Recommendations for Antiviral Therapy of Seasonal Influenza

Date: November 3, 2025

Purpose

This document provides recommendations for health care providers on the appropriate prescribing of antiviral therapy for children and adults with seasonal influenza. Antiviral treatment is not a substitute for influenza vaccination, which remains the most effective means of preventing influenza illness.[1,2] Recommendations related to influenza vaccination and other non-antiviral drug therapy aspects of seasonal influenza management (e.g., diagnostics, infection control practices) are beyond the scope of this document. See the ***Additional Resources*** section for more information about these topics.

Recommendations Development

The recommendations are informed by best available evidence retrieved from a systematic literature search conducted between May to July 2025 of peer-reviewed studies, review articles, Canadian guidelines, international guidelines and grey literature. The recommendations were developed by the Ontario Health Infectious Diseases program's guidance development working group with consensus-based feedback and contributions from Ontario Health's Infectious Diseases Advisory Committee (IDAC). This document was reviewed by multidisciplinary clinicians and health care administrators from Ontario Health's Primary Care Program, Renal Program, Systemic Treatment Program (Cancer Care), Regional Clinical Vice-Presidents and the Chief Medical Executive.

This guidance document shall be updated as needed to align with relevant changes in clinical best practice.

See the ***Authorship, Contributors and Acknowledgements*** section for additional information about the authors and contributors of this guidance document.

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Introduction

Infection due to seasonal influenza can be asymptomatic, or range from non-severe and self-limited to the upper respiratory tract to severe disease.[3] Influenza that progresses to severe disease may lead to complications and potentially life-threatening outcomes, including acute respiratory distress syndrome, multi-organ failure or death.[4] Influenza can also cause exacerbation of underlying chronic medical condition(s) (e.g., chronic obstructive pulmonary disease, asthma, heart failure).[4] The mortality risk for seasonal influenza is estimated to be 0.1% for non-severe illness and 3% for severe illness.[5] In Canada, influenza is one of the 10 leading causes of death and causes approximately 3,500 deaths each year.[6] Over 12,000 hospitalizations are attributed to seasonal influenza annually in Canada.[6]

Seasonal Influenza Severity Classification

The classification of influenza disease severity varies among different references and health authorities. ***Table 1*** outlines the classification of disease severity in Ontario that was adapted from Canadian and international guidelines.[3–5,7] Most people recover from the symptoms of non-severe influenza within a week, without requiring medical attention.[5] People with severe influenza typically require hospitalization.[5,7]

For the purposes of this document, non-severe or uncomplicated seasonal influenza shall be referred to as non-severe seasonal influenza. Severe or complicated seasonal influenza shall be referred to as severe seasonal influenza.

Table 1: Seasonal Influenza Severity Classification

Influenza Severity Category	Definition
Non-Severe	Patients with: • Signs and symptoms of influenza-like illness (e.g., fever, malaise, chills, myalgia), upper respiratory tract symptoms (e.g., rhinorrhea, cough) or gastrointestinal symptoms of influenza (e.g., diarrhea, vomiting) [3–5,7,8] **AND** • Absence of any features of severe influenza[5,7]
Severe	Patients with: • Signs and symptoms of progressive influenza illness suggesting more than non-severe influenza illness (e.g., chest pain, tachypnea, laboured breathing, low blood pressure)[3,4] **OR** • Signs of lower respiratory disease (e.g., hypoxemia, abnormal chest radiograph)[3,7] **WITH OR WITHOUT** any of the following: - Central nervous abnormalities (e.g., encephalitis, encephalopathy)[3,7] **OR** - Cardiovascular complications (e.g., acute ischemic heart disease, myocarditis)[9] **OR** - Renal abnormalities (e.g., acute kidney injury)[9] **OR** - Myositis or rhabdomyolysis[3] **OR** - Septic shock or multi-organ failure[3–5] **OR** - New or increase respiratory support and/or vasopressor/ionotropic therapy[5] **OR** - Exacerbation of chronic medical condition(s) (e.g., asthma, chronic obstructive pulmonary disease, heart failure)[3–5,7]

Risk Factors for Developing Influenza-Related Complications

Table 2 lists the risk factors that are associated with an increased risk of developing influenza-related complications. Complications of influenza include progression to severe disease, hospitalization and/or mortality.[3,5] An increased number of risk factors is associated with a higher risk of hospitalization due to seasonal influenza.[10] However, the degree to which each factor contributes to the risk may vary from patient to patient.

Table 2: Risk Factors Associated with Developing Influenza-Related Complications

Risk Category	Description of Risk Factors
Age	• Individuals aged 65 years or older[3,5,11,12] • Individuals aged younger than 5 years[3,13]
Immunocompromised Status	• Immunosuppression due to high-dose systemic corticosteroid therapy[*,7,12] • Congenital immunodeficiency or acquired immunodeficiency (e.g., HIV-infected patients with severe immunosuppression [CD4 less than 200/mm^3 or less than 15% of total lymphocytes in an adult or child aged older than 5 years; CD4 less than 500/mm^3 or less than 15% of total lymphocytes in a child aged 1 to 5 years])[3,7] • Current or within 6 months of receiving systemic therapy (e.g., chemotherapy, immunotherapy, targeted agents) or radiotherapy for malignancy[3,7,12] • Hematopoietic stem cell transplant recipients[3] • Solid organ transplant recipients on immunosuppressive therapy[7] • Patients with current graft-versus-host disease[7] • Patients currently or within last 6 months on other types of highly immunosuppressive therapy or where the patient's provider considers them immunosuppressed[7,12]
Medical Conditions	• Asthma and other chronic pulmonary disease (e.g., cystic fibrosis, emphysema, chronic bronchitis)[3,5,7,11] • Cardiovascular disease (excluding isolated hypertension)[3,5,7,11,12] • Chronic renal insufficiency[3,7,12] • Diabetes mellitus and other metabolic diseases[3,7,11,12] • Hemoglobinopathies (e.g., sickle cell disease)[3,12] • Individuals aged younger than 19 years who are on chronic acetylsalicylic acid or salicylate-containing medications[3,12] • Malignancy[3,5,11] • Neurological and neurodevelopmental disorders that compromise handling of respiratory secretions (e.g., cognitive dysfunction, seizure disorders, spinal cord injury)[3,5,7,11,12] • People with certain disabilities who may have trouble with muscle function, lung function, or difficulty coughing, swallowing, or clearing fluids from their airways[12]
Other groups	• Obesity with a body mass index 40 kg/m^2 or greater [3,7,12] • Pregnant people or people up to 2 weeks post-partum[7,11,12] • People of any age who are residents of nursing homes or chronic care facilities[3,12] • Indigenous people[3,11]

* For individuals who weigh more than 10 kg AND:
  - currently receiving a daily dose of prednisone 20 mg or higher (or an equivalent corticosteroid) for 2 weeks or more[3,14,15] OR
  - less than 1 month has passed since the end of a course of prednisone at a daily dose of 20 mg or higher (or an equivalent corticosteroid)[15]

Overview of Seasonal Influenza Treatment

Goals of Treatment

The goals of treatment in patients with seasonal influenza are to:

- Prevent mortality[3,16,17]
- Reduce the duration of influenza symptoms[3,5,16,17]
- Decrease the risk of influenza-related complications (e.g., pneumonia, exacerbation of pre-existing illnesses, organ damage and/or failure)[9,18]
- Reduce the risk of hospitalization[3,5,16,18]
- Reduce the duration of hospitalization[17]

Antiviral Activity and Susceptibility Considerations

The predominant influenza strains that circulate in Canada in any given season are unpredictable.[3] Resistance or reduced susceptibility of influenza A or B viruses to antivirals can occur sporadically or may emerge during or after antiviral therapy.[19] See Public Health Ontario's (PHO) ***Respiratory Virus Tool*** for the latest information about influenza virus activity and antiviral susceptibility data in Ontario.

Neuraminidase inhibitors (NAIs)

Antiviral activity

NAIs (e.g., oseltamivir, zanamivir, peramivir) block the neuraminidase enzyme and prevent the release of influenza viral particles from infected cells.[19] NAIs are a treatment option for seasonal influenza as they are active against influenza A and B viruses.[20] In vitro studies have found that influenza B viruses are less susceptible to NAIs compared to influenza A viruses.[20] However, it is unknown if the observed in vitro differences in susceptibility to NAIs result in clinically meaningful outcomes for patients.[20]

Antiviral susceptibility

A Canadian surveillance report for the 2024-2025 influenza season that included specimens from public health laboratories and some hospital laboratories detected oseltamivir resistance in fewer than 0.6% of seasonal influenza A isolates.[21] Zanamivir resistance was detected in fewer than 0.2% of seasonal influenza A isolates.[21] Resistance to oseltamivir or zanamivir was not detected in any of the seasonal influenza B isolates.[21] The Canadian respiratory virus surveillance report does not include resistance data of seasonal influenza viruses to peramivir. Global surveillance studies of peramivir resistance among influenza A and B viruses ranged from less than 1% to 3.2% between 2014 to 2018.[22,23]

More commonly reported influenza virus mutations that are associated with NAI resistance include the H275Y substitution and the H274Y substitution.[23–25] Influenza A viruses that possess the H275Y and/or H274Y substitution in the neuraminidase enzyme are cross-resistant to oseltamivir and peramivir, but remain susceptible to zanamivir.[19,23] The binding of zanamivir to the neuraminidase active site differs from that of oseltamivir and peramivir.[26]

Treatment-emergent resistance

The development of treatment-emergent resistance to oseltamivir is uncommon in immunocompetent individuals.[3] A clinical study found 3.56% of immunocompetent individuals developed treatment-emergent resistance following oseltamivir therapy.[27] Immunocompromised persons and young children are at increased risk of antiviral resistance due to prolonged influenza viral shedding and/or higher viral burden compared to other treatment groups.[3,19,22,28,29] Treatment-emergent resistance to zanamivir is uncommon, even in immunocompromised patients.[3,30,31] Due to the limited available data on peramivir use, the potential for resistance development following peramivir therapy remains unclear.[30]

Baloxavir

Antiviral activity

Baloxavir is a cap-dependent endonuclease enzyme inhibitor that prevents influenza virus replication.[32] Baloxavir is active against influenza A and B viruses, including strains that are resistant to neuraminidase inhibitors.[20,33,33] Cross-resistance between baloxavir and neuraminidase inhibitors has not been identified.[32] In vitro studies have found that influenza B viruses demonstrate lower susceptibility to baloxavir compared with influenza A viruses.[34] However, the relationship between antiviral activity in cell cultures and the inhibition of influenza virus replication in humans has not been established.[32]

Antiviral susceptibility

There is currently no published data from PHO or the Public Health Agency of Canada regarding seasonal influenza susceptibility to baloxavir. One surveillance study of influenza A and B in North and South America from 2018 to 2023 found reduced susceptibility to baloxavir in fewer than 0.2% of isolates.[35]

Treatment-emergent resistance

The rate of treatment-emergent resistance to baloxavir observed in clinical studies range from 2% to 23%.[30,36] Studies have found that treatment-emergent resistance following a single dose of baloxavir was more common in children younger than 5 years old compared to adults and adolescents (40% vs 7%).[37] Seasonal influenza A is also associated with a higher risk of treatment-emergent resistance to baloxavir compared to influenza B (14% vs 1%).[36,37] Clinical studies have not compared the rate of baloxavir treatment-emergent resistance in immunocompromised patients with seasonal influenza compared to those who are immunocompetent.[19]

Amantadine

Amantadine is no longer recommended for treatment of seasonal influenza in Canada because of high rates of resistance observed among circulating influenza A viruses.[8,38] Amantadine is not active against influenza B.[39]

Recommendations for Seasonal Influenza Treatment

The decision to initiate antiviral therapy should include a clinical assessment of the patient's signs and symptoms, along with consideration of their severity of illness, risk factor(s) for developing influenza-related complications, elapsed time from the onset of symptoms and epidemiologic factors (e.g., prevalence and strain of influenza virus circulating in the community).[11,40] Symptoms of influenza can be similar to symptoms of other respiratory illnesses.[11] Diagnostic testing (e.g., rapid antigen test, polymerase chain reaction test) may be used to confirm clinical suspicion and to inform decisions on the use of antiviral therapy.[11] Confirmation of influenza infection by microbiological testing is not a requirement for initiating empiric antiviral therapy when influenza is circulating in the community.[11,40,41] A specific positivity rate threshold for initiating presumptive antiviral treatment for influenza has not been established. For the latest information on influenza virus activity in Ontario, see PHO's ***Respiratory Virus Tool*** to help guide decisions regarding antiviral therapy.

Antiviral therapy should be started as soon as possible for individuals indicated for treatment, ideally within 48 hours of symptom onset for the greatest clinical benefit.[11,19] Antiviral therapy beyond 48 hours of symptom onset may also be considered in selected circumstances as described in the ***Treatment of Non-Severe Seasonal Influenza in Adults***, ***Treatment of Non-Severe Seasonal Influenza in Children Beyond 48 Hours of Symptom Onset*** and ***Treatment of Severe Seasonal Influenza in Adults and Children*** sections.

Adults and Children with Asymptomatic Seasonal Influenza

Antiviral therapy is not routinely recommended for individuals with asymptomatic influenza.[8,11] In exceptional circumstances where a clinician is concerned that an individual with asymptomatic influenza may be at high risk of developing influenza-related complications (e.g., individuals who are immunocompromised, organ transplant recipients, individuals with cancer), consult with specialist(s) as required (e.g., infectious diseases, transplant, oncology) to inform individualized treatment decisions.

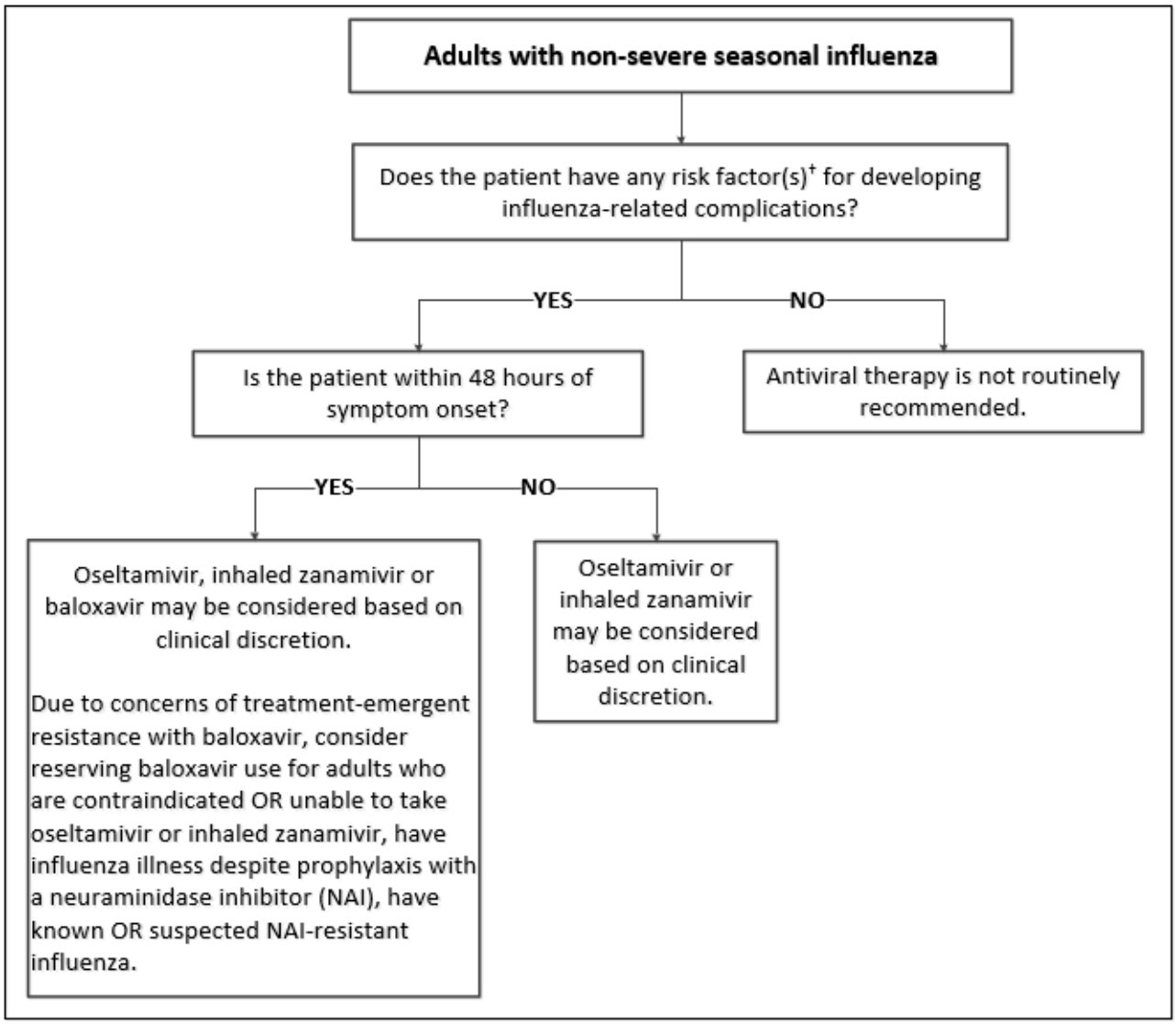
Treatment of Non-Severe Seasonal Influenza in Adults

See ***Figure 1*** for a suggested algorithm to treat adults with non-severe seasonal influenza.

1. For adults WITH risk factor(s)[†] for developing influenza-related complications and within 48 hours of symptom onset: oseltamivir, inhaled (INH) zanamivir or baloxavir may be considered based on clinical discretion.[19] Due to concerns of treatment-emergent resistance with baloxavir, consider reserving baloxavir use for adults who are contraindicated to OR unable to take oseltamivir or INH zanamivir, have influenza illness despite prophylaxis with a NAI, or have known OR suspected NAI-resistant influenza.
2. For adults WITH risk factor(s)[†] for developing influenza-related complications and beyond 48 hours of symptom onset: oseltamivir or INH zanamivir may be considered based on clinical discretion.[3,7]
3. For adults WITHOUT any risk factor(s)[†] for developing influenza-related complications (irrespective of time from symptom onset): antiviral therapy is not routinely recommended.[7]

See the ***Clinical Evidence*** section for a detailed description of the evidence summary and rationale that support each recommendation.

Figure 1: Treatment Algorithm for Non-Severe Seasonal Influenza in Adults



† See ***Table 2*** for the list of risk factors associated with developing influenza-related complications.

Treatment of Non-Severe Seasonal Influenza in Children Within 48 Hours of Symptom Onset

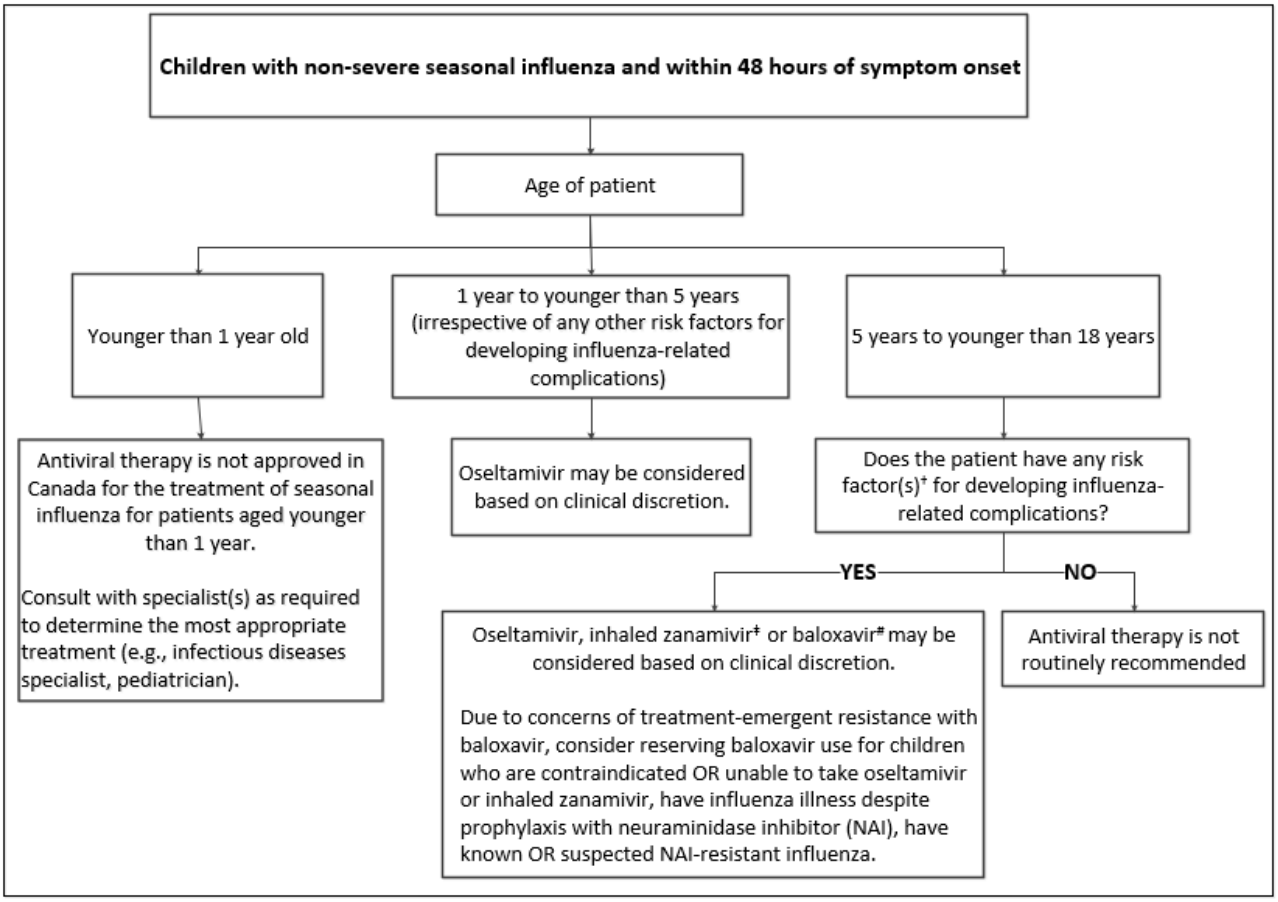
See ***Figure 2*** for a suggested algorithm to treat children with non-severe seasonal influenza and within 48 hours of symptom onset.

1. For children aged younger than 1 year and within 48 hours of symptom onset [irrespective of any other risk factor(s) for influenza-related complications]: antiviral therapy is not approved for this age group in Canada.[3,42] Consultation with a specialist (e.g., infectious diseases, pediatrician) is strongly recommended to determine the most appropriate treatment.
2. For children aged 1 year to younger than 5 years [irrespective of any other risk factor(s) for developing influenza-related complications] and within 48 hours of symptom onset: oseltamivir may be considered based on clinical discretion.[13,30]

3. For children aged 5 years to younger than 18 years WITH risk factor(s)† for developing influenza-related complications and within 48 hours of symptom onset: oseltamivir, INH zanamivir‡ or baloxavir# may be considered based on clinical discretion.[3,13,42] Due to concerns of treatment-emergent resistance with baloxavir, consider reserving baloxavir use for children who are contraindicated to OR unable to take oseltamivir or INH zanamivir, have influenza illness despite prophylaxis with a NAI, or have known OR suspected NAI-resistant influenza.
4. For children aged 5 years to younger than 18 years WITHOUT any risk factor(s)† for developing influenza-related complications and within 48 hours of symptom onset: antiviral therapy is not routinely recommended.[3]

See the ***Clinical Evidence*** section for a detailed description of the evidence summary and rationale that support each recommendation.

Figure 2: Treatment Algorithm for Non-Severe Seasonal Influenza in Children Within 48 Hours of Symptom Onset



† See ***Table 2*** for the list of risk factors associated with developing influenza-related complications.
‡ INH zanamivir is approved for the treatment of non-severe seasonal influenza in individuals aged 7 years and older in Canada.[43]
# Baloxavir is approved for the treatment of non-severe seasonal influenza in individuals aged 12 years and older in Canada.[32]

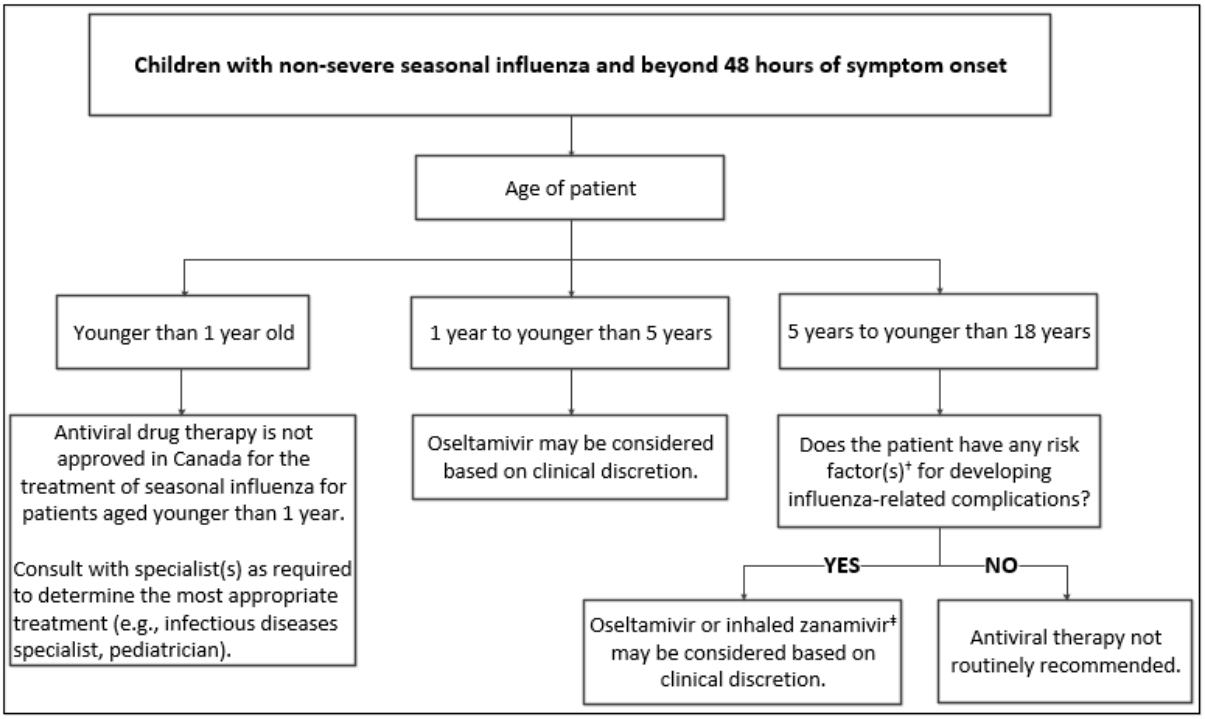
Treatment of Non-Severe Seasonal Influenza in Children Beyond 48 Hours of Symptom Onset

See ***Figure 3*** for a suggested algorithm to treat children with non-severe seasonal influenza and beyond 48 hours of symptom onset.

1. For children aged younger than 1 year and beyond 48 hours of symptom onset [irrespective of any other risk factor(s)for developing influenza complications]: antiviral therapy is not approved for this age group in Canada.[3,42] Consultation with a specialist (e.g., infectious diseases, pediatrician) is strongly recommended to determine the most appropriate treatment.
2. For children aged 1 to younger than 5 years [irrespective of any other risk factor(s) for developing influenza-related complications]: oseltamivir may be considered based on clinical discretion.[13]
3. For children aged 5 years to younger than 18 years WITH risk factor(s)† for developing influenza-related complications and beyond 48 hours from symptom onset: oseltamivir or INH zanamivir‡ may be considered based on clinical discretion.[3,19,42]
4. For children aged 5 years to younger than 18 years WITHOUT risk factor(s)† for developing influenza-related complications and beyond 48 hours of symptom onset: antiviral treatment is not routinely recommended.[3,42]

See the ***Clinical Evidence*** section for a detailed description of the evidence summary and rationale that support each recommendation.

Figure 3: Treatment Algorithm for Non-Severe Seasonal Influenza in Children Beyond 48 Hours of Symptom Onset



† See ***Table 2*** for the list of risk factors associated with developing influenza complications.
‡ INH zanamivir is approved for individuals aged 7 years and older in Canada for the treatment of non-severe seasonal influenza.[43]

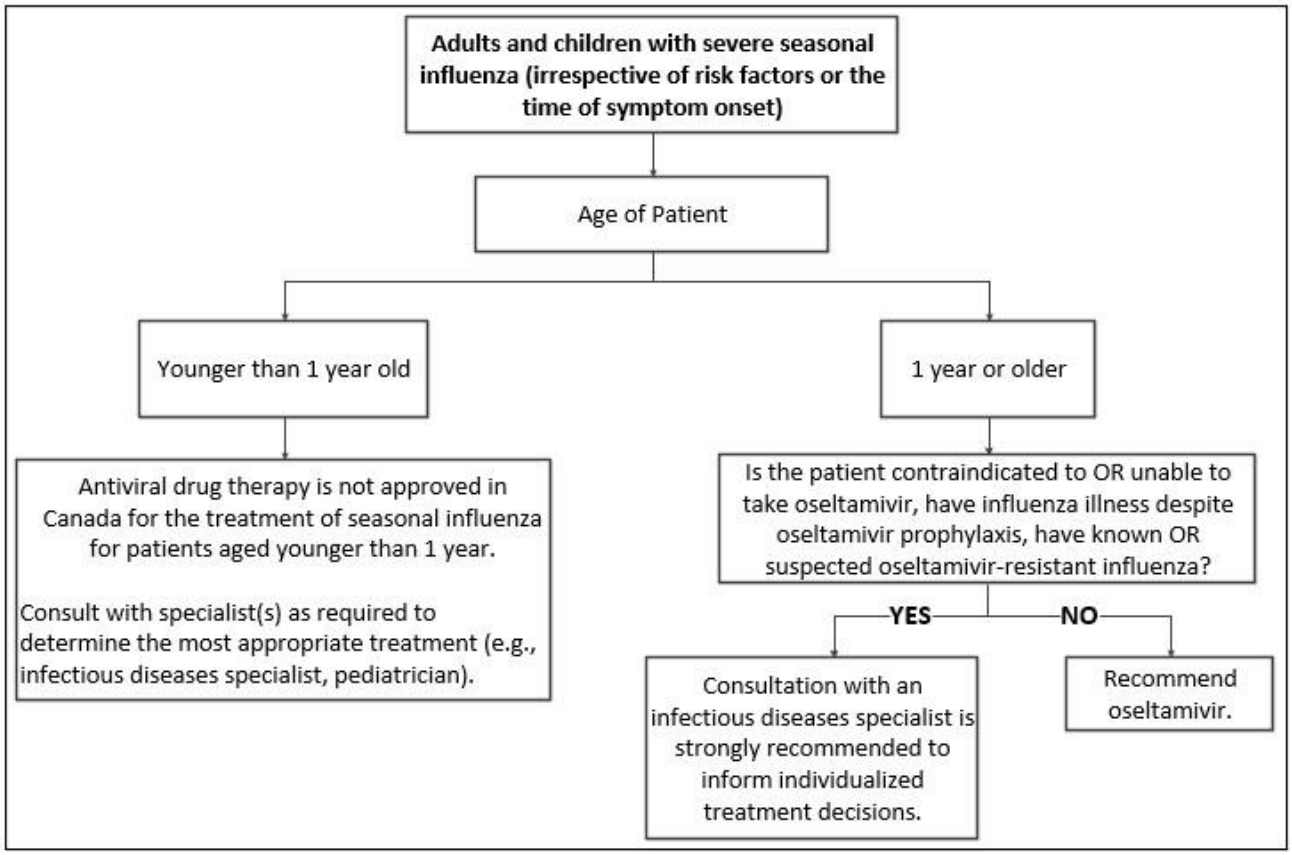
Treatment of Severe Seasonal Influenza in Adults and Children

See ***Figure 4*** for a suggested algorithm to treat adults or children with severe seasonal influenza.

1. For children aged younger than 1 year, antiviral therapy is not approved for this age group in Canada.[3] Consult with specialist(s) as required to determine the most appropriate treatment (e.g., infectious diseases specialist, pediatrician).
2. For patients aged 1 year and older who are contraindicated to OR unable to take oseltamivir, have influenza illness despite oseltamivir prophylaxis, or have known OR suspected influenza resistant to oseltamivir, consultation with an infectious diseases specialist is strongly recommended to inform individualized treatment decisions.
3. For patients aged 1 year and older [irrespective of any other risk factor(s) for developing influenza-related complications or the time of symptom onset]: oseltamivir is recommended as first-line therapy for severe seasonal influenza.[3,5,19]

See the ***Clinical Evidence*** section for a detailed description of the evidence summary and rationale that support each recommendation.

Figure 4: Treatment Algorithm for Severe Seasonal Influenza in Adults and Children



Clinical Evidence

Oseltamivir

In Canada, oseltamivir is approved for the treatment of non-severe seasonal influenza in individuals aged 1 year and older within 48 hours of symptom onset.[44] Oseltamivir for the treatment of severe seasonal influenza is considered off-label use in Canada.

Non-Severe Seasonal Influenza

In clinical trials of oseltamivir for the treatment of non-severe seasonal influenza, the enrolment of patients within 48 hours of symptom onset was a standard inclusion criterion.[30] A meta-analysis of randomized controlled trials of adults and children with non-severe seasonal influenza (with or without risk factors for developing influenza-related complications) found that oseltamivir therapy significantly reduced the mean time to alleviation of symptoms by 0.75 days compared to placebo or standard of care.[30] However, 0.75 days may not be considered a clinically important difference to patients or clinicians. There was no significant difference between the two treatment groups for admission to the intensive care unit (ICU) within 29 days or duration of hospitalization.[30] In the subgroup of patients with non-severe seasonal influenza who did not have risk factors for developing influenza-related complications, the same meta-analysis found no significant difference between oseltamivir therapy compared to placebo or standard of care for mortality or admission to hospital within 29 days.[30] Consistent results for mortality and admission to hospital were observed for the subgroup of patients with risk factors for developing influenza-related complications.[30]

In contrast, one observational study found an association between oseltamivir therapy and a reduced risk for hospital admission within 14 days of symptom onset in adults with diabetes (a risk factor for influenza-related complications) compared to no oseltamivir therapy.[45] Another observational of children 1 to 17 years of age with selected risk factors for influenza-related complications (e.g., immunosuppressive disorders, asthma or other respiratory disease, renal disease, neurologic or neuromuscular diseases that may compromise respiratory function) found an association between oseltamivir therapy and a lower risk of all-cause hospitalization within 29 days of symptom onset compared to no oseltamivir therapy.[46]

Clinical evidence to support oseltamivir therapy in individuals with non-severe seasonal influenza and with symptom onset beyond 48 hours is extremely limited. A secondary analysis of a randomized controlled trial found that oseltamivir therapy significantly reduced virus isolation from tissue culture on days 2 and 4 compared with placebo in individuals with non-severe seasonal influenza with symptom onset greater than 48 hours but within 120 hours.[47] However, there was no significant difference between the two treatment groups for virus isolation from tissue culture by day 7.[47] The same study also found no significant difference for the mean duration of symptoms between individuals who received oseltamivir greater than 48 hours but less than 120 hours of symptom onset and those who received placebo.[47] The follow-up period for symptoms monitoring in this study was 7 days after the resolution of symptoms.[47] The generalizability of the study's findings to adults may be limited because nearly 90% of the patients were younger than 18 years old.[47]

For comparisons between oseltamivir and other antiviral therapies to treat patients with non-severe seasonal influenza, see the ***Comparison of Neuraminidase Inhibitors*** and ***Comparison of Baloxavir and Neuraminidase Inhibitors*** sections for more information.

Severe Seasonal Influenza

A meta-analysis of randomized controlled trials in adults and children with severe seasonal influenza found that oseltamivir therapy significantly reduced the mean duration of hospitalization by 1.63 days compared to placebo or standard of care.[48] However, treatment with oseltamivir did not decrease the time to alleviation of symptoms, mortality or risk of ICU admission within 35 days compared to no oseltamivir treatment.[48,49] The under-representation of some patient groups (e.g., children, adults aged 60 years and older) in the meta-analysis may limit the generalizability of the study results to these populations.[48]

In contrast, an observational study of hospitalized adults with severe seasonal influenza in Ontario reported an association between oseltamivir therapy and reduced in-hospital mortality, fewer ICU admissions, earlier hospital discharge and reduced hospital readmission within 30 days after hospital discharge compared to no oseltamivir therapy.[50] Benefit with oseltamivir therapy was also observed in another retrospective study of hospitalized individuals aged 65 years and older in Canada with seasonal influenza.[51] The study found oseltamivir therapy was associated with a lower risk of 30-day mortality compared to no oseltamivir therapy.[51] A limitation of this study was that the published data did not include information on influenza disease severity.[51] Hospitalization was used as proxy for severe seasonal influenza, although some individuals may have had non-severe seasonal influenza.

For comparisons between oseltamivir and other antiviral therapies for patients with severe seasonal influenza, see the ***Comparison of Neuraminidase Inhibitors*** and ***Comparison of Baloxavir and Neuraminidase Inhibitors*** sections for more information.

Zanamivir

In Canada, INH zanamivir is approved for the treatment of non-severe seasonal influenza in individuals 7 years and older within 48 hours of symptom onset.[43] INH zanamivir for the treatment of severe seasonal influenza is considered off-label use in Canada.

Intravenous (IV) zanamivir has not been approved by Health Canada for the treatment of non-severe or severe seasonal influenza. However, IV zanamivir has been used in other countries to treat severe seasonal influenza in individuals aged 6 months and older.[1,52]

Non-Severe Seasonal Influenza

In adults and children with non-severe seasonal influenza (with or without risk factors for developing influenza-related complications), a meta-analysis of randomized controlled trials found that INH zanamivir therapy significantly reduced the mean time to alleviation of symptoms compared to placebo or standard care by 0.68 days.[30] However, 0.68 days may not be considered a clinically important difference to patients or clinicians. Similar reductions in the time to alleviation of symptoms were observed in a meta-analysis of observational studies that compared INH zanamivir and no antiviral therapy.[53] In another meta-analysis of randomized controlled trials of adults and children with non-severe seasonal influenza (with or without risk factors for developing influenza complications), the risk of influenza-related complications within 28 days of treatment (defined as pneumonia, bronchitis, otitis media, sinusitis, and other secondary illness, whether treated with antibiotics or not) was significantly reduced in patients treated with INH zanamivir compared to placebo.[54]

Mortality and hospitalization within 30 days were compared between INH zanamivir and no antiviral therapy in a meta-analysis of observational studies that included adults and children with non-severe seasonal influenza (with or without risk factors for developing influenza-related complications). The meta-analysis found no significant difference between the two treatment groups for either outcome.[53] A limitation of the meta-analysis was the use of outpatient therapy as a proxy for non-severe seasonal influenza, although some individuals may have had severe seasonal influenza.[55–59]

In adults and children with non-severe seasonal influenza who had risk factor(s) for developing influenza-related complications, a meta-analysis of randomized controlled trials found no significant difference between INH zanamivir therapy and placebo or standard care for mortality or admission to hospital within 29 days.[48] Consistent results were observed in adults and children with non-severe seasonal influenza who did not have risk factor(s) for developing influenza-related complications.[48]

Clinical trials of zanamivir to treat non-severe seasonal influenza only included patients within 48 hours of symptom onset.[30,54] Although the effectiveness of zanamivir for non-severe seasonal influenza when initiated beyond 48 hours of symptom onset has not been evaluated in clinical trials, INH zanamivir is listed as an alternative to oseltamivir for the treatment of non-severe seasonal influenza in adults beyond 48 hours of symptom onset in some Canadian and international guidelines.[3,7]

For comparisons between zanamivir and other antiviral therapies for patients with non-severe seasonal influenza, see the ***Comparison of Neuraminidase Inhibitors*** and ***Comparison of Baloxavir and Neuraminidase Inhibitors*** sections for more information.

Severe Seasonal Influenza

There is limited data on the use of zanamivir to treat severe seasonal influenza. Clinical trials have not directly compared zanamivir with placebo or standard care in this patient population.[5]

An indirect comparison from a meta-analysis of randomized controlled trials of adults and children with severe seasonal influenza found that the risk of mortality within 35 days of treatment was similar between INH or IV zanamivir and placebo or standard care.[48,49] The impact of timing of zanamivir therapy on clinical outcomes remains unclear, as the studies did not consistently report the interval between the time of symptom onset to the start of treatment.[48]

For comparisons between zanamivir and other antiviral therapies for patients with severe seasonal influenza, see the ***Comparison of Neuraminidase Inhibitors*** and ***Comparison of Baloxavir and Neuraminidase Inhibitors*** sections for more information.

Peramivir

In Canada, peramivir is approved for the treatment of non-severe seasonal influenza for individuals 18 years or older within 48 hours of symptom onset.[60] However, peramivir is used in the United States to treat non-severe seasonal influenza in individuals aged 6 months and older within 48 hours of symptom onset.[17,61]

The use of peramivir to treat severe seasonal influenza is a considered an off-label indication in Canada.

Non-Severe Seasonal Influenza

Peramivir is not included in the treatment algorithms to treat adults or children with non-severe seasonal influenza because peramivir can only be obtained through Health Canada's ***Special Access Program***. Travel requirements and other medication delivery-related barriers may also limit the use of peramivir in the outpatient setting as the drug is only available as an IV formulation and requires nursing support for administration.

In adults and children with non-severe seasonal influenza (with or without risk factors for developing influenza-related complications), a meta-analysis of randomized controlled trials found that peramivir therapy significantly reduced the mean time to alleviation of symptoms compared to placebo or standard care by 0.95 days.[30] However, 0.95 days may not be considered a clinically important difference to patients or clinicians. No significant difference was found between the two treatment groups for mortality within 29 days.[30] In a subgroup analysis that stratified patients by the presence or absence of risk factors for developing influenza-related complications, mortality within 29 days was not significantly different between peramivir and placebo or standard care in either subgroup.[30] The enrolment of patients within 48 hours of symptom onset was a standard inclusion criterion for all the peramivir trials included in the meta-analysis.[30]

An indirect comparison from the same meta-analysis of randomized controlled trials found no significant difference between peramivir therapy and placebo or standard care for the duration of hospitalization or ICU admission within 29 days in patients with or without risk factors for developing influenza-related complications.[30] One limitation of the meta-analysis was that patients aged 15 years or younger were excluded from the clinical trials, which may limit the generalizability of the study results to this population.[5]

The efficacy of peramivir in individuals with non-severe seasonal influenza who initiate peramivir beyond 48 hours of symptom onset has not been studied in clinical trials.[60]

For comparisons between peramivir and other antiviral therapies for patients with non-severe seasonal influenza, see the ***Comparison of Neuraminidase Inhibitors*** and ***Comparison of Baloxavir and Neuraminidase Inhibitors*** sections for more information.

Severe Seasonal Influenza

There is limited data from clinical trials for the use of peramivir to treat patients with severe seasonal influenza.[5]

An indirect comparison from a meta-analysis of randomized controlled trials in adults and children with severe seasonal influenza showed that peramivir therapy was associated with a significantly shorter mean duration of hospitalization by 1.73 days compared to standard of care or placebo.[48] However, a direct comparison found peramivir therapy was similar to standard of care or placebo for time to alleviation of symptoms, risk of mortality and ICU admission within 35 days.[48,49] One limitation of the meta-analysis was that patients aged younger than 11 years were excluded from the clinical trials, which may limit the generalizability of the study results to this population.[48]

For comparisons between peramivir and other antiviral therapies for patients with severe seasonal influenza, see the ***Comparison of Neuraminidase Inhibitors*** and ***Comparison of Baloxavir and Neuraminidase Inhibitors*** sections for more information.

Baloxavir

In Canada, oral baloxavir is approved for the treatment of non-severe seasonal influenza in individuals aged 12 years and older who weigh at least 40 kg and within 48 hours of symptom onset.[32] However, baloxavir has been used in the United States to treat non-severe seasonal influenza in individuals aged 5 years and older within 48 hours of symptom onset.[33]

Baloxavir for the treatment of severe seasonal influenza is considered an off-label indication in Canada.

Non-Severe Seasonal Influenza

In clinical trials of baloxavir for the treatment of non-severe seasonal influenza, the enrolment of patients within 48 hours of symptom onset was a standard inclusion criterion.[30,54] In adults and children with non-severe seasonal influenza (with or without risk factors for developing influenza-related complications), a meta-analysis of randomized controlled trials found that baloxavir significantly reduced the mean time to alleviation of symptoms by 1 day compared to placebo or standard care.[30] However, 1 day may not be considered a clinically important difference to patients or clinicians. Another meta-analysis of randomized controlled trials in individuals aged 12 years and older with non-severe seasonal influenza showed that baloxavir significantly reduced influenza-related complications within 14 days of treatment (defined as pneumonia, bronchitis, otitis media, sinusitis, and other secondary illness, whether treated with antibiotics or not) compared to placebo.[54]

In adults and children with non-severe seasonal influenza and without risk factor(s) for developing influenza-related complications, a subgroup analysis from a meta-analysis of randomized controlled trials found no significant difference between baloxavir therapy and placebo or standard care for mortality or admission to hospital within 29 days.[30]

In adults and children with non-severe seasonal influenza and with risk factor(s) for developing influenza-related complications, a subgroup analysis from a meta-analysis of randomized controlled trials found no significant difference between baloxavir therapy and placebo or standard care for mortality or admission to hospital within 29 days.[30] Another randomized controlled trial of patients in this population found baloxavir therapy significantly reduced the median time to alleviation of symptoms by 27 hours and the risk of influenza-related complications within 14 days compared to placebo.[62] However, 27 hours may not be considered a clinically important difference to patients or clinicians.

The effectiveness of baloxavir to treat non-severe seasonal influenza when initiated beyond 48 hours of symptom onset has not been studied in a clinical trial.[19]

For comparisons between baloxavir and other antiviral therapies for patients with non-severe seasonal influenza, see the ***Comparison of Neuraminidase Inhibitors*** and ***Comparison of Baloxavir and Neuraminidase Inhibitors*** sections for more information.

Severe Seasonal Influenza

There is insufficient evidence to support the routine use of baloxavir monotherapy in patients with severe seasonal influenza.[19,48] Consultation with an infectious diseases specialist is recommended to inform individualized treatment decisions.

Comparison of Neuraminidase Inhibitors

Oseltamivir vs Zanamivir

Non-Severe Seasonal Influenza

In clinical trials that compared oseltamivir and zanamivir to treat non-severe seasonal influenza, the enrolment of patients within 48 hours of symptom onset was a standard inclusion criterion.[30] A meta-analysis of randomized controlled trials of adults and children with non-severe seasonal influenza found the time to alleviation of symptoms was similar between oseltamivir therapy and INH zanamivir therapy.[30] This result was consistent in patients with risk factors for developing influenza-related complications and in those without risk factors for developing influenza-related complications.[30] In addition, an indirect comparison of oseltamivir and INH zanamivir from the same meta-analysis found no significant difference between the two drugs for duration of hospitalization, mortality or hospital admission within 29 days of treatment.[30]

A subgroup analysis that stratified patients by the presence or absence of risk factors for influenza-related complications found no significant difference between oseltamivir and INH zanamivir for risk of mortality or admission to hospital within 29 days in either patient subgroup.[30]

Severe Seasonal Influenza

In adults and children with severe seasonal influenza, a meta-analysis of randomized controlled trials found no significant difference between oseltamivir and INH or IV zanamivir for mortality within 35 days.[48] The study also found no significant difference between oseltamivir and zanamivir for progression to mechanical ventilation within 35 days or for the duration of mechanical ventilation.[48,49]

Oseltamivir vs Peramivir

Non-Severe Seasonal Influenza

A meta-analysis of randomized controlled trials in adults and children with non-severe seasonal influenza (with or without risk factors for developing influenza-related complications) found that oseltamivir therapy was comparable to peramivir therapy for time to symptom alleviation, duration of hospitalization, mortality and ICU admission within 29 days.[30] A subgroup analysis that stratified patients by the presence or absence of risk factors for developing influenza-related complications also found no significant difference between the two antivirals for mortality in either patient subgroup.[30]

Severe Seasonal Influenza

A meta-analysis of randomized controlled trials that compared oseltamivir and peramivir in individuals with severe seasonal influenza found no significant difference between the two antivirals for time to alleviation of symptoms, mortality, duration of hospitalization or ICU admission within 35 days.[48,49]

Zanamivir vs Peramivir

Non-Severe Seasonal Influenza

In adult and children with non-severe seasonal influenza (with or without risk factors for developing influenza-related complications), a meta-analysis of randomized controlled trials found INH zanamivir was comparable to peramivir for time to alleviation of symptoms.[30]

Indirect comparisons from a meta-analysis of randomized controlled trials found that the risk of mortality and duration of hospitalization were similar between INH zanamivir and peramivir within 29 days in patients with non-severe seasonal influenza (with or without risk factors for developing influenza-related complications).[30]

Severe Seasonal Influenza

In adults and children with severe seasonal influenza, an indirect comparison from a meta-analysis of randomized controlled trials reported that the risk of mortality was similar between INH or IV zanamivir and peramivir within 35 days of treatment.[48,49]

Comparison of Baloxavir and Neuraminidase Inhibitors

In clinical studies that compared baloxavir and NAIs for the treatment of non-severe seasonal influenza, the enrolment of patients within 48 hours of symptom onset was a standard inclusion criterion.[30] The effectiveness of baloxavir compared to NAI therapy for non-severe seasonal influenza initiated after 48 hours of symptom onset is unknown.

Baloxavir Versus Oseltamivir

Non-Severe Seasonal Influenza

Some retrospective studies suggested that baloxavir was associated with lower rates of hospitalization within 14 days of therapy compared to oseltamivir.[63,64] However, a meta-analysis of randomized controlled trials of adults and children with non-severe seasonal influenza (with or without risk factors for influenza-related complications) found no significant difference between baloxavir and oseltamivir for the risk of hospital admission within 29 days of therapy.[30] Although another meta-analysis of randomized controlled trials found that patients treated with baloxavir had significantly lower influenza virus titres on day 2 compared to oseltamivir therapy, no significant difference was found between the two treatment groups for illness duration.[65] A limitation of the study was that influenza virus titres were not compared between the two treatment groups after 5 days because baloxavir is administered as a single dose while the treatment course of oseltamivir is 5 days.

In adults and children with non-severe seasonal influenza who had risk factor(s) for influenza-related complications, a meta-analysis of randomized controlled trials found no significant difference between baloxavir and oseltamivir for time to alleviation of symptoms, mortality, or admission to hospital within 29 days.[30] Another randomized controlled trial in this patient population found no significant difference between baloxavir and oseltamivir therapy for the risk of influenza-related complications (defined in the study as bronchitis, sinusitis or requiring antibiotics for suspected or proven secondary infections).[62]

Severe Seasonal Influenza

No prospective clinical trial has compared oseltamivir with baloxavir monotherapy in patients with severe seasonal influenza.

In adults with severe seasonal influenza, inconsistent results for hospital length of stay were reported in retrospective studies that compared baloxavir therapy with oseltamivir therapy.[65–67] In a meta-analysis of retrospective studies, no significant difference was found between baloxavir therapy and oseltamivir therapy for 30-day mortality.[65] A limitation of the meta-analysis was the inconsistent reporting of patients' severity of influenza disease at baseline.[66,67] Hospitalization was used as proxy for severe seasonal influenza, although some hospitalized individuals may have had non-severe seasonal influenza. Another retrospective study found comparable clinical outcomes between baloxavir and oseltamivir for the treatment of severe seasonal influenza in immunocompromised adults, including solid organ transplant recipients.[68] No significant difference was found between the two treatment groups for time to resolution of hypoxia or fever, duration of hospitalization, ICU admission, ICU length of stay or 30-day mortality.[68]

For information about oseltamivir compared to combination therapy with baloxavir and oseltamivir, see the ***Combination of Baloxavir and Neuraminidase Inhibitors*** section.

Baloxavir Versus Zanamivir

Non-Severe Seasonal Influenza

A retrospective study of children with non-severe seasonal influenza (with or without risk factors for influenza-related complications) suggested an association between baloxavir therapy and fewer hospital admissions within 14 days compared to inhaled zanamivir therapy.[63] However, an indirect comparison from a meta-analysis of randomized controlled trials that included adults and children with non-severe seasonal influenza (with or without risk factors for influenza-related complications) found no significant difference between the two antivirals for hospital admission within 29 days.[30] Among patients with risk factors for influenza-related complications, an indirect comparison between baloxavir therapy and inhaled zanamivir therapy also found comparable rates of hospital admission within 29 days of treatment.[30]

Indirect comparisons from the same meta-analysis found baloxavir and INH zanamivir therapy were comparable for other clinical outcomes such as time to alleviation of symptoms and mortality within 29 days of treatment.[30]

Severe Seasonal Influenza

No clinical study has compared zanamivir with baloxavir monotherapy in patients with severe seasonal influenza. For information about zanamivir compared to combination therapy with baloxavir and zanamivir, see the ***Combination of Baloxavir and Neuraminidase Inhibitors*** section.

Baloxavir Versus Peramivir

Non-Severe Seasonal Influenza

In adults and children with non-severe seasonal influenza (with or without risk factors for influenza complications), an indirect comparison from a meta-analysis of randomized controlled trials found no significant difference between baloxavir and peramivir for time to alleviation of symptoms or mortality within 29 days of treatment.[30]

Severe or Complicated Seasonal Influenza

No clinical study has compared peramivir with baloxavir monotherapy in patients with severe seasonal influenza. For information about peramivir compared to combination therapy with baloxavir and peramivir, see the ***Combination of Baloxavir and Neuraminidase Inhibitors*** section.

Combination of Baloxavir and Neuraminidase Inhibitors

Place in therapy

Non-Severe Seasonal Influenza

There is insufficient evidence to support the routine use of baloxavir in combination with a NAI in patients with non-severe seasonal influenza. Clinical trials have not evaluated the impact of combination therapy of baloxavir plus a NAI in this population.

Severe Seasonal Influenza

Current available evidence does not support the routine use of baloxavir in combination with a NAI in patients with severe seasonal influenza.

Favourable virological and clinical outcomes by combination therapy with baloxavir and a NAI for the treatment of severe seasonal influenza were suggested by in vitro and observational studies.[69] However, a randomized controlled trial (FLAGSTONE) of hospitalized adults and children with severe seasonal influenza found that combination therapy did not improve clinical outcomes compared with NAI monotherapy with oseltamivir, zanamivir or peramivir.[70] Even though combination therapy significantly reduced the time of viral shedding compared to NAI monotherapy, no significant difference was found between the two treatment groups for time to clinical improvement, mortality, time to hospital discharge, ICU admission, ICU length of stay or duration of mechanical ventilation up to day 35.[70] The results were consistent in subgroup analyses that stratified patients by influenza virus type (influenza A or influenza B), time from symptom onset to study treatment (within 48 hours or greater than 48 hours), age (younger than 65 years old or 65 years and older; younger than 80 years old or 80 years and older), influenza viral titre at baseline, and need for ICU level care or mechanical ventilation at baseline.[70]

A post hoc analysis of the FLAGSTONE trial in a subgroup of patients with one or more risk factors for influenza-related complications (defined as immunosuppression, diabetes and/or chronic lung diseases) found that combination therapy with baloxavir and a NAI was associated with a significantly faster time to cessation of viral shedding and significantly lower risk of 28-day mortality compared to NAI therapy.[10] However, no significant difference was found between the two treatment groups for other clinical outcomes such as time to clinical improvement, ICU admission rate or hospital discharge.[10] One limitation of the post hoc analysis was the lack of stratification by the number and type of risk factors for influenza-related complications. Prospective trials that stratify patients by their risk profile for influenza-related complications are needed to assess the potential benefit of combination therapy of baloxavir and a NAI.

Combination of Neuraminidase Inhibitors

Treatment of seasonal influenza with a combination of NAIs is not recommended and could increase the risk of patient harm.[16,71]

Clinical evidence suggests potential antagonism can occur with oseltamivir and zanamivir combination therapy.[72] A randomized controlled trial compared oseltamivir and INH zanamivir combination therapy with oseltamivir or INH zanamivir monotherapy for the treatment of non-severe seasonal influenza A in adults within 36 hours of symptom onset.[72] Compared to oseltamivir monotherapy, significantly fewer patients treated with combination therapy achieved viral load below 200 cgeq/mL by day 2 or symptom resolution by day 5.[72] Compared to INH zanamivir monotherapy, the combination therapy group had significantly more patients who achieved viral load below 200 cgeq/mL by day 2.[72] However, no significant difference was seen between combination therapy and zanamivir monotherapy for symptom resolution by day 5.[72]

There is no robust evidence that oseltamivir and peramivir combination therapy improves clinical outcomes compared to NAI monotherapy.[7]

Role of Adjunctive Therapies

There is insufficient evidence to support the use of adjunctive drug therapies to treat seasonal influenza.[16]

Corticosteroids

Individuals with suspected or confirmed seasonal influenza should not receive corticosteroid adjunctive therapy unless they have another clinical indication for the drug due to the potential risk of harm.[16]

The use of corticosteroid as adjunctive immunomodulatory therapy to treat severe seasonal influenza has not been studied in a clinical trial.[5] A systematic review of observational studies of children and adults with severe seasonal influenza found that systemic corticosteroid therapy was associated with increased 30-day mortality compared to no corticosteroid therapy.[73]

Other adjunctive therapies

There is insufficient evidence to support the use of other adjunctive therapies such as macrolides, or non-steroidal anti-inflammatory agents (NSAIDs) for the treatment of seasonal influenza.[5] Acetylsalicylic acid use during viral illnesses, including influenza infection, has been linked to Reye's syndrome.[3,74]

The list of adjunctive therapies noted above is not exhaustive. See the ***Additional Resources*** section for more information.

Supplemental Drug Information

Oseltamivir

Dose and duration recommendations for seasonal influenza treatment

Table 3 provides age-specific dosing recommendations for the treatment of seasonal influenza with oseltamivir. No dose adjustment is necessary for obese patients.[75,76] Oseltamivir dosing recommendations for its approved indication to treat non-severe seasonal influenza has also been used for its off-label indication to treat severe seasonal influenza.[19]

The recommended duration of oseltamivir therapy is 5 days.[3] In exceptional circumstances where a prolonged course of oseltamivir therapy beyond 5 days may be considered for selected patients (e.g., immunocompromised patients with persistent symptoms and evidence of ongoing viral replication), consultation with an infectious diseases specialist is strongly recommended. Extended courses of antiviral therapy may increase the risk of developing of antiviral resistance.[3,7]

Table 3. Oseltamivir Dose and Duration Recommendations for Seasonal Influenza Treatment

Age and Weight Group	Dose
1 year and older, AND weight greater than 40 kg	75 mg orally (PO) or by oro/nasogastric tube (OG/NG) twice daily[44]
13 years and older, AND weight 40 kg or less	60 mg PO/OG/NG twice daily[7,29]
1 to 12 years, AND weight greater than 23 to 40 kg	60 mg PO/OG/NG twice daily[44]
1 to 12 years, AND weight greater than 15 kg to 23 kg	45 mg PO/OG/NG twice daily[44]
1 to 12 years, AND weight 15 kg or less	30 mg PO/OG/NG twice daily[44]
Full-term infants 9 months to younger than 12 months	3.5 mg/kg/dose PO/OG/NG twice daily[**,††,13]
Full-term infants younger than 9 months	3 mg/kg/dose PO/OG/NG twice daily[**,13]
Premature infants, AND older than 40 weeks postmenstrual age [PMA]	3 mg/kg/dose PO/OG/NG twice daily[**,42]
Premature infants, AND 38 through 40 weeks PMA	1.5 mg/kg/dose PO/OG/NG twice daily[**,42]
Premature infants, AND born younger than 38 weeks PMA	1 mg/kg/dose PO/OG/NG twice daily[**,42]

[**]Health Canada has not approved oseltamivir for treating seasonal influenza in patients younger than 1 year of age.[44] Due to limited data for oseltamivir use in this age group, treatment should only be considered after a thorough risk assessment and in consultation with specialist(s) as required (e.g., infectious diseases specialist, pediatrician).[42]

[††] The American Academy of Pediatrics recommends 3.5 mg/kg orally twice daily instead of 3 mg/kg orally twice daily for infants in this age group to achieve target oseltamivir exposure.[13,77] It is unknown whether the higher dose will improve efficacy or prevent the development of antiviral resistance.[19] However, there is no evidence that the 3.5 mg/kg dose increases adverse events in infants from this age group.[19]

Dose adjustment for renal impairment

Table 4 provides dosage recommendations for adults with renal impairment.

Table 4: Oseltamivir Dose Recommendations for Adults with Renal Impairment

Creatinine Clearance (mL/min) or Renal Replacement Modality	Oseltamivir Dose
Greater than 60	No dose adjustment necessary[44]
Greater than 30 to 60	30 mg PO/NG/OG twice daily[44]
10 to 30	30 mg PO/OG/NG once daily[44]
Less than 10	75 mg PO/OG/NG for 1 dose[3,78]
Intermittent hemodialysis (IHD)	75 mg PO/OG/NG for 1 dose, then 75 mg PO after each dialysis session[3,79]
Continuous Ambulatory Peritoneal Dialysis (CAPD)	30 mg PO/OG/NG for 1 dose[44]

Table 5 provides dosage recommendations for children with renal impairment.

Table 5: Oseltamivir Dose Recommendations for Children with Renal Impairment

Estimated Glomerular Filtration Rate (mL/min) or Renal Replacement Modality	Oseltamivir Dose
60 and above	No dose adjustment necessary[80]
30 to less than 60	Give 40% of the age and weight-based dose in *Table 3* twice daily[80]
10 to less than 30	Give 40% of the age and weight-based dose in *Table 3* once daily[80]
Less than 10	Oseltamivir is not recommended[80]
Children receiving IHD, AND weight greater than 40 kg	The first dose is based on the age and weight-based dose in *Table 3*, then 30 mg PO/OG/NG after each dialysis session[81]
Children receiving IHD, AND weight greater than 23 kg to less than or equal to 40 kg	The first dose is based on the age and weight-based dose in *Table 3*, then 15 mg PO/OG/NG after each dialysis session[81]
Children receiving IHD, AND weight greater than 15 kg to less than or equal to 23 kg	The first dose is based on the age and weight-based dose in *Table 3*, then 10 mg PO/OG/NG after each dialysis session[81]
Children receiving IHD, AND weight less than or equal to 15 kg	The first dose is based on the age and weight-based dose in *Table 3*, then 7.5 mg PO/OG/NG after each dialysis session[81]

Dose adjustment for hepatic impairment

No dose adjustment is necessary for patients with mild to moderate hepatic impairment.[44] The safety and efficacy of oseltamivir in patients with severe hepatic impairment has not been studied.[44]

Administration considerations

Oseltamivir may be administered orally or via OG/NG tube.[3] Oseltamivir is well absorbed after administration via OG/NG tube in patients who require enteral feeding (e.g., mechanically ventilated patients), including critically ill individuals.[3]

Oseltamivir is available as a suspension, but oseltamivir capsules may also be opened and mixed with sweetened food products or liquids for individuals who are unable to swallow whole capsules.[44]

Clinically relevant contraindications

Oseltamivir is contraindicated in people who are hypersensitive to the drug or to any ingredient in the formulation.[44]

Clinically relevant drug-drug interactions

Clinically significant drug-drug interactions involving oseltamivir are uncommon because the drug has low protein binding and is not metabolized by the liver.[44] However, oseltamivir is a substrate of OAT 1/3 and may increase serum concentrations of OAT 1/3 substrates (e.g., probenecid, vaborbactam).[81] Monitoring for potential adverse effects is advised if oseltamivir is used concurrently with OAT 1/3 substrates.[81]

Clinically relevant adverse effects

Oseltamivir is generally well tolerated.[82] The most common adverse effects of oseltamivir are nausea and vomiting.[82] In post-marketing studies, rare cases of transient neuropsychiatric events (e.g., self-injury, delirium) have been reported in individuals following oseltamivir use, primarily among children.[44] A causal link between the use of oseltamivir and neuropsychiatric events has not been established.[44] However, influenza infection can also cause neuropsychiatric symptoms.[80]

The list of potential adverse effects listed above is not exhaustive. See the oseltamivir product monographs in the ***Additional Resources*** section for more information.

Pregnancy

Oseltamivir may be used during pregnancy.[83] In pregnant people, oseltamivir is preferred over other antiviral medications (e.g., zanamivir, peramivir, baloxavir) to treat seasonal influenza because it has the most studies to suggest that it is safe and effective.[84] Observational studies have not detected any significant increase in adverse maternal, fetal or neonatal outcomes (e.g., preterm delivery, low birth weight) among pregnant people treated with oseltamivir during pregnancy or in infants exposed to oseltamivir in utero compared to those with no oseltamivir exposure.[85]

Breastfeeding or chest-feeding

Oseltamivir may be used by people who are breastfeeding or chest-feeding.[83] Oseltamivir is preferred over other antiviral medications (e.g., zanamivir, peramivir, baloxavir) to treat seasonal influenza in people who are breastfeeding.[86] Less than 1% of the oseltamivir dose is excreted in breast milk and would not be expected to cause any adverse effects in nursing infants.[87,88] The doses of oseltamivir used to treat seasonal influenza in children exceed the amounts reported in breast milk.[86]

Zanamivir

Dose and duration for seasonal influenza treatment

Table 6 provides age-based dosing recommendations for INH zanamivir to treat non-severe seasonal influenza. No dose adjustment of INH zanamivir is required for obese patients.[3]

Table 6. Inhaled Zanamivir Dose Recommendations for Treatment of Non-Severe Seasonal Influenza

Age	Dose
7 years and older	10 mg INH twice daily[43] (A second dose should be administered on the first day of treatment whenever possible, provided there is at least 2 hours between doses. On subsequent days, doses should be 12 hours apart at approximately the same time each day.[43])
Younger than 7 years	Health Canada has not approved INH zanamivir for use in this age group.[43]

Table 7 provides age-based dosing information from the European Medicines Agency for IV zanamivir to treat severe seasonal influenza, an off-label indication in Canada. No dose adjustment of IV zanamivir is required for obese patients.[29] Consultation with an infectious diseases specialist is strongly recommended to inform individualized treatment if off-label use of the drug is being considered.

Table 7. Intravenous Zanamivir Dosing for Treatment of Severe Seasonal Influenza‡‡

Age	Dose
18 years and older	600 mg IV every 12 hours[89]
6 years to younger than 18 years	12 mg/kg IV every 12 hours (up to a maximum of 600 mg/dose)[89]
6 months to younger than 6 years	14 mg/kg IV every 12 hours[89]

‡‡ IV zanamivir for the treatment of severe seasonal influenza is considered off-label use in Canada.

The recommended treatment duration for zanamivir is 5 days.[3,19] In exceptional circumstances where a prolonged course of zanamivir therapy beyond 5 days may be considered for selected patients (e.g., immunocompromised patients with persistent symptoms and evidence of ongoing viral replication), consultation with an infectious diseases specialist is strongly recommended. Extended courses of antiviral therapy may increase the risk of developing of antiviral resistance.[7]

Dose adjustment for renal impairment

No dose adjustment is provided for INH zanamivir in the manufacturer's labelling for individuals with renal impairment.[43]

Table 8, *Table 9*, *Table 10* and *Table 11* provide age- and weight-specific IV zanamivir dosing information for the treatment of severe seasonal influenza in individuals with renal impairment.

Table 8. IV Zanamivir Dosing for Severe Seasonal Influenza Treatment in Individuals Aged 6 Years and Older with a Body Weight of 50 kg or Above

Creatinine Clearance (mL/min) or Renal Replacement Modality	Dose
80 and above	600 mg IV every 12 hours[89]
50 to less than 80	Initial dose of 600 mg IV, then maintenance doses of 400 mg IV every 12 hours (begin maintenance dose 12 hours after the initial dose)[89]
30 to less than 50	Initial dose of 600 mg IV, then maintenance doses 250 mg IV every 12 hours (begin maintenance dose 12 hours after the initial dose)[89]
15 to less than 30	Initial dose of 600 mg IV, then maintenance doses 150 mg IV every 12 hours (begin maintenance dose 24 hours after the initial dose)[89]
Less than 15	Initial dose of 600 mg IV, then maintenance doses 60 mg IV every 12 hours (begin maintenance dose 48 hours after the initial dose)[89]
IHD	Initial dose of 600 mg IV, then maintenance doses 60 mg IV every 12 hours (begin maintenance dose 48 hours after the initial dose; on dialysis days, administer the dose after the dialysis session)[89,90]
CAPD	Initial dose of 600 mg IV, then maintenance doses 60 mg IV every 12 hours (begin maintenance dose 48 hours after the initial dose)[91]

Table 9. IV Zanamivir Dosing for Severe Seasonal Influenza Treatment in Individuals Aged 6 Years to Less than 18 Years with Body Weight Less Than 50 kg

Creatinine Clearance (mL/min) or Renal Replacement Modality	Dose
80 and above	12 mg/kg IV every 12 hours (up to a maximum of 600 mg/dose)[89]
50 to less than 80	Initial dose of 12 mg/kg IV, then maintenance doses of 8 mg/kg IV every 12 hours (begin maintenance dose 12 hours after the initial dose)[89]
30 to less than 50	Initial dose of 12 mg/kg IV, then maintenance doses of 5 mg/kg IV every 12 hours (begin maintenance dose 12 hours after initial dose)[89]
15 to less than 30	Initial dose of 12 mg/kg IV, then maintenance doses of 3 mg/kg IV every 12 hours (begin maintenance dose 24 hours after initial dose)[89]
Less than 15	Initial dose of 12 mg/kg IV, then maintenance doses of 1.2 mg/kg IV every 12 hours (begin maintenance dose 48 hours after initial dose).[89]
IHD	Initial dose of 12 mg/kg IV, then maintenance doses of 1.2 mg/kg IV every 12 hours (begin maintenance dose 48 hours after initial dose; on dialysis days, administer the dose after the dialysis session).[89,91]
CAPD	Initial dose of 12 mg/kg IV, then maintenance doses of 1.2 mg/kg IV every 12 hours (begin maintenance dose 48 hours after initial dose).[89,91]

Table 10. IV Zanamivir Dosing for Severe Seasonal Influenza Treatment in Individuals Aged 6 Months to Younger than 6 Years with a Body Weight of 42.8 kg or Above

Creatinine Clearance (mL/min) or Renal Replacement Modality	Dose
80 and above	14 mg/kg IV every 12 hours[89]
50 to less than 80	Initial dose of 600 mg/kg IV, then maintenance doses of 400 mg IV every 12 hours (begin maintenance dose 12 hours after the initial dose)[89]
30 to less than 50	Initial dose of 600 mg IV, then maintenance doses of 250 mg IV every 12 hours (begin maintenance dose 12 hours after the initial dose)[89]
15 to less than 30	Initial dose of 600 mg IV, then maintenance doses of 150 mg IV every 12 hours (begin maintenance dose 24 hours after the initial dose)[89]
Less than 15	Initial dose of 600 mg IV, then maintenance doses of 60 mg IV every 12 hours (begin maintenance dose 48 hours after the initial dose)[89]
IHD	Initial dose of 600 mg IV, then maintenance doses of 60 mg IV every 12 hours (begin maintenance dose 48 hours after the initial dose; on dialysis days, administer the dose after the dialysis session)[89,91]
CAPD	Initial dose of 600 mg IV, then maintenance doses of 60 mg IV every 12 hours (begin maintenance dose 48 hours after the initial dose)[89,91]

Table 11. IV Zanamivir Dosing for Severe Seasonal Influenza Treatment in Individuals Aged 6 Months to Younger than 6 Years with a Body Weight Less Than 42.8 kg

Creatinine Clearance (mL/min) or Renal Replacement Modality	Dose
80 and above	14 mg/kg IV every 12 hours[89]
50 to less than 80	Initial dose of 14 mg/kg IV, then maintenance doses of 9.3 mg/kg IV every 12 hours (begin maintenance dose 12 hours after the initial dose)[89]
30 to less than 50	Initial dose of 14 mg/kg IV, then maintenance doses of 5.8 mg/kg IV every 12 hours (begin maintenance dose 12 hours after initial dose)[89]
15 to less than 30	Initial dose of 14 mg/kg IV, then maintenance doses of 3.5 mg/kg IV every 24 hours (begin maintenance dose 24 hours after initial dose)[89]
Less than 15	Initial dose of 14 mg/kg IV, then maintenance doses of 1.4 mg/kg IV every 12 hours (begin maintenance dose 48 hours after initial dose)[89]
IHD	Initial dose of 14 mg/kg IV, then maintenance doses of 1.4 mg/kg IV every 12 hours (begin maintenance dose 48 hours after initial dose; on dialysis days, administer the dose after the dialysis session) [89,91]
CAPD	Initial dose of 14 mg/kg IV, then maintenance doses of 1.4 mg/kg IV every 12 hours (begin maintenance dose 48 hours after initial dose)[89,91]

Dose adjustment for hepatic impairment

No dose adjustment is provided for INH or IV zanamivir in the manufacturer's labelling for individuals with hepatic impairment.[43,89]

Administration considerations

Inhalation formulation

The inhalation formulation of zanamivir is not recommended for individuals who require administration of the drug by nebulization or mechanical ventilation.[43] Lactose contained in the inhaled powder formulation may obstruct proper functioning of the equipment and compromise patient safety if made into an extemporaneous solution.[43]

The zanamivir inhaler device does not require the patient to coordinate release of the dose with inspiration.[92] However, proper administration technique may be challenging for some patients such as young children, individuals with cognitive impairment or impaired manual dexterity.[92,93]

Intravenous formulation

The IV formulation of zanamivir should not be administered via nebulizer to intubated patients.[5]

Clinically relevant contraindications

Zanamivir is contraindicated in patients who are hypersensitive to the drug or to any ingredient in the formulation.[43,89] The inhalation formulation of zanamivir contains lactose, which contains milk protein.[43]

Clinically relevant drug-drug interactions

Clinically significant drug-drug interactions with zanamivir are unlikely.[43,89] Zanamivir has low protein binding, does not undergo hepatic metabolism and is excreted unchanged in urine.[43,89]

Clinically relevant adverse effects

The inhalation formulation of zanamivir may trigger serious bronchospasm in individuals with underlying airway disease (e.g., asthma, chronic obstructive pulmonary disease).[19] Sinusitis and dizziness have been reported with zanamivir use.[19] Rare cases of neuropsychiatric events have been reported in individuals treated with zanamivir (e.g., self-injury or delirium were reported primarily among children).[43,89] A causal link between the use of zanamivir and neuropsychiatric events has not been established.[43] However, influenza infection can also cause neuropsychiatric symptoms.[80]

The list of potential adverse effects listed above is not exhaustive. See the zanamivir product monographs in the ***Additional Resources*** section for more information.

Pregnancy

INH zanamivir may be used during pregnancy.[83] However, the risk of impaired pulmonary distribution of inhaled zanamivir may be increased during the second and third trimesters of pregnant individuals due to the reduced vital capacity of their lungs.[94] An association between an increased risk of adverse pregnancy outcomes and INH zanamivir use has not been shown by the limited data from case reports and observational studies.[83]

There is insufficient data regarding the use of IV zanamivir in pregnant people to determine the risk of adverse pregnancy outcomes.[89] In animal studies, no drug-related embryotoxicity, fetal malformations or maternal toxicity were observed following IV administration of zanamivir at doses up to 90 mg/kg/day.[43]

There is no information about the placental transfer of zanamivir in humans.[83,89] Animal studies have demonstrated placental transfer of zanamivir after treatment with INH or IV zanamivir, but there was no evidence of teratogenicity.[43,83,89]

Breastfeeding or chest-feeding

Zanamivir may be used by people who are breastfeeding or chest-feeding.[83,86]

There is no published evidence on the use of zanamivir in people who are breastfeeding.[83,86] It is unknown whether zanamivir is excreted in human milk.[43,89] However, zanamivir transfer in human milk is likely due to its low molecular weight, low plasma protein binding, moderately long elimination half-life and lack of hepatic metabolism.[83] In animal studies of rats, low amounts of zanamivir were detected in milk.[89]

The effect of zanamivir exposure in a nursing infant is unknown. However, systemic absorption after inhalation of zanamivir is low and only a minimal amount of the drug is expected to pass into human milk.[86] Use of IV zanamivir will likely result in higher serum concentrations and more of the drug may pass into human milk.[86] However, zanamivir has poor bioavailability and a relatively short half-life so the amount absorbed by the nursing infant is limited and not expected to cause significant adverse effects.[86]

Peramivir

Dose and duration for treatment of severe seasonal influenza

Peramivir is not approved to treat severe seasonal influenza in Canada.[60] Consultation with an infectious diseases specialist is strongly recommended to inform individualized treatment if off-label use of the drug is being considered.

Table 12 summarizes the United States (US) Food and Drug Agency's (FDA) recommendations for peramivir dosing when the drug was authorized for emergency use to treat severe influenza A(H1N1) in selected hospitalized patients.[95] Peramivir dosing does not require adjustment based on patient weight in individuals aged 18 years and older.[60]

The optimal duration of peramivir therapy for the treatment of severe seasonal influenza infection is unknown.[5] One clinical trial used peramivir for a minimum of 5 days to treat hospitalized patients with severe seasonal influenza.[19,96]

Table 12: Peramivir Dosing for Treatment of Severe Seasonal Influenza

Age	Dose[95]
18 years and older	600 mg IV once daily
6 through 17 years	10 mg/kg IV once daily (up to a maximum of 600 mg)
181 days through 5 years	12 mg/kg IV once daily (up to a maximum of 600 mg)
91 through 180 days	10 mg/kg IV once daily[##]
31 through 90 days	8 mg/kg IV once daily[##]
Birth through 30 days	6 mg/kg IV once daily[##]

[##] The safety of peramivir in patients younger than 6 months of age has not been established in clinical trials. Post-marketing studies have reported peramivir use in children as young as 28 days of age.[97–99] The FDA's peramivir dosing recommendations for children younger than 6 months of age are based on modelling and simulation of pharmacokinetic data from adults.[95]

Dose adjustment for renal impairment

Table 13 provides peramivir dosing information for adults with severe seasonal influenza and renal impairment.

Table 13: Peramivir Dose for Treatment of Severe Seasonal Influenza in Individuals Aged 18 Years and Older with Renal Impairment

Creatinine Clearance (mL/min) or Renal Replacement Modality	Dose[95]
Equal to or greater than 50	No dose adjustment required
31 to 49	150 mg IV once daily
10 to 30	100 mg IV once daily
Less than 10	100 mg IV on day 1, then 15 mg IV once daily starting on day 2
IHD	100 mg IV once, then 100 mg IV given 2 hours after each IHD session on dialysis days only
CAPD	There is no information available specific to the administration of peramivir in patients receiving CAPD.

Table 14 provides peramivir dosing information for children with severe seasonal influenza and renal impairment.

Table 14: Peramivir Dose for Treatment of Severe Seasonal Influenza in Children with Renal Impairment***

Age	Estimated Glomerular Filtration Rate (mL/min/1.73 m^2) or Renal Replacement Modality[95]				
	50-80	31-49	10-30	Less than 10 and not receiving dialysis	IHD
6 through 17 years	10 mg/kg IV once daily (up to a maximum of 600 mg/day)[100]	2.5 mg/kg IV once daily (up to a maximum of 150 mg/day)[100]	1.6 mg/kg IV once daily (up to a maximum of 100 mg/day)[100]	1.6 mg/kg IV on day 1 (up to a maximum of 100 mg/day), then 0.25 mg/kg once IV daily starting on day 2 (up to a maximum of 15 mg/day)[100]	1.6 mg/kg IV on day 1, then 1.6 mg/kg IV given 2 hours after each IHD session on dialysis days only (up to a maximum of 100 mg/day)[100]
181 days old through 5 years	12 mg/kg IV once daily	3 mg/kg IV once daily	1.9 mg/kg IV once daily	1.9 mg/kg IV on day 1, then 0.3 mg/kg once IV daily starting on day 2	1.9 mg/kg IV on day 1, then 1.9 mg/kg IV given 2 hours after each IHD on dialysis days only
91 days through 180 days	10 mg/kg IV once daily	2.5 mg/kg IV once daily	1.6 mg/kg IV once daily	1.6 mg/kg IV on day 1, then 0.25 mg/kg once IV daily starting on day 2	1.6 mg/kg IV on day 1, then 1.6 mg/kg IV given 2 hours after each IHD on dialysis days only
31 days through 90 days	8 mg/kg IV once daily	2 mg/kg IV once daily	1.3 mg/kg IV once daily	1.3 mg/kg IV on day 1, then 0.2 mg/kg IV once daily starting on day 2	1.3 mg/kg IV on day 1, then 1.3 mg/kg IV given 2 hours after each IHD on dialysis days only
Birth through 30 days	6 mg/kg IV once daily	1.5 mg/kg IV once daily	1 mg/kg IV once daily	1mg/kg IV on day 1, then 0.15 mg/kg once IV daily starting on day 2	1 mg/kg IV on day 1, then 1 mg/kg IV given 2 hours after each IHD on dialysis days only

*** Dosing information for children was derived from modelling and simulation of pharmacokinetic data from adult healthy volunteers, adult patients with influenza and information on renal maturation and body weight.[95]

Dose adjustment for hepatic impairment

No dose adjustment is provided in the manufacturer's labelling for peramivir in individuals with hepatic impairment.[61]

Clinically relevant contraindications

Peramivir is contraindicated in patients who are hypersensitive to the drug or to any ingredient in the formulation.[61]

Clinically relevant drug-drug interactions

The potential for drug interactions is low because peramivir is not a substrate for CYP enzymes.[61]

Clinically relevant adverse effects

The most commonly reported adverse effect of peramivir is diarrhea.[61] Clinically significant laboratory abnormalities reported in clinical trials following peramivir use include neutropenia (neutrophils less than 1 x 10^9/L), increase in alanine aminotransferase (greater than 2.5 times the upper limit of normal [ULN]) and increase in creatinine phosphokinase (equal to greater than or 6 times ULN).[61] Post-marketing studies have identified anaphylaxis and serious skin reactions (e.g., Stevens-Johnson syndrome) as rare adverse effects of peramivir use.[61] Neuropsychiatric events (e.g., hallucinations, delirium) have been reported following peramivir use.[61] A causal link between the use of zanamivir and neuropsychiatric events has not been established.[61] However, Influenza infection can also cause neuropsychiatric symptoms.[80]

The list of potential adverse effects listed above is not exhaustive, see the peramivir product monographs in the ***Additional Resources*** section for more information.

Pregnancy

Peramivir may be considered for use during pregnancy.[83] Although the placental transfer of peramivir in humans is unknown, peramivir is expected to cross the placenta due to its low molecular weight, low plasma protein binding, long elimination half-life and absence of significant drug metabolism.[83] In animal studies, fetal abnormalities (e.g., reduced renal papilla, dilated ureters) were observed in rats when peramivir was administered as a continuous infusion.[83] However, no maternal or fetal adverse effects were observed in rats when peramivir was administered as an IV bolus at 8 times the recommended human dose.[83]

Breastfeeding or chest-feeding

Peramivir use has not been studied in breastfeeding or chest-feeding individuals.[83] Peramivir is expected to be excreted into breast milk due to its low molecular weight, low plasma binding, absence of significant metabolism and long elimination half-life.[83] However, peramivir is poorly absorbed from the gastrointestinal tract so it is unlikely that significant amounts of peramivir from breast milk will enter the baby's system.[87]

Baloxavir

Dose and duration for seasonal influenza treatment

Table 15 provides weight-based dosing recommendations for baloxavir to treat non-severe seasonal influenza. No dose adjustment is necessary for obese patients.[32]

A single dose of baloxavir is recommended to treat non-severe seasonal influenza.[32]

In exceptional circumstances where an extended course of baloxavir therapy may be considered for selected patients (e.g., immunocompromised patients with persistent symptoms and evidence of ongoing viral replication), consultation with an infectious diseases specialist is strongly recommended. Extended courses of antiviral therapy may increase the risk of developing of antiviral resistance.[7]

Table 15. Baloxavir Dose for Non-Severe Seasonal Influenza Treatment in Individuals Aged 5 Years and Older†††

Weight	Dose
Less than 15 kg	Single dose of 2 mg/kg[33]
15 kg to less than 20 kg	Single dose of 30 mg[33]
20 kg to less than 80 kg	Single dose of 40 mg[33]
80 kg or greater	Single dose of 80 mg[32]

††† Baloxavir for the treatment of non-severe seasonal influenza in individuals younger than 12 years old who weigh less than 40 kg is considered off-label use in Canada. Baloxavir dosing information for individuals aged 5 years to younger than 12 years is adapted from the US baloxavir product monograph where the drug is approved for the treatment of non-severe seasonal influenza in individuals aged 5 years and older.[32]

Baloxavir is not approved to treat severe seasonal influenza in Canada or the US.[32,33] Consultation with an infectious diseases specialist is strongly recommended to inform individualized treatment if baloxavir is considered for off-label use. *Table 16* summarizes the baloxavir dosing regimen and treatment duration used by a clinical trial to treat severe seasonal influenza in patients aged 12 years and older.[70]

Table 16. Baloxavir Dosing for Severe Seasonal Influenza Treatment in Individuals Aged 12 Years and Older‡‡‡

Weight	Dose
40 kg to less than 80 kg	40 mg on day 1 and day 4, with an additional dose on day 7 if no clinical improvement by day 5###,[70]
80 kg or greater	80 mg on day 1 and day 4, with an additional dose on day 7 if no clinical improvement by day 5###,[70]

‡‡‡ Baloxavir is not approved to treat severe seasonal influenza in Canada.[32]
No clinical improvement was defined in the clinical trial as fulfilling at least one of the following criteria: ongoing mechanical ventilation, persistent fever, being severely immunocompromised, having pneumonia, confirmed or suspected influenza-related complication.[70]

Dose adjustment for renal impairment

No dose adjustment for baloxavir is provided in the manufacturer's labelling for individuals with renal impairment.[32] The safety and efficacy of baloxavir have not been established in patients with renal impairment.[32,70] As baloxavir is primarily excreted through the fecal pathway, renal impairment is unlikely to have a significant impact on its clearance.[32]

Dose adjustment for hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment.[32] Baloxavir has not been studied in patients with severe hepatic impairment.[32]

Administration considerations

Crushing or splitting baloxavir tablets is not recommended.[101]

Extemporaneous preparation of baloxavir tablets into an oral solution has not been studied in humans.[101] However, whole baloxavir tablets may be dissolved in 100 mL of water to make an oral solution for patients with difficulty swallowing tablets according to the manufacturer.[101] The oral solution should be prepared immediately prior to dose administration. The safety and efficacy of administering partial doses from extemporaneous preparations of baloxavir have not been evaluated.[101]

Clinically relevant contraindications

Baloxavir is contraindicated in patients who are hypersensitive to the drug or to any ingredient in the formulation.[32]

Clinically relevant drug-drug interactions

Baloxavir should not be administered with products containing polyvalent cation (e.g., dairy products, calcium-fortified beverages, polyvalent cation containing laxatives or antacids, or oral supplements containing iron, zinc, selenium, calcium, magnesium) due to decreased baloxavir absorption.[32]

Clinically relevant adverse effects

Baloxavir is generally well tolerated.[102] Reported adverse effects include nausea, sinusitis and headache.[19] Cases of hypersensitivity reactions, including anaphylaxis, have been reported after baloxavir use in post-marking studies.[19,44] Although neuropsychiatric events have been reported following baloxavir use, a causal link has not been established.[102] However, influenza infection can also cause neuropsychiatric symptoms.[80]

The list of potential adverse effects listed above is not exhaustive. See the baloxavir product monographs in the ***Additional Resources*** section for more information.

Pregnancy

Baloxavir is not recommended for the treatment of influenza during pregnancy because its use has not been studied in pregnant people.[13,19,83]

It is not known if baloxavir crosses the human placenta.[83] However, baloxavir is expected to cross the human placenta due to its low molecular weight.[83,103] In animal studies, no fetal malformations were observed at exposures 2 to 3 times the human exposure of the maximum recommended dose.[32]

Breastfeeding or chest-feeding

Baloxavir is not recommended for the treatment of influenza in people who are breastfeeding.[13,19] It is not known whether baloxavir is excreted in human milk, but the drug is expected to pass into human milk due to its low molecular weight.[83,104] Animal studies have demonstrated the transfer of baloxavir into the milk of lactating rats.[32] The effect of baloxavir on the nursing infant is unknown.[13,19]

Additional Resources

- Ontario Health: Influenza Clinical Guidelines and Resources
- Ministry of Health: Ontario public health standards - influenza
- Ministry of Health: Universal influenza immunization program
- Public Health Ontario: Laboratory testing for influenza
- Public Health Ontario: Best practices for the prevention of acute respiratory infection transmission in all health care settings
- Association of Medical Microbiology and Infectious Disease Canada: Influenza
- Canadian Paediatric Society: The use of antiviral drugs for influenza
- American Academy of Pediatrics: Influenza
- U.S. Centers for Disease Control and Prevention: Influenza
- U.K. Health Security Agency: Influenza treatment and prophylaxis using antiviral agents
- World Health Organization 2024: Clinical practice guidelines for influenza
- Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza
- Public Health Agency of Canada: Canadian immunization guide - influenza vaccines
- Product monographs
  - Baloxavir product monograph (Canada)
  - Baloxavir product monograph (U.S.)
  - Oseltamivir product monograph (Canada)
  - Peramivir product monograph (Canada)
  - Peramivir product monograph (U.S.)
  - Zanamivir (inhaled) product monograph (Canada)
  - Zanamivir (IV) product monograph (European Medicines Agency)

Questions

For any questions on the contents of this document, please contact the Provincial Drug Reimbursement Programs (PDRP) at OH-CCO_InfoPDRP@ontariohealth.ca.

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About IDAC

The Ontario Health Infectious Diseases Advisory Committee (IDAC) provides Ontario Health with timely evidence-based clinical and health system guidance on infectious diseases matters. It is a multidisciplinary committee comprised of health care professionals practising throughout Ontario who specialize or have a focus in treating infectious diseases in the hospital or community setting.

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Disclosures

Ontario Health Infectious Diseases Program staff and IDAC members must disclose conflicts of interest. Depending on the nature of the disclosure, Ontario Health will develop and implement a mitigation plan with strategies to address the disclosure.

The Ontario Health Infectious Diseases Program staff reports no disclosures for conflicts of interest.

One IDAC member had received honoraria for speaking engagements from GlaxoSmithKline. Mitigation strategies have been developed and implemented to address this disclosure.

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