk of otitis media and sinusitis in both adults and children.

In prophylaxis trials, oseltamivir and zanamivir reduced the risk of symptomatic influenza in individuals (oseltamivir: risk difference [RD], 3.05% [95% CI, 1.83 to 3.88]; zanamivir: RD, 1.98% [95% CI, 0.98 to 2.54]) and in household contacts (oseltamivir: RD, 13.6% [95% CI, 9.52 to 15.47]; zanamivir: RD, 14.84%

[95% CI, 12.18 to 16.55]). There was no significant effect on asymptomatic influenza (oseltamivir: RR, 1.14 [95% CI, 0.39 to 3.33]; zanamivir: RR, 0.97 [95% CI, 0.76 to 1.24]).

Oseltamivir in the treatment of adults increased the risk of nausea (RD, 3.66%; 95% CI, 0.9 to 7.39) and vomiting (RD, 4.56%; 95% CI, 2.39 to 7.58). The proportion of participants with 4-fold increases in antibody titer was significantly lower in the treated group compared to the control group (RR, 0.92; 95% CI, 0.86 to 0.97; $I^2$=0) (5% absolute difference between arms). Oseltamivir significantly decreased the risk of diarrhea (RD, 2.33%; 95% CI, 0.14 to 3.81) and cardiac events (RD, 0.68%; 95% CI, 0.04 to 1) compared to placebo during the on-treatment period. There was a dose-response effect on psychiatric events in the 2 oseltamivir "pivotal" treatment trials, WV15670 and WV15671, at 150 mg (standard dose) and 300 mg daily (high dose) (p=0.038). In the treatment of children, oseltamivir induced vomiting (RD 5.34%; 95% CI, 1.75 to 10.29). There was a significantly lower proportion of children on oseltamivir with a 4-fold increase in antibodies (RR, 0.9; 95% CI, 0.8 to 1; $I^2$=0).

In oseltamivir prophylaxis studies, psychiatric adverse events were increased in the combined on- and off-treatment periods (RD, 1.06%; 95%, CI 0.07 to 2.76). Oseltamivir increased the risk of headaches (RD 3.15%; 95% CI, 0.88 to 5.78), renal events while on treatment (RD, 0.67%; 95% CI, -2.93 to 0.01), and nausea (RD, 4.15%; 95% CI, 0.86 to 9.51).

Trials with oseltamivir or zanamivir could not demonstrate a reduction in complications of influenza (such as pneumonia) due to lack of diagnostic definitions. Treatment of adults and children with oseltamivir had no significant effect on hospitalizations. Zanamivir hospitalization data were not reported.[79]

## Adults

A 2009 systematic review included randomized placebo-controlled studies of neuraminidase inhibitors in otherwise healthy adults exposed to naturally occurring influenza.[80,81] A total of 20 trials were included. In the 4 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% (RR, 0.39; 95% CI, 0.18 to 0.85). Inhaled zanamivir 10 mg daily was 62% efficacious (RR, 0.38; 95% CI, 0.17 to 0.85). In postexposure prophylaxis trials, oseltamivir had an efficacy of 58% (95% CI, 15 to 79) and 84% in 2 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 (RR, 0.55; 95% CI, 0.22 to 1.35).

A 2015 meta-analysis evaluated the efficacy of oseltamivir treatment for influenza in adults.[82] Data from 9 trials including 4,328 patients was used in the analysis. The analysis showed that oseltamivir in adults with influenza accelerates time to clinical symptom alleviation, reduces risk of lower respiratory tract complications, and admittance to hospital, but increases the occurrence of nausea and vomiting. In the analysis, time to alleviation of all symptoms was 21% shorter for oseltamivir versus placebo in the intention to treat infected population (time ratio, 0.79; 95% CI, 0.74 to 0.85; p<0.0001). The analysis also showed fewer lower respiratory tract complications requiring antibiotics more than 48 hours after randomization (RR, 0.56; 95% CI, 0.42 to 0.75; p=0.0001) and also fewer admittances to hospital for any cause (RR, 0.37; 95% CI, 0.17 to 0.81; p=0.013) in the intention to treat infected population. Regarding

safety, oseltamivir increased the risk of nausea (RR, 1.6; 95% CI, 1.29 to 1.99; p<0.0001) and vomiting (RR, 2.43; 95% CI, 1.83 to 3.23; p<0.0001).

### Children

A 2009 systematic review evaluated the effects of the neuraminidase inhibitors in treatment of children (≤ 12 years old) with seasonal influenza and prevention of transmission to children in households.[83] Published and unpublished data were considered. A total of 4 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 (1 trial for oseltamivir, 2 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 2 trials. A 10-day duration of postexposure prophylaxis with zanamivir or oseltamivir resulted in an 8% (95% CI, 5 to 12) decrease in the incidence of symptomatic influenza. Based on only 1 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. Because of the possibility of emergence of antiviral resistance viruses, widespread or routine use of antiviral medications for chemoprophylaxis is not recommended and use of these agents should be reserved for appropriate high-risk populations.

Agents approved for influenza prevention and treatment include amantadine, rimantadine (Flumadine), oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapivab), and baloxavir marboxil (Xofluza). The Centers for Disease Control and Prevention (CDC) does not recommend the use of amantadine or rimantadine for the treatment or prophylaxis of influenza A due to viral resistance. Baloxavir marboxil offers a treatment option with a novel mechanism of action and with a convenient single dose for influenza treatment. In clinical trials it has shown comparable efficacy to oseltamivir. Greater reduction in viral load was seen 1 day after drug administration with baloxavir marboxil compared to oseltamivir and placebo. Baloxavir marboxil may also have activity against select oseltamivir-resistant strains and Avian strains (H7N9, H5N1).

The CDC recommends antiviral treatment of influenza in hospitalized patients, patients with severe, complicated or progressive illness, and patients at high risk for influenza complications. The CDC prefers use with oseltamivir in these patient populations over zanamivir, peramivir, or baloxavir marboxil. Antiviral 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. In the outpatient setting, antiviral treatment can also be considered for any previously healthy individual with confirmed or suspected influenza who are not at high risk for influenza complications; no preference for use of baloxavir marboxil, oseltamivir, or zanamivir is given by the CDC. However, in the setting of an antiviral medication shortage, the CDC urges prioritization of antiviral treatment for those with laboratory-confirmed influenza who are at highest risk for severe disease and who test positive for influenza within 2 days of illness onset. The Infectious Diseases Society of America (IDSA) does not include a

recommendation for baloxavir marboxil use to treat influenza since the product was FDA approved after the guidelines were finalized. Antiviral chemoprophylaxis generally should be reserved for people at higher risk for influenza-related complications who have had contact with someone likely to have been infected with influenza.

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