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This document is provided by the Scientific Advisory Committee. The recommendations are interim and based on information available at the time of development. This document is subject to review and change as new information becomes available, given the emerging situation of Influenza A H1N1 (SOIV).

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## Interim Treatment Recommendations for Pregnant & Breastfeeding Women with H1N1 (SOIV)

### Background:

- Neuraminidase inhibitors have been deemed effective treatment options in the context of H1N1 (SOIV) infection.
- Available options include: oseltamivir (Tamiflu®) and zanamivir (Relenza®).
- Oseltamivir and zanamivir are both rated risk category C (FDA) in pregnancy.
- Pregnant women have been identified as a group at increased risk for severe disease from influenza, and of influenza-related complications, both with seasonal influenza viruses, and with H1N1 (SOIV).

### **A1. Interim Recommendations for treatment of pregnant women with confirmed\* H1N1 (SOIV) infection**

1. Pregnant women with confirmed H1N1 (SOIV) infection should be counseled about the increased risk of severe illness and influenza-related complications in pregnant women, and they should be offered treatment in this context.
2. Treatment should ideally be initiated within 48 hours of symptom onset and as soon as possible, but may be considered after 48 hours of onset of illness in severe cases.
3. Treatment with either zanamivir or oseltamivir is considered acceptable choices in pregnancy.
4. Pregnant women should be offered the choice of either inhaled zanamivir or oral oseltamivir. Zanamivir **may be the preferred choice** for many pregnant women as it is administered by inhalation and is poorly absorbed systemically.

***In cases of severe disease***, oseltamivir **may be the preferred choice** based on a theoretical risk of systemic viremia.

Oseltamivir may also be preferred for patients with a history of severe asthma or severe reactive airways to avoid potential bronchospasm which could be associated with zanamivir use.

Infectious Disease specialist consultation is advised if further assistance is needed in choosing the most appropriate treatment plan.

*\* Laboratory confirmation of influenza A H1N1 (SOIV) virus infection with or without clinical symptoms is by one or more of the following tests: RT-PCR, viral culture, or a four-fold rise in swine influenza A (H1N1) virus specific neutralizing antibodies. Treatment should also be considered for pregnant women with "non-typeable" influenza A, while awaiting the final confirmatory typing results. Public Health may consider treatment of symptomatic household contacts of confirmed cases of H1N1 (SOIV), if the ill household contact is at an increased risk of complications related to influenza (including pregnant women).*

## **A2. Interim Recommendations for treatment of pregnant women who are close or household contacts of confirmed cases of H1N1 (SOIV)**

Public Health recommends early treatment of close or household contacts of confirmed cases of Influenza A H1N1 (SOIV) if the contact:

- has typical influenza-like illness (fever and cough or myalgias or sore throat), and
- is at high risk for influenza-related complications, and
- presents within 48 hours of symptom onset.

Pregnant women are at high risk for influenza-related complications and should be offered treatment if they meet the other criteria. (Refer to the treatment recommendations for pregnant women with confirmed H1N1 (SOIV) infection for specific anti-viral recommendations.)

## **B1. Interim Recommendations for treatment of breastfeeding women with confirmed H1N1 (SOIV)**

1. Breastfeeding women should be counseled about the modes of transmission of influenza, about effective hand washing, and to consider using a mask when breastfeeding to protect their nursing child from respiratory infection. They should be encouraged to **continue** breastfeeding. (Please refer to recommendations for breastfeeding practices below).
2. Treatment is indicated for most symptomatic breastfeeding women on the basis that their household contacts (children under 24 months of age) are identified as vulnerable contacts. They should be counseled about the theoretical risks and benefits of antiviral therapy in breastfeeding, and offered treatment in this context.
3. When treatment is indicated for breastfeeding women, either zanamivir or oseltamivir would be considered acceptable, but the **preferred** agent is zanamivir. Oseltamivir may be considered as an alternative when zanamivir is not well tolerated, or when the mother is known to have severe reactive airway disease, or severe influenza infection.

## **B2. Interim Recommendations for breastfeeding practices in the context of Influenza A H1N1 (SOIV)**

Though there is no specific information about breastfeeding and this new influenza virus, the following recommendations are based on experience from seasonal influenza. The risk of transmission of virus through breast milk is unknown but thought to be very small because reports of viremia that could result in influenza virus in breast milk during seasonal influenza are extremely rare.

1. Various agencies (CDC and the Academy of Breastfeeding Medicine) recommend that breastfeeding mothers who have confirmed/probable/suspect influenza A H1N1 (SOIV) continue to breastfeed and even increase feeding because breastfeeding can limit the severity of respiratory infections in infants. Clinicians should promote this recommendation during influenza outbreaks.
2. Infants who are ill with confirmed/probable/suspect influenza A H1N1 should continue to breastfeed for the same reason.
3. If mother or infant are too ill to breastfeed, breast milk should be pumped and given as expressed milk to the infant.

4. A mother who is ill may use a mask to reduce the risk of transmission to her nursing infant. Respiratory etiquette should be practiced at all times, avoiding coughing or sneezing into the infant's face.
5. Parents should limit close contact of the infant to non-caregivers, and avoid taking the infant out into crowds.

Good hygiene measures should be practiced:

- washing adult and infant hands frequently with soap and water, especially after infants place their hands in theirs or others' mouths
- limiting sharing of toys and other items that have been in infants' mouths, and cleaning them after use
- keeping pacifiers out of adults' mouths or other infants' mouths prior to giving to the infant

## SELECTED REFERENCES:

Dodds L, McNeil SA, Fell DB, et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. CMAJ 2007;176:463--8.

Novel Influenza A (H1N1) Virus Infections in Three Pregnant Women --- United States, April--May 2009. MMWR May 12, 2009 / 58(Dispatch);1-3.

McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis 2007;45:1568-75.

UD Allen, FY Aoki, HG Stiver, for the Canadian Paediatric Society and the Association of Medical Microbiology and Infectious Disease Canada. The use of antiviral drugs for

influenza: Recommended guidelines for practitioners. Can J Infect Dis Med Microbiol 2006;17(5):273-284.

CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. MMWR 2008;57(No. RR-7).

Annex E - The Use of Antiviral Drugs in Canada During a Pandemic (Updated: May 12, 2009) [http://www.phac-aspc.gc.ca/cpip-pclcpi/pdf-e/annex\\_e0513-eng.pdf](http://www.phac-aspc.gc.ca/cpip-pclcpi/pdf-e/annex_e0513-eng.pdf).

Accessed May 19, 2009.

Management guidelines for pregnant women and neonates born to women with suspected or confirmed swine-origin H1N1 influenza A (draft), May 8 2009.

[http://bcphp.ca/sites/bcrp/files/spotlight/guideline\\_h1n1\\_interim\\_draft.pdf](http://bcphp.ca/sites/bcrp/files/spotlight/guideline_h1n1_interim_draft.pdf)

Accessed May 17, 2009.

CDC. What Pregnant Women Should Know About H1N1 (formerly called swine flu) Virus May 3, 2009 3:00 PM ET [www.cdc.gov/h1n1flu/guidance/pregnant.htm](http://www.cdc.gov/h1n1flu/guidance/pregnant.htm) Accessed May 19, 2009

Academy of Breastfeeding Medicine. Breastfeeding and H1N1 Influenza A – Information for Physicians. <http://www.bfmed.org/> Accessed May 19, 2009

<b>Medications and selected background information:</b>		
<b>Medication</b>	zanamivir	oseltamivir
<b>Pregnancy risk category</b>	<p><b>Rating C (FDA)</b></p> <p>Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.</p> <p><b>from Micromedix:</b></p> <p><b>A) Teratogenicity/Effects in Pregnancy</b>  <b>1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Relenza®, 2003) (All Trimesters)</b>  <b>a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.</b>            See Drug Consult reference: <a href="#">PREGNANCY RISK CATEGORIES</a>  <b>2) Crosses Placenta: Unknown</b>  <b>3) Clinical Management</b>  <b>a) Zanamivir has been shown to cross the placenta in rats and rabbits (Prod Info Relenza®, 2003). There is insufficient clinical experience with zanamivir to confirm its safety in human pregnancy. Zanamivir should only be used in women during pregnancy if the maternal benefit justifies the potential risk to the fetus (Prod Info Relenza®, 2003).</b>  <b>4) Literature Reports</b>  <b>a) No reports describing the use of zanamivir during human pregnancy have been located. According to the manufacturer, fertility studies in rats did not show adverse reproductive effects in males and females given intravenous doses of up to 90 mg/kg/day. It was estimated that this dose would produce blood concentrations (AUC) more than 300 times the human dose in humans using inhalation therapy. No malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses using a similar dose. Zanamivir crosses the placenta in rats and rabbits, although fetal blood concentrations are considerably lower than those in the mother (Prod Info Relenza(R), 2003).</b>  <b>b) The offspring of rats given zanamivir doses of 1, 9, or 80 mg/kg three times daily (highest dose approximates 1000 times the maximum recommended human exposure) from days 7 to 17 of gestation showed an increased incidence of minor skeletal alterations. However, the individual incidence rates of the malformations remained within that normally expected in the population (Prod Info Relenza(R), 2003).</b></p> <p><b>from Lexidrug:</b></p> <p>PREGNANCY IMPLICATIONS — Zanamivir has</p>	<p><b>Rating C (FDA)</b></p> <p>Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.</p> <p><b>from Micromedix:</b></p> <p><b>A) Teratogenicity/Effects in Pregnancy</b>  <b>1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Tamiflu®, 2001a) (All Trimesters)</b>  <b>a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.</b>            See Drug Consult reference: <a href="#">PREGNANCY RISK CATEGORIES</a>  <b>2) Crosses Placenta: Unknown</b>  <b>3) Clinical Management</b>  <b>a) There is insufficient clinical experience with oseltamivir to confirm its safety in pregnancy. Until additional data are available, caution should be exercised with the use of oseltamivir in pregnant women.</b>  <b>4) Literature Reports</b>  <b>a) No human studies of pregnancy outcomes after exposure to oseltamivir have been published, and there have been no reports of outcomes after inadvertent exposure during pregnancy.</b></p> <p><b>from Lexidrug:</b></p> <p>PREGNANCY IMPLICATIONS — There are insufficient</p>

	<p>been shown to cross the placenta in animal models, however, no evidence of fetal malformations has been demonstrated. There are no adequate and well-controlled studies in pregnant women.</p>	<p>human data to determine the risk to a pregnant woman or developing fetus. Studies evaluating the effects on embryo-fetal development in rats and rabbits showed a dose-dependent increase in the rates of minor skeleton abnormalities in exposed offspring. The rate of each abnormality remained within the background rate of occurrence in the species studied.</p>
<b>Breastfeeding</b>	<p><b>from Lexidrugs:</b></p> <p>LACTATION — Excretion in breast milk unknown/use caution</p> <p>BREAST-FEEDING CONSIDERATIONS — Zanamivir has been shown to be excreted in the milk of animals, but its excretion in human milk is unknown. Caution should be used when zanamivir is administered to a nursing mother.</p> <p><b>from Micromedix:</b></p> <p><b>B) BREASTFEEDING</b></p> <p><b>1) Thomson Lactation Rating:</b> Infant risk cannot be ruled out.</p> <p><b>a)</b> Available evidence and/or expert consensus are inconclusive or are inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.</p> <p><b>2) Clinical Management</b></p> <p><b>a)</b> It is not known if zanamivir is excreted into human breast milk, although it has been shown to be present in the milk of lactating rats (Prod Info Relenza®, 2003a). The effects on the nursing infant from possible exposure to the drug in milk are unknown. Zanamivir should be used with caution in nursing women (Prod Info Relenza®, 2003a).</p> <p><b>3) Literature Reports</b></p> <p><b>a)</b> No reports describing the use of zanamivir during human lactation or measuring the amount, if any, of the drug excreted into milk have been located.</p>	<p><b>from Lexidrugs:</b></p> <p>LACTATION — Enters breast milk/not recommended</p> <p>BREAST-FEEDING CONSIDERATIONS — Oseltamivir and its carboxylate metabolite have been detected in breast milk. Breast milk samples were obtained from a single patient (~9 months post-partum) over the course of 5 days of treatment. The maximum total concentration of oseltamivir (expressed as parent drug and metabolite) was 81.6 ng/mL. Using a milk concentration of 81.6 ng/mL, the estimated exposure to the breastfeeding infant would be ~0.5% of the weight adjusted maternal dose (in a 60 kg woman).</p> <p><b>from Micromedix:</b></p> <p><b>B) BREASTFEEDING</b></p> <p><b>1) Thomson Lactation Rating:</b> Infant risk cannot be ruled out.</p> <p><b>a)</b> Available evidence and/or expert consensus are inconclusive or are inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.</p> <p><b>2) Clinical Management</b></p> <p><b>a)</b> It is not known whether oseltamivir is excreted into human breast milk and the potential for adverse effects in the nursing infant from exposure to the drug are unknown.</p> <p><b>3) Literature Reports</b></p> <p><b>a)</b> No reports describing the use of oseltamivir during human lactation or measuring the amount, if any, of the drug excreted into milk have been located. Oseltamivir and oseltamivir carboxylate are excreted into the milk of lactating rats (Prod Info Tamiflu®2001).</p> <p><b>4) Drug Levels in breast milk</b></p> <p><b>a) Active Metabolites</b></p> <p><b>1) oseltamivir carboxylate (Prod Info Tamiflu®, 2001)</b></p>
<b>Adverse effects</b>	<p><b>from Lexidrugs:</b></p> <p>WARNINGS / PRECAUTIONS</p> <p>Concerns related to adverse effects:</p> <p>Allergic reactions: Allergic-like reactions, including anaphylaxis, oropharyngeal edema, and serious skin rashes have been reported.</p> <p>Neuropsychiatric events: Rare occurrences of neuropsychiatric events (including confusion, delirium, hallucinations, and/or self-injury) have been reported from post marketing surveillance; direct causation is difficult to establish (influenza infection may also be associated with behavioral and neurologic changes).</p> <p>Respiratory effects: Bronchospasm, decreased lung function, and other serious adverse reactions, including those with fatal outcomes,</p>	<p><b>from Lexidrugs:</b></p> <p>ADVERSE REACTIONS SIGNIFICANT</p> <p>&gt;10%: Gastrointestinal: Vomiting (2% to 15%)</p> <p>1% to 10%: Gastrointestinal: Nausea (3% to 10%), abdominal pain (2% to 5%)</p> <p>&lt;1% (Limited to important or life-threatening): Allergy, anaphylactic/anaphylactoid reaction, arrhythmia, confusion, dermatitis, diabetes aggravation, eczema, erythema multiform, hepatitis, liver function tests abnormal, neuropsychiatric events (self-injury, confusion, delirium), rash, seizure, Stevens-Johnson syndrome, swelling of face or tongue, toxic epidermal necrolysis, urticaria</p> <p>CONTRAINDICATIONS — Hypersensitivity to oseltamivir or any component of the formulation</p> <p>WARNINGS / PRECAUTIONS</p>

	<p>have been reported in patients with and without airway disease; discontinue with bronchospasm or signs of decreased lung function. For a patient with an underlying airway disease where a medical decision has been made to use zanamivir, a fast-acting bronchodilator should be made available, and used prior to each dose.</p> <p>Disease-related concerns:</p> <p>Renal impairment: Safety and efficacy of use in patients with severe renal impairment have not been established.</p> <p>Respiratory disease: Not recommended for use in patients with underlying respiratory disease, such as asthma or COPD, due to lack of efficacy and risk of serious adverse effects.</p>	<p>Concerns related to adverse effects:</p> <p>Anaphylaxis/hypersensitivity: Rare but severe hypersensitivity reactions (anaphylaxis, severe dermatologic reactions) have been associated with use.</p> <p>Neuropsychiatric events: Rare occurrences of neuropsychiatric events (including confusion, delirium, hallucinations, and/or self-injury) have been reported from post marketing surveillance; direct causation is difficult to establish (influenza infection may also be associated with behavioral and neurologic changes).</p> <p>Disease-related concerns:</p> <p>Cardiovascular disease: Use with caution in patients with chronic cardiac disease; efficacy has not been established.</p> <p>Hepatic impairment: Use with caution in patients with severe hepatic impairment; safety and efficacy have not been established.</p> <p>Renal impairment: Use with caution in patients with renal impairment; dosage adjustment is required for creatinine clearance &lt;30 mL/minute.</p> <p>Respiratory disease: Use with caution in patients with respiratory disease; efficacy has not been established.</p>
<p><b>Approximate cost for an Alberta regional hospital pharmacy:</b></p>	<p>\$35.70 for one treatment course.</p>	<p>\$ 39.00 for one treatment course.</p>
<p><b>Pharmacody Namics / Kinetics</b></p>	<p><b>from Lexidrugs:</b></p> <p>Absorption: Inhalation: ~4% to 17%</p> <p>Protein binding, plasma: &lt;10%</p> <p>Metabolism: None</p> <p>Half-life elimination, serum: 2.5-5.1 hours</p> <p>Excretion: Urine (as unchanged drug); feces (unabsorbed drug)</p>	<p><b>from Lexidrugs:</b></p> <p>Absorption: Well absorbed</p> <p>Distribution: Vd: 23-26 L (oseltamivir carboxylate)</p> <p>Protein binding, plasma: Oseltamivir carboxylate: 3%; Oseltamivir: 42%</p> <p>Metabolism: Hepatic (90%) to oseltamivir carboxylate; neither the parent drug nor active metabolite has any effect on the cytochrome P450 system</p> <p>Bioavailability: 75% as oseltamivir carboxylate</p> <p>Half-life elimination: Oseltamivir: 1-3 hours; Oseltamivir carboxylate: 6-10 hours</p> <p>Excretion: Urine (&gt;90% as oseltamivir carboxylate); feces</p>