

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
Regence BlueCross BlueShield of Utah • Regence BlueShield of Idaho
Independent licensees of the Blue Cross and Blue Shield Association**

Medication Policy Manual

Policy No: dru038

Topic: Tamiflu[®], oseltamivir

Date of Origin: January 2001

Revised/Effective Date: April 30, 2009

Next Review Date: April 2010

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Oseltamivir (Tamiflu[®]) is an anti-viral medication (neuraminidase inhibitor) administered orally for the treatment or prevention of influenza.

For the treatment of adults with influenza, the FDA-approved dose of oseltamivir is one capsule (75 mg) twice daily for five days (a total of 10 capsules per course).

For prevention of influenza in a household setting, the FDA-approved dose of oseltamivir is one capsule (75 mg) once daily for ten days (a total of 10 capsules per course).

Policy/Criteria

- I.** Most contracts require prior authorization approval of oseltamivir for coverage of quantities greater than 20 capsules (two courses), or six 25 ml bottles of suspension (two courses) every six months. Oseltamivir in quantities up to 20 capsules or six 25 ml bottles of suspension every six months may be considered medically necessary and may be covered without prior authorization.

- II.** Oseltamivir in quantities up to 42 capsules, or eleven 25 ml bottles of suspension (a six week course) every six months may be considered medically necessary for seasonal prophylaxis of influenza when both criteria A and B below are met.
 - A.** The current influenza vaccination is contraindicated or not effective against prevalent circulating strains.

AND

- B.** There is a high risk of complications from influenza (see Appendix 1 for high risk criteria).

III. Administration, Quantity Limitations and Authorization Period

- A.** Regence considers oseltamivir to be a self-administered medication.

- B.** When policy criteria are met, oseltamivir may be authorized in quantities up to 42 capsules, or eleven 25 ml bottles of suspension (a six week course) every six months. Quantities exceeding 42 capsules, or eleven 25 ml bottles of suspension every six months are considered investigational.

- C.** Authorization shall be reviewed every six months to confirm that medical necessity criteria are met and the medication is effective.

Position Statement

- Influenza vaccination is the primary method for preventing influenza and its severe complications particularly in individuals at high risk for influenza-related complications.
- Oseltamivir has only been shown to be effective for the treatment of influenza if started within the first two days of symptom onset. ^[2-8]
- One treatment course of oseltamivir every six months will provide coverage for the typical influenza season.

Summary

- Oseltamivir is used for:
 - * Treatment of uncomplicated acute illness due to influenza A and B virus in adults and children one year of age and older who have been symptomatic for no more than 2 days. ^[2]
 - * For prevention of influenza in adults and children one year of age and older. ^[2]
- Vaccination is the primary method of preventing and controlling influenza. ^[3] Therefore, prevention of influenza during community outbreaks with oseltamivir should be reserved for patients at high risk for the complications of influenza.
- Oseltamivir has only been shown to be effective for the treatment of influenza if started within the first two days of symptom onset. ^[5-16]
- The demonstrated benefit with neuraminidase inhibitors (oseltamivir and zanamivir) is limited to a modest increase in the rate of symptom improvement. ^[2-3, 18]
- There is renewed interest in use of oseltamivir because of the high rates of resistance reported to amantadine and rimantadine.
 - * Currently, up to 92% of influenza isolates are resistant to amantadine and rimantadine in the U.S. according to CDC reports. ^[8]
 - * The CDC does not currently recommend amantadine or rimantadine for the prevention or treatment of influenza virus. ^[8]

- There has been an increase in oseltamivir-resistant influenza A in the U.S. and other countries.
 - * Approximately 10% of influenza A (H1N1) isolates were resistant to oseltamivir during the 2007 - 2008 influenza season. ^[8]
 - * Because rates of resistance are relatively low, oseltamivir and zanamivir are still recommended by the CDC as preferred options for chemoprophylaxis in high risk individuals after exposure to influenza. ^[8]
 - * Immunization with influenza vaccine as a means to prevent influenza may help limit unnecessary exposure to oseltamivir and zanamivir, thereby slowing the spread of resistance.
- Oseltamivir does not have activity against bacterial infections.
- The FDA has received reports of patients with serious bacterial infections who initially had influenza-like symptoms and who had progressions of bacterial infection during treatment with anti-influenza drugs alone. ^[3]

Clinical Efficacy

- There is no evidence for oseltamivir (or other neuraminidase inhibitors, such as Relenza) regarding its efficacy in the treatment or prevention of avian influenza ('bird flu') or H1N1 flu ('swine flu').
 - * Potential for efficacy is based on in vitro virological data and extrapolation from use in treating ordinary human influenza.
- Treatment of influenza A or B with neuraminidase inhibitors decreased the duration of symptoms by about a day when compared with placebo. ^[2-3, 18]
- Treatment with oseltamivir provided no benefit in the time it took patients with influenza to return to normal activity levels. ^[18]
- There are no head-to-head trials that compare the efficacy or effectiveness of oseltamivir (Tamiflu) or zanamivir (Relenza), and influenza vaccine in the prevention of influenza.
- The potential benefit versus risk with neuraminidase inhibitors has not been established in patients at high risk for complication from influenza.

- Oseltamivir was studied in 548 frail, elderly residents of residential and nursing homes for community outbreak prophylaxis. Patients were stratified by vaccination status and coexisting chronic obstructive pulmonary disease (COPD).^[4]
 - * Most patients had multiple concomitant diseases with a mean of six diseases per patient. There was a mean of 7.7 concomitant medications per patient.
 - * Approximately 14% of the population had coexisting COPD. Approximately 80% of the patients were vaccinated before the influenza season.
 - * Oseltamivir 75 mg orally once per day or placebo was initiated for six weeks when influenza was confirmed in the home or reported in the area.
 - * Lab-confirmed influenza and influenza-like illness occurred in 12 of 272 (4.4%) patients receiving placebo versus 1 of 276 (0.4%) patients receiving oseltamivir.
 - * The reported protective efficacy was 92 % (p = 0.002) for oseltamivir.
 - * The absolute risk reduction (ARR) and number needed to treat (NNT) were 4.1% and 1,000, respectively, for oseltamivir.

Dosing and Administration

- One treatment course of oseltamivir every six months will provide coverage for the typical influenza season.
- Dosing of oseltamivir for treatment of influenza A and B:
 - * *Adults and adolescents (13 years and older):* 75 mg orally twice a day for five days.^[2]
 - * *Pediatric patients (1 to 13 years of age):*^[2]

Weight	Recommended dose for 5 days	Number of 25 ml bottles needed for recommended dose
≤ 33 lbs (≤ 15 kg)	30 mg (2.5 ml) twice daily	1
> 33 lbs to 51 lbs (> 15 kg to 23 kg)	45 mg (3.75 ml) twice daily	2
> 51 lbs to 88 lbs (> 23 kg to 40 kg)	60 mg (5 ml) twice daily	2
> 88 lbs (> 40 kg)	75 mg (6.25 ml) twice daily	3

- Dosing of oseltamivir for prevention of influenza A and B:

* *Adults and adolescents (13 years and older): 75 mg orally once a day for ten days.* ^[2]

* *Pediatric patients (1 to 13 years of age):* ^[2]

Weight	Recommended dose for 10 days	Number of 25 ml bottles needed for recommended dose
≤ 33 lbs (≤ 15 kg)	30 mg (2.5 ml) once daily	1
> 33 lbs to 51 lbs (> 15 kg to 23 kg)	45 mg (3.75 ml) once daily	2
> 51 lbs to 88 lbs (> 23 kg to 40 kg)	60 mg (5 ml) once daily	2
> 88 lbs (> 40 kg)	75 mg (6.25 ml) once daily	3

- Swine-origin influenza antiviral medication dosing recommendations (U.S. Centers for Disease Control and Prevention): ^[20]

Medication, Group	Treatment	Prophylaxis
<i>Oseltamivir (Tamiflu)</i>		
Adults	75 mg twice daily x 5 days	75 mg once per day
Children (age ≥ 12 months) weight:	< 15 kg	30 mg twice per day
	15-23 kg	45 mg twice per day
	24-40 kg	60 mg twice per day
	> 40 kg	75 mg twice per day
<i>Zanamivir (Relenza)</i>		
Adults	Two inhalations (10 mg) twice per day	Two inhalations (10mg) once per day
Children	Two inhalations (10 mg) twice per day (≥ 7 years)	Two inhalations (10mg) once per day (≥ 5 years)

Note: Doses are identical to those used for treatment and prophylaxis of influenza A and B.

- Swine-origin influenza antiviral medication dosing recommendations for oseltamivir in children less than 1 year of age: ^[20]

Age	Treatment (5 days)	Prophylaxis (10 days)
< 3 months	12 mg twice daily	Not recommended unless situation judged critical due to limited data in this age group
3 to 5 months	20 mg twice daily	20 mg once daily

Safety

- The most common adverse effects reported with oseltamivir administration include nausea, vomiting, and diarrhea. ^[2]
- The number needed to harm for 1 patient to experience nausea or vomiting with oseltamivir treatment over five days is 10 patients.
- Oseltamivir is classified as Pregnancy Category C and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus based on the physician's medical judgment in consultation with the patient. ^[2]

Preventing the spread of influenza: ^[20]

- Influenza is thought to spread mainly by person-to-person through coughing or sneezing of infected people.
 - * Cover your nose and mouth with a tissue when you cough or sneeze. Throw the tissue in the trash after you use it.
 - * Wash your hands often with soap and water, especially after you cough or sneeze. Alcohol-based hand cleaners are also effective.
 - * Avoid touching your eyes, nose, or mouth. Germs spread that way.
 - * Stay home if you get sick. The CDC recommends that you stay home from work or school and limit contact with others to keep from infecting them.

Appendix 1: Individuals at High Risk for Complications from Influenza. ^[18]

1.	Equal to or greater than 65 years old.
2	All children aged 6–23 months.
3.	Residents of nursing homes and other chronic-care facilities with residents of any age who have chronic medical conditions.
4.	Persons aged 2–64 years with underlying chronic medical conditions such as
a.	Chronic pulmonary diseases (e.g., asthma or chronic airway obstructive disorders)
b.	Cardiovascular disease
c.	Chronic metabolic disease (e.g., diabetes)
d.	Kidney dysfunction
e.	Blood disorders (e.g., hemoglobinopathies)
f.	Immune system problems (e.g., HIV infection; immunosuppressed by medication, chemotherapy, or radiation therapy)
g.	Neurological or neuromuscular disorders (such as spinal cord injuries, neuromuscular disorders, cognitive dysfunction)
5.	Children and adolescents aged 6 months to 18 years on chronic aspirin therapy. These patients may be at risk for developing Reye Syndrome after influenza infection.
6.	All women who will be pregnant during the influenza season.

References

1. CDC: <http://www.cdc.gov/nip/flu-vac-supply/flu-qa-top.htm>
2. Tamiflu® (oseltamivir) Prescribing Information. Roche Laboratories, Inc.; Nutley, NJ, December 2005.
3. FDA Talk Paper. FDA Reminds Prescribers of Important Considerations Before Prescribing Flu Drugs. T00-3. January 12, 2000. Food and Drug Administration. U.S. Department of Health and Human Services, Rockville, MD.
4. DeBock V, et al. Prophylaxis of influenza in frail elderly by oseltamivir. Abstract WeP256. European Congress of Clinical Microbiology and Infectious Disease (ECCMID) Proceedings; May 28-31, 2000. Stockholm, Sweden.
5. Hayden FG, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized, controlled trials for prevention and treatment. *JAMA* 1999;282:1240-1246.
6. Oxford J, et al. Short-term prophylaxis with oral oseltamivir effectively prevents the spread of influenza A and B. Abstract LB12. International Symposium on Influenza and Other Respiratory Viruses Meeting; December 10 - 12, 1999, Grand Cayman, Grand Cayman Islands.
7. Hayden FG, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med* 1999;341:1336-43.
8. Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2008;57(No. RR-10):1-60.
Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e717a1.htm>.
9. Hayden FG, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med* 1999;341:1387-8.
10. Kashiwagi S, et al. Efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir for prophylaxis against influenza-placebo-controlled double-blind multicenter phase III trial. (Abstract) *Kansenshogaku Zasshi* 2000;74:1062-76.
11. Kashiwagi S, Kudoh S, Watanabe A, Yoshimura I. [Clinical efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir in treating acute influenza--placebo-controlled double-blind multicenter phase III trial]. *Kansenshogaku Zasshi*. 2000;74:1044-61.

12. Treanor JJ, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. *J Am Med Assoc.* 2000;283:1016-24.
13. Imamura T, et al. [The study on efficacy of oseltamivir for influenza A in children] *Kansenshogaku Zasshi.* 2003;77:971-6. Japanese.
14. Li L, Cai B, et al. A double-blind, randomized, placebo-controlled multicenter study of oseltamivir phosphate for treatment of influenza infection in China. *Chin Med J (Engl).* 2003;116:44-8.
15. Hayden FG, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without post-exposure prophylaxis. *J Infect Dis.* 2004;189:440-9.
16. Chik KW, et al. Oseltamivir prophylaxis during the influenza season in a pediatric cancer center: prospective observational study. *Hong Kong Med J.* 2004;10(2):103-6.
17. The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. Avian Influenza A (H5N1) in humans. *N Engl J Med.* 2005;353:1374-85.
18. Jefferson T, Demicheli V, Deeks J, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *The Cochrane Database of Systematic Reviews* 1999, Issue 2. Art. No.: CD001265. DOI: 10.1002/14651858.CD001265.
19. Matheson NJ, Symmonds-Abrahams M, Sheikh A, Sheppard S, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children. *The Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD002744. DOI: 10.1002/14651858.CD002744.
20. U.S. Centers for Disease Control and Prevention. Interim guidance on antiviral recommendations for patients with confirmed or suspected Swine Influenza A (H1N1) virus infection in close contacts. Available at: <http://www.cdc.gov/h1n1flu/recommendations.htm#table1>. Accessed on May 1, 2009.

Cross References
Relenza [®] , zanamivir, dru113

Codes	Number	Description
N/A		